9th International Conference on Frontotemporal Dementias
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O.1 Clinical presentation of frontotemporal dementia

Bruce L. Miller

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Abstract: Frontotemporal lobar degeneration (FTLD) and related pathologies are a common cause for dementia. Differentiating patients with FTLD from those with Alzheimer's disease (AD) during life has greatly improved over the past 20 years and further advances are still emerging. The clinical phenotypes associated with FTLD-spectrum neuropathology include behavioral variant frontotemporal dementia (bvFTD), sematic variant primary progressive aphasia (svPPA), nonfluent/agrammatic variant primary progressive aphasia (nfvPPA), progressive supranuclear palsy (PSP), corticobasal syndrome (CBS) and amyotrophic lateral sclerosis (ALS). While the new research criteria for bvFTD, PPA and PSP, along with the use of amyloid biomarkers, has improved the accurate diagnosis of FTD-spectrum disorders and has helped to differentiate them from patients with AD pathology, new diagnostic problems have emerged. Two remaining diagnostic issues are separating non-FTD related psychiatric syndromes from FTD and capturing the prodromal and preclinical stages of FTD. Also, separation of FTD-tau related syndromes from those with FTD-TDP43 or FTD-FUS is still difficult. New approaches to understanding the early features of FTD are needed. Often, in the clinical setting, the rich set of prodromal symptoms provided by the patient or the patient's caregivers, is difficult to link in a definitive way to FTD. Yet, these symptoms, usually psychiatric, offer insights into the early stages of FTD and into the psychiatric manifestations of neurological disorders. Gene carriers offer a unique opportunity to study the clinical and imaging features of patients in the early stages of FTD. Additionally, molecular PET will offer new insights into clinical and molecular correlates of FTD.

O.2 Evolving themes in primary progressive aphasia (PPA)

M-Marsel Mesulam, Emily Rogalski, Tamar Gefen, Robert Hurley, Changiz Geula, Sandra Weintraub, Eileen Bigio

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Asbtract: PPA is being recognized with increasing frequency. The 2011 classification guidelines have standardized subtyping but may require modification to reduce the number of patients who remain unclassifiable or who fit more than one variant. Patients with PPA continue to offer new insights into the biology of language and have helped to clarify the language-related specializations and asymmetrical connectivity of the left anterior temporal lobe. The neuropathologic correlates of PPA keep expanding and now include AD, DLBD, FTLD-tau (Pick-, CBD- and PSP-types) and FTLD-TDP (types A, B and C). Alzheimer pathology in PPA displays atypical tangle distributions and a lack of association with ApoE4, suggesting that AD may be more heterogeneous than suspected and that some forms may not follow the Braak staging system. PPA has also broadened the clinical spectrum of FTLD-TDP type B, which now includes anomic, logopenic and agrammatic aphasias that emerge without clinical motor neuron dysfunction. The multiple pathologies of PPA show that dementia phenotypes reflect complex interactions between patient-specific factors, which influence regional vulnerabilities, and disease-specific factors, which determine underlying mechanisms of neurosynaptic destruction. The patient-specific factors in PPA that make the left hemisphere language network selectively vulnerable to multiple neurodegenerative entities deserve further investigation.

O.3 Atypical presentations of frontotemporal lobar degeneration

Bradley F. Boeve

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Abstract: While the behavioral variant frontotemporal dementia (bvFTD) and primary progressive aphasia (PPA) phenotypes are the most common and well-known presentations of frontotemporal lobar degeneration (FLTD), there are several other FTLD variants which are less common and/or more variably characterized. In this review, the following atypical presentations of FTLD are discussed: corticobasal syndrome (CBS), progressive supranuclear palsy phenotype/Richardson's syndrome (PSP-RS), prosopagnosia/associative agnosia variant, primary progressive apraxia of speech (PPAOS), psychosis-predominant variant, primary lateral sclerosis (PLS) +/- spastic dysarthria, parkinsonism and/or ALS associated with FTD/PPA, and FTD/PPA associated other manifestations such as Paget's disease, inclusion body myositis, and leukodystrophy. For each variant, the clinical features, topography of degeneration, neuroimaging findings, and associated genetic and/or pathologic findings are described. This review highlights that FTLD represents a spectrum of clinical variants, each associated with a characteristic topography of degeneration and profile of abnormal neuroimaging findings, but each has more variably associated genetic and/or pathologic findings. This variability underscores the need for identifying or refining biomarkers for the underlying proteinopathies in order to improve diagnostic accuracy and plan for disease-modifying therapies.

O.4 The evolution of behavioural variant frontotemporal dementia – key prognostic factors

Emma Devenney, Michael Hornberger, Chris Hoon, Lauren Bartley, Glenda Halliday, Matthew Kiernan, Olivier Piguet, John Hodges

Neuroscience Research Australia; University of Cambridge; Brain Mind Research Institute, University of Sydney

Abstract: To conform to a diagnosis of bvFTD patients must exhibit features as described in international diagnostic criteria. These patients do not always satisfy criteria for 'probable' but instead are categorised as 'possible' bvFTD. This study aimed to longitudinally examine a bvFTD cohort to determine 1) the frequency of 'possible' and 'probable' bvFTD, 2) the outcome of these cases over time and, 3) imaging changes across the cohort. BvFTD patients (n=140) were prospectively assessed at the FTD clinic over a five-year period. Patients with at least two years of follow-up were included (n=65). All patients underwent a standardised clinical assessment, neuropsychological testing, MRI and were classified as 'possible' or 'probable' bvFTD. At presentation one-third of cases met 'possible' - exclusively due to lack of imaging abnormalities, while two-thirds met 'probable' criteria. At follow-up 'possible' cases were equally likely to become 'probable' (progressors) as to remain 'possible' (non-progressors). The majority (80%) of progressors harboured the C9orf72 mutation. Key features of progression were abnormal clinical signs (p=0.04), positive family history (p=0.02), and deficits on memory tasks (p=0.035). Voxel-based morphometry analysis revealed hippocampal as well as frontal and temporal atrophy in the progressors, compared to no significant atrophy in the non-progressors. The findings suggest that memory deficits may manifest early in 'progressors' and occur before the onset of overt atrophy on visual inspection of MRI. A high number of C9orf72 carriers failed to satisfy probable bvFTD at presentation suggesting that revisions to diagnostic criteria may be required when considering the C9orf72 mutation.

O.5 Physiological phenotyping of frontotemporal lobar degenerations

Jason Warren, Phillip Fletcher, Jennifer Agustus, Jennifer Nicholas, Laura Downey, Hannah Golden, Colin Mahoney, Camilla Clark, Catherine Mummery, Martin Rossor, Jonathan Schott, Simon Mead, Jonathan Rohrer, Nick Fox, Crutch Sebastian

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Abstract: The frontotemporal lobar degenerations (FTLD) present substantial problems of diagnosis and nosology and often produce complex behavioural derangements that are difficult to characterize using conventional metrics. The systems physiology of distributed brain networks is targeted by these diseases: physiologically-motivated approaches are potentially a rich source of phenotypic data and can suggest mechanisms whereby brain network dysfunction produces fundamental changes in sensory experience and output behaviors. However, physiological techniques have not been widely applied in characterizing dementia diseases. Here I summarize a linked series of experiments to define physiological phenotypes in a large cohort of patients representing all canonical syndromes and major genetic subtypes of FTLD (including C9orf72 and MAPT mutations), using somatosensory, autonomic (pupillometric) and psychoacoustic modalities with structural and functional neuroanatomical correlation, in relation to cohorts of healthy older individuals and patients with Alzheimer's disease. Key findings include neuroanatomical signatures of abnormal tactile and auditory coding in frontotemporal dementia and semantic dementia syndromes; and pupillometric signatures of abnormal acoustic salience and valence processing across FTLD syndromes. Collectively, this program of work suggests that systems physiological indices can capture generic mechanisms of altered information processing in FTLD that have some specificity for molecular substrates, transcend conventional syndromic boundaries and establish novel linkages between clinical symptoms and culprit brain network disintegration.

O.6 Identifying unique clinical symptoms of bvFTD versus differential psychiatric diagnoses in a 'frontal' neuropsychiatric cohort

Annemiek Dols, Saskia van Liempt, Flora Gossink, Welmoed Krudop, Yolande Pijnenburg, Max Stek

GGZinGeest, VU University Medical Center

Abstract: Early differentiation between psychiatric disorders and behavioral variant Frontotemporal dementia (bvFTD) is of paramount importance in patients with'Late Onset Frontal lobe syndrome' (LOF). As bvFTD patients will progress, psychiatric disorders are treatable. To date, misdiagnosis often occurs due to an overlap of symptoms and lack of specific biomarkers. In a naturalistic prospective multicentre study 137 patients (aged 45-75, 72% males) with a LOF were included based on their scores on the Frontal Behavioral Inventory (FBI) and the Stereotypy Rating Inventory (SRI). Diagnosis was based upon elaborate neuropsychological testing, MRI, 18F-FDG-PET, and clinical examination by a neurologist and a psychiatrist (including Montgomery Asberg Depression Scale (MADRS)). 50 subjects were diagnosed with a psychiatric diagnosis, 11 with possible bvFTD and 44 with probable bvFTD. A logistic regression analysis was performed with "FTD or psychiatry" as depended variable, and clinical variables (MADRS, SRI, FBI) as regressors. Our data show that a positive history of psychiatric illness and higher MADRS scores, were predictive for psychiatric illness, while higher scores on SRI were predictive for bvFTD. Interestingly, the total score of FBI and loss of insight were not indicative of bvFTD. This study shows that bvFTD is characterized by symptoms of impulsivity, personal neglect, stereotypy, and restlessness while the likelihood for FTD is lower in the presence of substantial depressive symptoms, irritability, inattentiveness and a positive history of psychiatric illness. Specific subtyping of clinical symptoms in patients with LOF may differentiate bvFTD patients from psychiatric patients, and provide guidance in patient management.

O.7 *C9orf72* and other new FTD genes

Rosa Rademakers

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Abstract: Three major genes have been identified to cause frontotemporal lobar degeneration (FTLD). Mutations in the microtubule associated protein tau (MAPT) cause FTLD with tau pathology, while mutations in progranulin (GRN) and a GGGGCC-repeat expansion in chromosome 9 open reading frame 72 (C9ORF72) cause FTLD with TAR DNA-binding protein 43 (FTLD-TDP). Importantly, in contrast to MAPT and GRN, C9ORF72 repeat expansions are also a major cause of amyotrophic lateral sclerosis (ALS). Despite heterogeneity across populations, C9ORF72 repeat expansions are the most common cause of FTLD, explaining the disease in roughly a quarter of familial and 5% of sporadic FTLD. Using southern blotting, we showed substantial variation in repeat sizes between samples prepared from brain, peripheral tissues and blood. Within an individual, repeat sizes in blood did not predict repeat sizes in brain and repeat sizes were not associated with disease phenotype; however, the repeat size did correlate with disease severity, especially in the cerebellum. Using cohorts of C9ORF72 expansion carriers we further identified TMEM106B as the first C9ORF72 disease modifier, protecting patients from the development of FTLD but not ALS. Despite these major advances, the cause of disease in approximately 50% of familial and most sporadic FTLD patients remains unknown. To identify novel FTLD genes, our laboratory is using whole-exome and whole-genome sequencing in FTLD families and in cohorts of unrelated FTLD patients with pathological confirmation of FTLD-TDP or atypical FTLD with FUS pathology (FTLD-FUS). Identification of additional FTLD genes is expected to provide important novel insights into FTLD pathogenesis.

O.8 Integrated approach to identify FTLD genes and modifiers

Christine Van Broeckhoven

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Abstract: A considerable fraction of the genetic etiology of frontotemporal lobar degeneration (FTLD) is not yet been resolved. In cohorts, mutations in the FTLD genes are observed in around 10% of patients while 40% of the families remain unexplained. Also, genetic factors underlying the typical wide spread in onset ages of 30 to 45 years are largely unmapped. In large pedigrees and patient cohorts, we use next-generation sequencing (NGS) to identify new FTLD genes and/or genetic modifier genes. For these studies, distant related patients are selected of extended families while of cohorts patients with extreme phenotypes (familial, early-onset age, pathology confirmed, etc.) are included. For example, we identified in unrelated FTLD patients 4.8% missense mutations in VPS13C lowering protein expression. Further, we screened a functional candidate, FLNC, which is upregulated in frontal cortex of GRN mutation carriers and identified 11 loss-of-function mutations. In mutation carriers, we use different NGS approaches to identify genetic modifiers. We screen the FTLD patients using an multiple amplicon, exon-targeted sequencing-based MASTR assay (www.multiplicom.com), for genetic variation in set of 30 genes associated with neurodegenerative brain diseases. In 7%, we identified rare variants potentially affecting the protein including 21 that were definitely or probably pathogenic. In the Belgian GRN founder pedigree, we identified a quantitative trait locus of 7 Mb explaining up to 91% of the genetic variance in onset age. To identify putative modifying genetic variants, we link the genetic data to biological data obtained by brain transcriptomics and serum proteomics of the GRN mutation carriers.

O.9 Novel mutations in RNA binding proteins in FTD alter RNA granule dynamics

J. Paul Taylor

Department of Cell and Molecular Biology, St. Jude Children's Research Hospital, Memphis

Abstract: Recent observations implicate disturbances in RNA metabolism as an underlying cause of certain degenerative diseases of CNS and muscle. Amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and certain vacuolar myopathies such as inclusion body myopathy (IBM) are characterized by the accumulation of nuclear or cytoplasmic RNA-binding proteins (RBPs) that are components of endogenous RNP granules. Mutations impacting some of these same RBPs (e.g. TDP-43, FUS/TLS, hnRNPA1, hnRNPA2B1) are sufficient to cause disease. Importantly, the disease-causing mutations in these RBPs sometimes impact regions of these proteins we have defined as "prion-like domains" (PrLDs). These PrLDs mediate the normal assembly of RNA granules, and this activity is pathologically enhanced by mutations leading to abnormal accumulation of cytoplasmic RBP aggregates. Mutations in VCP are causative of the same spectrum of muscle and brain diseases characterized by abnormal accumulation of cytoplasmic RBP aggregates. Recent observations indicate that VCP regulates RNA granule dynamics and that disease mutations in VCP impair normal RNA granule disassembly and clearance. In this talk I will present recent data indicating that a disturbance in the normal regulation of RNA granule dynamics, and the consequential alteration of RNA metabolism, is a fundamental pathogenic feature of a spectrum of brain and muscle diseases that may be categorized as 'multisystem proteinopathies.'

O.10 Variation within *C9orf72* hides a significant proportion of expansion carriers

Stuart Pickering-Brown

Manchester University

Abstract: Repeat expansion mutations in C9orf72 are the most common genetic cause of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) identified to date. The expansion is generally detected using repeat-primed PCR (RP-PCR). As part of the screening of the Manchester FTD cohort we identified two brothers that had an apparently normal C9orf72 gene with just six repeats as detected using RP-PCR. However, both brothers had ubiquilin-2 positive cerebellar inclusions that are thought to be specific to patients with C9orf72 expansions. Surprisingly, Southern blot analysis revealed an approximately 20kb expansions in both brothers which was undetectable using RP-PCR. Extensive gene analysis of C9orf72 has revealed variation that prevents the RP-PCR from detecting the expansion in people who carry it. Genotyping of the Manchester FTD cohort with a modified version of the RP-PCR assays has revealed an increase of 20% in FTD patients that carry the expansion and the frequency of ALS carriers has almost doubled. These data suggest that C9orf72 expansions are a more common cause of FTD and ALS than previously thought.

O.11 Next generation sequencing identifies mutations in *VPS13C* associated with decreased expression of endogenous protein in Frontotemporal lobar degeneration

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Abstract: Frontotemporal lobar degeneration (FTLD) is a heterogeneous group of neurodegenerative dementias and mainly affects people younger than 65 years of age. In about 60% of the families with FTLD, the genetic cause is still unknown. Therefore, we performed whole genome sequencing on 16 unrelated familial FTLD patients to identify rare, highly penetrant mutations. Annotation and analysis of the genome sequences was performed using GenomeComb and variants were filtered and prioritized using multiple genetic and functional criteria. Analysis of these variants in 392 Flanders-Belgian FTLD patients and 900 control individuals revealed the presence of two novel coding missense variants (p.W395C and p.A444P) in the vacuolar protein sorting 13 homolog C (VPS13C) gene. The p.A444P missense mutation was present in a WGS patient and two additional index patients. The p.W395C missense mutation was present in an affected sib pair who was also carrying the p.A444P mutation. Screening of the 86 coding exons of VPS13C in the Flanders-Belgian FTLD population was performed using the Multiplex Amplification of Specific Targets for Resequencing (MASTR) technology and resulted in the identification of 13 additional missense mutations that were absent in at least 351 age- and geographically matched control individuals, resulting in an overall mutation frequency of 4.8% (19 of 392 FTLD patients). Immunocytochemistry of lymphoblast cells of five patients with a VPS13C mutation suggested a 44-80% decreased expression ($p<0.001$) of VPS13C protein compared to mutation-negative controls (n=4). Extended neuropathological and cell biological studies are needed to support the role of VPS13C in FTLD.

O.12 Imaging in familial FTD: results of the Genetic FTD Initiative (GENFI)

Jonathan D Rohrer

Frontotemporal Dementia Initiative

Abstract: The Genetic Frontotemporal dementia Initiative (GENFI) comprises eleven sites across Europe (UK, Italy, Netherlands, Sweden) and Canada. Participants were recruited who were either known carriers of a pathogenic mutation in GRN, MAPT or C9orf72, or who were at risk of carrying a mutation because a first-degree relative was a known symptomatic carrier. Participants underwent a standardized clinical assessment including the Cambridge Behavioural Inventory-Revised (CBI-R). The neuropsychological battery consisted of the MMSE, tests from the Uniform Data Set and WASI Block Design. MRI was performed and grey matter volumes for the frontal, temporal, parietal, occipital, cingulate and insular cortices generated using a cortical parcellation of the volumetric T1-weighted scan. Linear mixed effects models were used to examine whether the association between values of markers and time to expected onset of symptoms differed between mutation carriers and noncarriers. Data were analysed from 220 participants consisting of 118 mutation carriers (40 symptomatic, 78 asymptomatic) and 102 noncarriers. MMSE, CBI-R and most neuropsychology markers showed mean differences between mutation carriers and noncarriers around 5 years before onset, with digit span backward and the digit symbol task showing differences 10 years before onset. For the imaging markers, differences in group means between mutation carriers and noncarriers were seen at the earliest time point for the insula (around 10 years before onset) whilst frontal, temporal and parietal lobe volumes differed around 5 years before onset. Imaging and cognitive changes can be identified up to ten years before the onset of symptoms in genetic FTD.

O.13 Imaging diverse tau fibril strains in tauopathies

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Abstract: Visualization of fibrillar tau aggregates in Alzheimer's disease (AD) and other tauopathies including frontotemporal lobar degeneration (FTLD) provides insights into roles of tau deposition in neurodegeneration, and a diagnostic adjunct to these illnesses. We recently developed a positron emission tomographic (PET) imaging agent for tau lesions, PBB3, and demonstrated its capability in detecting tau accumulation in diverse tauopathies. PBB3-PET also indicated spreading of tau pathology from the hippocampal formation to extensive neocortical areas in transition from normal aging to advanced AD. In FTLD patients, distributions of PBB3 retention differed between progressive supranuclear palsy (PSP) and corticobasal syndrome, and were also distinct from those in AD. Furthermore, PET and autoradiography with PBB3 have revealed regionality of PBB3-positive tau deposition in a manner characteristic of familial tau gene mutations. Notably, PBB3 and various other tau ligands displayed differential reactivity with tau aggregates in FTLDs. These data support the presence of distinct strains of tau fibrils presumably attributed to different isoform compositions and mutations of tau as well as interactions of tau with non-tau aggregates, and the same non-mutant tau isoforms may also produce minor conformational variations in PSP and corticobasal degeneration. These strains define regional, cellular and subcellular localization of tau inclusions, and would be identified in living brains using a set of tau PET ligands. PBB3 may be utilized as a versatile ligand reacting with tau lesions in the vast majority of tauopathies, and development of its fluorinated derivatives aimed at a wider use is in progress.

O.14 Pattern classification in FTD: Multimodal imaging and meta-analyses

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Abstract: Recently, new diagnostic criteria including imaging biomarkers have been proposed for frontotemporal lobar degeneration (FTLD), in particular for its behavioural variant and language subtypes. These imaging criteria shall enable individual diagnosis. Here, we validate these imaging criteria by conducting quantitative anatomical likelihood estimate meta-analyses according to the QUOROM/PRISMA statement across studies published in the literature. These meta-analyses have identified the neural correlates for each of FTLD's subtypes and underline disease-specificity of the imaging criteria. Analyses were conducted separately for atrophy measured with magnetic resonance imaging (MRI) and glucose metabolism measured with [F18]fluorodeoxyglucose positron emission tomography (FDG-PET). Both imaging methods were associated with specific regional patterns at least in behavioural variant FTLD and semantic dementia. Results might open the road to method-specific imaging criteria as already suggested for Alzheimer's disease. If new imaging criteria are valid they shall enable early individual diagnosis in single patients. To prove the potential for individual diagnosis we investigated whether FTLD might be diagnosed with cutting edge pattern classification algorithms in multimodal imaging data. Support vector machine classification (SVM) with multimodal imaging data (MRI & FDG-PET) enabled early individual detection of FTLD and discrimination between FTLD and Alzheimer's disease. Limiting SVM classification regionally to meta-analytically identified disease networks even improved discrimination accuracy. Analyses were also reliable in multi-centric data. In conclusion, (i) our results support and refine the application of imaging criteria, and (ii) suggest that pattern classification algorithms enable early individual diagnosis and differential diagnosis of FTLD subtypes - a precondition for early intervention strategies.

O.15 Imaging tau pathology in vivo in FTLD: initial experience with [18F] T807 PET

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Abstract: A critical unmet need for FTLD research, especially therapeutic trials, is the development of biomarkers to distinguish FTLD-tau from FTLD-TDP and other non-tau FTLD pathologies. We are using [18F] T807, a novel PET ligand, to scan a series of patients with FTLD, to date including one MAPT P301L mutation carrier with moderate severity FTD dementia, an asymptomatic carrier of the same mutation, 10 patients with sporadic mild primary progressive aphasia, 2 patients with bvFTD, and three patients with progressive supranuclear palsy. We analyzed SUVR (cerebellum reference) data to localize and quantify [18F] T807 signal. We also co-registered analyzed [18F] T807 images to MRI images for visualization and calculation of % atrophy relative to controls. [18F] T807 signal was elevated in frontal, insular, and anterior temporal cortex in the MAPT carrier with dementia, and colocalized with atrophy. In aphasic patients, [18F] T807 signal was highest in inferior frontal and middle temporal gyri and temporal pole with marked asymmetry, most prominent in the dominant hemisphere, and localized remarkably well with atrophy. The asymptomatic carrier had mildly elevated signal in frontal, insular, and anterior temporal cortex as well as white matter. PSP patients showed elevated brainstem, basal ganglia, thalamic/subthalamic, cerebellar, and frontal signal. T807 is a promising new PET ligand for imaging tau pathology in vivo in patients with FTLD.

O.16 Longitudinal structural and functional connectivity in presymptomatic familial frontotemporal dementia

Lize Jiskoot, Elise Dopper, Tom den Heijer, J. Roos de Graaf, John van Swieten, Inge de Koning, Anke Hammerschlag, Harro Seelaar, William Seeley, Ilya Veer, Mark van Buchem, Patrizia Rizzu, Serge Rombouts

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Abstract: Sensitive biomarkers to detect early frontotemporal dementia (FTD) and track disease progression are crucial in light of future therapeutic trials. Grey matter atrophy is a standard diagnostic tool for FTD, but may be absent or too subtle to detect in early disease. Previous studies have shown alterations in structural and functional connectivity in presymptomatic FTD using diffusion tensor imaging (DTI) and resting-state fMRI (rs-fMRI). We aimed to investigate whether longitudinal connectivity changes can be measured in presymptomatic FTD. Forty subjects with a GRN or MAPT mutation and 34 controls (20-70 years) underwent MRI and neuropsychological assessment at baseline and two-year follow-up. T1-weighted and DTI scans were acquired and analysed using voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS) in FSL. We used bilateral seeds in the anterior midcingulate cortex, frontoinsula and posterior cingulate cortex (PCC) for rs-fMRI analyses in FSL. Neuropsychological assessment demonstrated conversion to clinical FTD in two subjects, and lower scores on several executive and social cognitive tests in carriers compared to controls. VBM and TBSS analyses revealed no longitudinal differences between carriers and controls. However, carriers showed a stronger reduction in functional connectivity between the right frontoinsula and other temporal regions over two years compared to controls. Conversely, PCC connectivity with right parietal regions and frontoinsula connectivity with subcortical areas decreased more in controls. This study demonstrates that longitudinal functional connectivity changes differ between presymptomatic carriers and controls. Therefore, rs-fMRI might be a suitable biomarker for early disease detection and progression in future trials for early FTD.

O.17 Transmission of misfolded proteins in neurodegenerative disorders: a common mechanism of disease progression

Virginia Lee

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Abstract: The accumulation of misfolded proteins is a fundamental pathogenic process in neurodegenerative diseases. However, the factors that trigger aggregation and spreading of these disease proteins in brain are poorly understood. Recent studies demonstrate that misfolded disease proteins including tau in frontotemporal degeneration can be propagated from cell-to-cell through the recruitment of their endogenous normal counterparts. Moreover, pathologic misfolded aggregates propagated along major central nervous system (CNS) pathways to regions far beyond injection sites and appear to follow neuroanatomical interconnectomes. This spreading of pathology could account for the clinical progression of these neurodegenerative diseases thus opening up new avenues for understanding the mechanisms of disease progression and for developing novel therapeutics.

O.18 Other diseases mimicking frontotemporal dementia

John C. van Swieten, Elise G.P. Dopper, Harro Seelaar, Lieke Meeter, Tsz Hang Wong, Yolande Pijnenburg, Annemiek Rozenmuller

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Abstract: Robust clinical criteria for frontotemporal dementia (FTD) and its subtypes (behavioural variant of FTD, semantic dementia, progressive non-fluent aphasia) have been established over the last decade. Despite these criteria, the clinical diagnosis can be hampered by atypical presentations of other diseases involving frontal lobes and their connections. These other disorders can be distinguished into progressive neurodegenerative disorders and those without over progression, including psychiatric disorders and benign FTD. Familial segregation has been found in a considerable percentage of cases. The group of neurodegenerative disorders mimicking FTD includes Alzheimer's disease, Progressive Supranuclear Palsy with frontal presentation, Creutzfeldt Jakob disease, and neurofilamentopathy. The clinical presentation of these disorders often consists of dementia with an atypical cognitive profile, and extrapyramidal and or cerebellar disorders. Cerebrospinal fluid analysis usually does not differentiate between these disorders, and neuroimaging often shows aspecific features. Using novel biochemical and genetic tools, including whole exome sequencing and proteomics, new disease neurodegenerative disease entities have discovered by over recent years, for example mutations in the gene coding for the regulatory beta subunit of protein kinase A (PRKAR1B) or in the STUB1 gene. Neuropathological examination is an absolute requisite for establishing the correct diagnosis in cases with atypical FTD presentation. Future biomarkers and genetic tests will enable the clinician to improve diagnostic accuracy during life in the clinical setting of presenile dementias.

O.19 Interpretation of multiple genetic findings in single individuals with neurodegenerative disease

John Anthony Hardy

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Abstract: With the identification of multiple pathogenic loci for neurodegenerative diseases and especially for frontotemporal dementia, there have now been several reports of cases with mutations in more than one gene. This phenomenon has also been extensively reported in ALS and in Parkinson's disease. These reports raise the question as to whether these findings are of statistical, biological and pathogenic significance. I will review this issue and discuss the findings with respect to the following issues: 1) are either or both variants known to be independently pathogenic? 2) are the findings the result of selective sequencing and reporting 3) can we interpret these data with respect to the mechanisms of, and pathways to, cell death? I will suggest that only by having access to large series of control data as well as from cases series from different populations can we truly interpret these findings.

O.20 The bvFYD phenocopy syndrome

John R Hodges

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Abstract: The long-term follow up of Cambridge patients diagnosed clinically as bvFTD revealed a subgroup of males with excellent prognosis who failed to progress even after a decade. Later work revealed that such cases typically lacked brain atrophy and have normal FDG-PET uptake. Their activities of daily living main intact and compared to typical progressive cases they do well on tests of executive function and memory. Such cases were initially labeled as non-progressive bvFTD but later we adopted the term bvFTD phencopy. These finding contributed to the 2011 revised Internal Consensus Criteria for bvFTD which proposed the categories of possible and probable bvFTD in that phenocopy cases would meet criteria for the former but not the later. Subsequent work from UCSF showed that some phenocopy cases habour the C9orf72 gene mutation. We have confirmed that patients with the mutation may present atypically and have a long indolent prodrome dominated by neuropsychiatric symptoms with little brain atrophy. The question arises therefore of the frequency of the mutation in phenocopy cases. We recently explored this in patients with possible bvFTD seen in Sydney. A half of such patients remain possible after 3 years and lack the C9orf72 mutation and appear true phenocopy cases. The other half met criteria for probable bvFTD and the majority habour the C9orf72 mutation. The latter group were distinguished by psychotic features and, often, by a family history of dementia or ALS. The nature of the phenocopy syndrome remains a controversial topic of active interest.

O.21 Clinicopathological aspects of FTLD-tau

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Abstract: There are four major subtypes of FTLD-tau characterised by different cellular structures, 1) three-repeat (3R) tau in Pick bodies (Pick's disease; PiD), 2) four-repeat (4R) tau in tufted astrocytes (progressive supranuclear palsy; PSP), 3) 4R tau in astrocytic plaques (corticobasal degeneration; CBD), and 4) 4R tau in oligodendroglial globular glial inclusions (GGI), with MAPT mutations showing either these or rarer subtypes (e.g. tangle-only dementia). Around 30% of clinic patients have FTLD-tau compared with 40-45% of autopsy cases. This difference is due to a proportion of pathological FTLD cases having clinical Alzheimer's disease (AD). As may be expected, PiD differs significantly from the other forms of FTLD-tau with significantly longer mean disease durations. In the Sydney-Cambridge dementia cohorts, PiD represents the majority of autopsy cases (45%), with about 25% diagnosed with clinical AD. These characteristics may contribute to the relatively low prevalence of PiD in FTD clinics. CBD represents the next most common FTLD-tau dementia subtype (~30% of cases) while PSP and GGI have a similar prevalence (~10% each). No major demographic differences occur between the 4R tauopathies, including those with motor only phenotypes, suggesting a similar pathogenesis across these disorders, although most PSP cases had additional extrapyramidalism (75%), while GGI were mainly dementia only (~70%). These data suggest that PiD should be differentiated from the 4R tauopathies in the spectrum on FTLD-tau, and efforts to refine this separation are needed. Recent data shows that higher CSF tau predicts shorter survival, with such cases most likely to be the 4R tauopathies.

O.22 Clinico-pathological aspects of FTLD-TDP and FTLD-FET

Manuela Neumann

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Abstract: TDP-43 accumulation is the hallmark lesion in about 60% of FTLD cases. FTLD-TDP subsumes sporadic and genetic forms with mutations in GRN, C9ORF72 and VCP that present with a broad spectrum of clinical phenotypes including bvFTD with and without MND, SD and PFNA, in addition extrapyramidal symptoms can be present. Overall, a good correlation exists between the distribution and severity of TDP-43 pathology with degeneration and clinical features in all FTLD-TDP forms implying a central role of TDP-43 dysmetabolism in disease pathogenesis. This is further supported by the association of specific patterns of cortical TDP-43 pathology (subtypes A-D) with distinct clinical phenotypes and underlying genetic defects. However, the recognition of mixed subtypes and heterogeneity particularly among C9ORF72 mutation carriers highlighted the need to re-evaluate criteria used to subtype FTLD-TDP in order to further determine the significance and molecular mechanisms underlying TDP-43 patterns. C9ORF72 mutation cases represent a special FTLD-TDP subgroup due to its complex neuropathology with additional TDP-43-negative inclusions composed of dipeptide repeat proteins and presence of RNA foci. However, their pathomechanistic relevance remains unclear due to the current lack of clear clinico-pathological correlations. FTLD-FET subsumes three sporadic conditions aFTLD-U, BIBD, NIFID with overlapping, but distinct clinico-pathological features, that share the presence of inclusions immunoreactive for all FET proteins (FUS, TAF15, EWS) and their nuclear import receptor transportin. The immunohistochemical profile of inclusions allows separating FTLD-FET from cases with a FUS mutation that are usually associated with pure MND and implicate arginine hypomethylation in the disease pathogenesis of FTLD-FET.

O.23 Alzheimer's pathology presenting as FTD

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Abstract: Although most cases presenting clinically as behavioral variant FTD (bvFTD) and the semantic and nonfluent variants of Primary Progressive Aphasia (PPA) have one of taupathies, TDP-43pathies or FUSopathies as their pathological substrate, a subset shows Alzheimer's disease pathology (ADP), with neuritic plaques and neurofibrillary tangles. There are 3 possible explanations for such focal presentation of ADP. First, the pathological process selectively involves the relevant areas. In all reported cases, the ADP is widespread, and the limbic structures associated with AD are more severely involved than language or fronto-orbital areas. On the other hand, morphometric analysis, and sometimes semi-quantitative assessment, show side-appropriate asymmetry in most (but not all cases) and an increased ratio of lesion density in language or frontal areas to limbic structures as compared to cases with Dementia of the Alzheimer type (DAT). It is unclear how the small difference in lesion density would translate into such selective clinical manifestations. The second possibility is that of a mixed dementia, with one of the know substrates of FTLD associated with ADP. TDP-43 pathology has been conclusively shown to be inversely correlated with focal manifestations of ADP, being much more common in amnestic DAT, concordant with its association with hippocampal sclerosis. The third possibility is the presence of a different pathology. Argyrophilic thorny astrocytic clusters are present in the white and cortex of some, but not all ADP cases with focal presentation, much more frequently than in amnestic DAT. Finally, it is possible that idiosyncratic features present prior to the development of ADP influence its expression, as suggested by cases presenting with primary progressive aphasia and cranial asymmetry, indicative of an early developmental process resulting in greater vulnerability of specific areas.

O.24 A novel mutation P112H in the *TARDBP* gene associated with frontotemporal lobar degeneration without motor neuron disease, TDP-43 inclusions and abundant tau-negative neuritic plaques

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Abstract: TARDBP mutations account for less than 5% of familial ALS. The association of TARDBP mutations with pure FTD is less robust: less than 15 cases have been reported, and only three received neuropathological confirmation. Curiously, the majority did not present family history of FTD or MND. Notably, most of the mutations described in ALS/MND are missense changes in exon 6, encoding the Gly-rich region and C-terminus of TDP-43. Here, we report the clinical, neuroimaging, neuropathologic and genetics characteristics of two siblings belonging to a pedigree presenting with an autosomal dominant complex, novel double contiguous variant, at codon 112 of the TARDBP gene in exon 3. At variance with most TARDBP mutations, the variation described here is found outside the C-terminal tail of the protein, in an area encoding the first RNA-binding motif of TDP-43 (RRM1). Previous few reports of sequence variants affecting the RRM1 domain were described in sporadic ALS patients. Exome sequencing in the proband confirmed that both variants were on the same chromosome. Multiple computational approaches for in silico prediction of the pathogenicity all indicate a deleterious effect of the amino acid change. Both individuals presented with frontotemporal dementia without motor neuron disease with age at onset in the 7th decade. Neuropathological examination conducted at the UCSF/ Neurodegenerative Disease Brain Bank showed similar neuropathological aspects in both cases: unclassifiable TDP-43-positive inclusions, tau-negative abundant β-amyloid neuritic plaques and argyrophilic grain disease.

O.25 Heritability in non-Alzheimer's disease tauopathies

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Abstract: A positive family history is present in up to 40% of FTD patients and heritability varies between clinical FTD syndromes. Several genes with autosomal dominant patterns of inheritance have been identified that cause FTD. MAPT mutations account for ~20% of familial cases and are associated with FTLD-tau at autopsy of which four main subtypes are recognised: 1) Pick's disease (PiD), 2) corticobasal degeneration (CBD), 3) progressive supranuclear palsy (PSP), 4) globular glial tauopathy (GGT). Using Wood pedigree classification criteria, we investigated the degree of heritability in pathologically proven FTLD-tau with dementia at any time in the Sydney-Cambridge cohorts and determined if heritability influenced survival. Of the total FTLD-tau cohort (n=134), average age of onset was 65±8 years and disease duration 7±4 years. PSP has a significantly older age of onset than CBD (~6 years), and PiD has a significantly longer mean disease duration than PSP and CBD (~4 years). Approximately 14% of cases have high, 7% medium and 16% low likelihood of a hereditary cause of FTD, 63% are apparently sporadic. GGT is associated with strongest heritability, 40% having high likelihood for a hereditary cause of FTD followed by CBD (21%), PiD (11%) and PSP (6%). Within the FTLD-tau cohort and within each pathological subtype, there was no difference in age of onset or disease duration in cases with stronger inheritance. These data suggests that the underlying subtype of FTLD-tau pathology influences survival but not the pattern of heritability and, similar to clinical FTD subgroups, heritability varies between pathological subtypes.

O.26 Frontoinsular von Economo neuron and fork cell vulnerability in sporadic behavioral variant FTD

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Abstract: Behavioral variant frontotemporal dementia (bvFTD) is characterized by progressive loss of social-emotional functions. Nearly half of bvFTD patients show frontotemporal lobar degeneration with TDP-43-immunoreactive inclusions (FTLD-TDP). Patients with bvFTD demonstrate early, selective degeneration of frontoinsular cortex (FI) and anterior cingulate cortex. These regions further show a selective loss of von Economo neurons (VENs) and fork cells in layer 5. The mechanisms underlying this selective vulnerability of VENs and fork cells remain unknown. To determine whether FI VENs and fork cells show greater vulnerability to TDP-43 inclusion formation in bvFTD and to investigate how VEN degeneration relates to FI neuronal loss and gliosis, we are studying 15 sporadic bvFTD patients (Broe stages 0-2, disease duration 3-10 years) with FTLD-TDP with or without comorbid motor neuron disease (MND), and 10 matched controls. Fifty micron thick sections were Nissl stained or immunostained against TDP-43 or GFAP. Digital, high magnification, z-stack images of layer 5 of the FI were acquired, and VENs, fork cells, and neighboring layer 5 neurons were counted using unbiased stereological cell counting. Preliminary counts reveal that VENs and fork cells are more prone to TDP-43 inclusion formation compared to neighboring layer 5 neurons across a range of neurodegeneration severities. This process was associated with VEN and fork cell loss and increased astrogliosis. These findings suggest early vulnerability of frontoinsular VENs and fork cells to TDP-43 aggregation. Ongoing experiments will determine whether TDP-43 aggregation or astrogliosis occurs in patients lacking quantifiable neuron loss.

O.27 Emotional empathy deficits in behavioral variant FTD

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Abstract: Loss of empathy is a hallmark feature of behavioral variant FTD (bvFTD). Impairment in emotional empathy, an evolutionarily conserved behavioral and autonomic affect-sharing mechanism that promotes emotional understanding through simulation of others' affective states, may play a role in the socioemotional deficits that characterize bvFTD. We assessed emotional empathy in 39 bvFTD, 34 Alzheimer's disease (AD), and 33 healthy control participants by measuring their behavioral (facial expression) and autonomic nervous system reactivity while they watched film clips in which a target character displayed a particular emotion. Patients with bvFTD displayed less empathic facial behavior than patients with AD during the affection, enthusiasm, disgust, and fear films ($p<.05$). Patients with bvFTD generally showed the lowest levels of facial behavior, patients with AD showed the highest levels, and healthy controls fell in between. A comparison of participants' mean physiological levels during the baseline and film-viewing periods revealed a significant main effect of diagnosis on skin conductance level and significant interactions of diagnosis X measurement period on heart rate and respiration rate during the enthusiasm film ($p<.05$). Examining these effects, patients with bvFTD were largely unresponsive to the film and had lower skin conductance levels (during both the baseline and film) and faster heart and respiration rates during the baseline period compared to the healthy controls. In bvFTD, degeneration of emotion-relevant networks may alter baseline autonomic physiology and emotional reactivity in ways that interfere with emotional empathy, thus creating difficulties with social interactions and understanding the emotions of others.

O.28 Social cognition in frontotemporal dementia

Facundo Manes

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Abstract: Social neuroscience has made important progress in elucidating the neurobiology of the social brain by introducing a novel multilevel (neural, hormonal, molecular and genetic) explanation of social cognition in neuropsychiatry. The use of different levels of scientific inquiry assessing a) behavioral social cognition sensitivity to neuropsychiatric impairment, b) neural networks engaged in social behaviors, c) the genetic underpinnings of social phenomena, and d) the influence of the social environment on biological processes, have all been investigated in the last years. The social neuroscience approach has raised new opportunities for research and translational applications in FTD. Social cognition assessment in bvFTD has allowed for the detection of early and subtle behavioral impairments, appearing even before imaging signatures of brain atrophy, or a clear decline in formal cognitive status. It has been proposed that models of social cognition associated with a degeneration of the fronto-insulo-temporal (social context network model) or fronto-insular (salience network) regions may explain the myriad of bvFTD social cognition impairments. An inter-level social neuroscience approach combining the study of social behavior, neural networks, genetic influences, and the interactions between social behaviors and social cognition would help to provide a more in-depth understanding of bvFTD, as well as of the overlaps of this disorder with the symptomatology and social cognition impairments of several neuropsychiatric conditions. Many social cognition domains (social emotions, decision making, theory of mind, empathy, moral cognition, and social norms) may be impacted differentially in various neuropsychiatric conditions, and the differences in such parameters could be built into technologies for diagnosis and measurement of treatment efficacy.

O.29 Cognitive neuroscience of language and primary progressive aphasia

Maria Luisa Gorno-Tempini

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Abstract: Different speech and language systems are involved in PPA, providing the opportunity to study the anatomy and the functional relevance of neural lesions whose distributions is not related to vascular anatomy. We will consider cognitive features and patterns of structural and functional connectivity of the neural systems involved in speech, phonology and semantic processing. We will review factors that might influence phenotypic presentations of PPA and present preliminary findings on clinico-pathological correlations in the UCSF PPA cohort.

O.30 Altered pain and temperature processing in frontotemporal lobar degeneration

Phillip Fletcher, Laura Downey, Hannah Golden, Nick Fox, Martin Rossor, Jason Warren

University College London

Abstract: Frontotemporal lobar degeneration (FTLD) is frequently associated with clinical symptoms suggesting altered pain and temperature awareness, however thermal and nociceptive processing has been little studied in these patients. We investigated this issue in a large, well characterised cohort of patients fulfilling current consensus criteria for canonical FTLD syndromes of behavioural variant frontotemporal dementia (bvFTD), semantic dementia (SD) and progressive non-fluent aphasia (PNFA) using a structured caregiver questionnaire about patients' pain and temperature awareness with neuroanatomical correlation using voxel-based morphometry. Pain and temperature symptoms were reported in 32 / 58 patients (55% of combined cohort), most frequently in bvFTD (16/21; 76%) and SD (11/18 61%) but also in PNFA (5/19 26%); such symptoms were described by all patients with C9ORF72 mutations (6/6, 100%) included in the cohort. The most common symptoms were abnormal pain and temperature perception and localisation but patients also reported ill-defined dysasthesia and showed abnormal somatising behaviours. Neuroanatomical associations of altered pain and temperature perception were identified in right anterior temporal lobe, posterior and middle insula and posterior thalamus. Our findings suggest that alterations of pain and temperature processing may be a significant clinical issue in FTLD (particularly if associated with C9orf72 mutations) and further suggest that such alterations are underpinned by damage involving a distributed, hierarchical cortico-thalamic network previously implicated in coding the sensory, affective and cognitive value of somatosensory and visceral sensory experiences. The findings speak to the emerging theme of physiological phenotypes in these diseases.

O.31 Depression in preclinical frontotemporal dementia: nature vs. nurture?

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Abstract: Depression is a common comorbidity in frontotemporal dementia. It is unclear whether the high frequency of depression in these families are due to stress experienced by all members, or whether they are related to the pathophysiology of the neurodegenerative process. We compared frequency of depression and depressive symptoms in our cohort of pre-dementia family members (N=59) at risk of developing frontotemporal dementia from GRN or C9ORF72 (C9) mutations using X2 statistics. History of depression is defined by having at least one major depressive episode on medical review. Symptoms of depression are measured by the Beck Depression Inventory. The overall frequency of depression in our cohort is 39.6%, similar to the prevalence reported in other studies. There are significantly more subjects with a documented history of depression in mutation carriers (69.2%, p=0.012) vs. non-carriers (30%). This difference is more prominent in C9 families (p=0.038) than GRN families (p=0.155). However, in longitudinal assessments, there are more GRN carriers remaining symptomatic (BDI>14) than non-carriers (75%, p=0.053), while the frequency of anti-depressant use is similar in both groups (37%, p=0.309). Odds ratio estimated by logistic regression for developing depression in mutation carriers (either GRN or C9) is 5.2 (95% C.I. 1.35-20.4). This remains constant after adjustment with age, sex, education, MMSE score, or functional rating scale. Our findings suggest that GRN and C9 mutation carriers are at an elevated risk for developing depression in the pre-dementia stage, despite all being blinded to their genetic status.

O.32 Dipeptide repeat expression with *C9orf72* mutation

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Abstract: A significant portion of patients suffering from amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) carry an expanded non-coding hexanucleotide repeat in the C9orf72 gene, a condition commonly referred to as c9FTD/ALS. We and others have demonstrated that the RNA structure of GGGGCC repeats may cause neurodegeneration via their accumulation into discrete structures in the nucleus, termed RNA foci, and by serving as a template for the synthesis of aggregation-prone dipeptide repeat “c9RAN proteins” by repeat-associated non-ATG (RAN) translation. During the session, we will explore the significance of RAN translation, specifically in terms of the toxicity that results from RAN translation in various cell models, including models generated from patient-derived fibroblasts, and in vivo systems. Our analyses of the expression of various dipeptide repeats (DPRs) in cell culture and animal model systems show that poly(GA), in particular, mediates toxicity through endoplasmic-reticulum-associated mechanisms. We will also discuss therapeutic strategies targeting the RNA structures necessary for RAN translation and foci formation for the treatment of c9FTD/ALS and the use of DPRs as a potential biomarker for c9FTD/ALS.

O.33 *C9orf72* G4C2 repeat expansions: the case for RNA toxicity

Chris Shaw, Youn-Bok Lee, Jorge Gomez, Han-Jou Chen, Joao Peres, Agnes Nishimura, Carole Shum, Prenetha Baskaran, Yoshi Adachi, Alan Stepto, Jean-Marc Gallo, Frank Hirth, Corinne Houart, Sarah Guthrie

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Abstract: The hexanucleotide (GGGGCC; G4C2) repeat expansion in intron 1 of C9ORF72 is the most common genetic cause of Frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) but the pathogenic mechanism(s) driving neurodegeneration is not yet clear. We have demonstrated that expanded G4C2 RNA form toxic intranuclear foci that bind and sequester a subset of RNA binding proteins in transfected neurons and C9ORF72 FTD/ALS brain tissues (Lee et al. 2014), however G4C2 RNA transcripts may also generate potentially toxic dipeptide proteins (GA, GP, GR, PA, and PR) due to repeated associated non-ATG (RAN) translation. The relative contribution of RNA foci and dipeptides to neurodegeneration in ALS/FTD have not yet been established. To distinguish between RNA and dipeptide toxicity, we have engineered an alternative non-G4C2, non-repeating transcript that are not predicted to form RNA foci but encode the same dipeptide proteins (GA, GP, GR, PA and PR). Data on their relative toxicty in cellular and in vivo models will be presented.

O.34 *TREM2* mutations linked to neurodegeneration impair cell surface transport and phagocytosis

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Ludwig-Maximilians University Munich; Washington University School of Medicine; Stanford University School of Medicine; Istanbul University; VIB; University of Antwerp; German Center for Neurodegenerative Diseases (DZNE); Universitat Autònoma de Barcelona; ICN Hospital Clinic i Universitari; University of Bonn; Hospital Network Antwerp (ZNA), Middelheim and Hoge Beuken; University of Tübingen; University of Gothenburg; University College London

Abstract: Genetic variants in the triggering receptor expressed on myeloid cells 2 (TREM2) have been linked to Nasu-Hakola disease, Alzheimer's disease (AD), Parkinson's disease, amyotrophic lateral sclerosis, frontotemporal dementia (FTD) and FTD-like syndrome without bone involvement. TREM2 is an innate immune receptor preferentially expressed in microglia and involved in inflammation and phagocytosis. Whether and how TREM2 missense mutations affect TREM2 function is elusive. Here we report that missense mutations associated with FTD and FTD-like syndrome reduce TREM2 maturation, abolish shedding by ADAM proteases and impair phagocytosis. As a consequence of reduced shedding TREM2 is virtually absent in the cerebrospinal fluid (CSF) and plasma of a patient with FTD-like syndrome. Lower levels of TREM2 were also observed in CSF of AD and FTD patients further supporting that reduced TREM2 function may contribute to the risk for two prominent neurodegenerative disorders.

O.35 Genome-wide association study identifies prosaposin as a novel regulator of progranulin levels in human plasma

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Abstract: Mutations in progranulin (GRN) gene leading to progranulin protein (PGRN) haploinsufficiency are a major cause of familial frontotemporal lobar degeneration (FTLD), while common variants leading to a partial loss of PGRN may increase FTLD risk. Increasing PGRN levels has therefore been proposed as a therapy for FTLD patients; yet the molecular mechanisms that underlie normal PGRN level regulation remain largely unknown. To identify novel PGRN regulators, we now performed a genome-wide association study using more than 27 million variants identified by whole-genome sequencing in 1046 non-demented individuals and plasma PGRN levels measured by ELISA as a quantitative trait. Genome-wide significant association was identified on chromosome 1p13.3 near the previously discovered sortilin gene (SORT1; top SNP rs646776 p=8.11x10-42) and on chromosome 10q22.1 near the gene encoding the lysosomal protein, prosaposin (PSAP; top SNP rs1867977 p=1.39x10-8). Follow-up studies in neuronal and non-neuronal cells showed that decreasing PSAP levels significantly increased secreted PGRN in a dose-dependent manner. Furthermore, PSAP knockdown rescued extracellular PGRN levels in human fibroblast cells derived from patients with GRN mutations. To determine whether these effects are observed in vivo, we are presently measuring Pgrn levels in Psap -/- mice and in Pgrn +/- mice injected with Psap shRNA rAAV1. Together, our data suggest PSAP as a novel regulator of PGRN levels and a novel potential FTLD therapeutic target. Our current work focuses on the mechanism by which PSAP mediates PGRN levels and addresses whether the observed increase in PGRN is protective against FTLD-related neurodegeneration in our model systems.

O.36 Progranulin haploinsufficiency causes neuronal ceroid lipofuscinosis-like clinicopathological features in humans

Michael Ward, Robert Chen, Alice Taubes, Hsin-Yi Huang, Sakura Minami, Meredith Chabrier, Shannon Leslie, Yaqiao Li, William Seeley, Bruce Miller, Ian Mackenzie, John Staropoli, Eric Huang, Sue Cotman, Ari Green, Li Gan

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Abstract: Heterozygous mutations in the GRN gene lead to progranulin (PGRN) haploinsufficiency and cause frontotemporal dementia (FTD). Complete loss of PGRN expression due to homozygous GRN mutations was recently discovered. Unexpectedly, complete PGRN loss caused symptoms and pathologic features consistent with neuronal ceroid lipofuscinosis (NCL), a group of related pediatric neurodegenerative disorders characterized by vision loss, seizures, and autofluorescent intracellular storage material deposition. Here, we provide evidence of NCL-like clinical and pathological features in humans with partial PGRN loss due to heterozygous GRN mutations. Post-mortem cortex from GRN mutation carriers exhibited increased lipofuscinosis compared to controls, as well as electron-dense intraneuronal storage material. Lymphoblasts from a heterozygous GRN-mutation carrier who carried a clinical diagnosis of NCL harbored vacuolated intracellular structures and prominent rectilinear-pattern storage material, both characteristic NCL findings. Further analysis of lymphoblasts isolated from five separate GRN mutation carriers showed similar findings, which were rescued by overexpression of PGRN. Because retinal degeneration is a prominent feature of NCL, we sought to determine if retinal abnormalities occurred in settings of PGRN deficiency. Indeed, Grn KO mice developed substantial retinal lipofuscinosis and retinal degeneration. In addition, using optical coherence tomography we discovered substantial retinal thinning in humans with GRN mutations, including those who were cognitively asymptomatic. Confocal scanning laser ophthalmoscopy revealed abnormal autoflourescent deposits in retinas of GRN mutation carriers. Our findings indicate that PGRN haploinsufficiency causes accumulation of NCL-like storage material and early retinal abnormalities in humans. Taken together, they suggest that GRN-associated FTD and the NCLs may share similar mechanisms.

O.37 iPSC models of *GRN* and *C9orf72* mutations

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Abstract: Induced pluripotent stem cell (iPSC) technology allows neurodegenerative diseases to be modeled in human neurons and glia containing pathogenic mutations in their native genetic contexts. This strategy alleviates some inherent caveats of animal models and ectopic overexpression approaches. We generated multiple iPSC lines containing two of the most common genetic mutations in FTD: progranulin (PGN) and GGGGCC repeat expansion in C9ORF72. In human neurons differentiated from patient-specific iPSCs, we recapitulated several key molecular and pathological features of FTD, such as progranulin hapoinsufficiency and RNA foci. We also revealed several disease–relevant cellular phenotypes, such as increased sensitivity to ER stress and inhibitors of specific kinase pathways and the autophagy pathway. In this presentation, our recent findings on iPSC-derived FTD neurons and microglia will also be presented.

O.38 Drosophila models of RNA metabolism

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Abstract: RNA metabolism has been recently demonstrated to play a major role in correct maintenance of neuronal activity and survival. In the eukaryotic nucleus, many proteins that are involved in regulating the correct processing, stability, and transport of RNA molecules belong to the heterogeneous Ribonucleoproteins (hnRNPs) family. Most importantly, these hnRNP proteins can form multimeric complexes, either with themselves or with different factors, and this can affect its functional properties. This may be particularly important with regards to ALS and other related diseases, where alterations in the localization and solubility of several hnRNP factors have been recently shown to represent a possible cause of disease. Accordingly, we have recently started to engineer a wide range of Drosophila models to determine which of the major hnRNP proteins (that possess clear sequence homologues in humans) can induce neurodegeneration or affect synaptic functionality. For the moment, we have already gathered evidence that the interplay between the Drosophila homologues of TDP-43 and hnRNP A/B can be critical for neurodegeneration. The purpose of our studies is to characterize the functional mechanisms responsible for these effects, in particular those that involve alteration of specific neuronal RNA processing events. The final aim of this work is to determine how hnRNP proteins can generally contribute positively or negatively to the action of well known disease-causing protein/factors (e.g.TDP-43, FUS, and GGGGCC/CUG repeat expansions).

O.39 Mouse models for *C9orf72* disease

Clotilde Lagier-Tourenne, Jie Jiang, Qiang Zhu, Michael Baughn, Shuying Sun, Christopher E. Shaw, John Ravits, Don W. Cleveland

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Abstract: Expanded GGGGCC hexanucleotide repeats in a non-coding region of the C9orf72 gene were recently identified as the most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), two neurodegenerative conditions with genetic and pathological overlap. The pathogenic mechanisms of this expansion are not understood, but initial observations point to either a loss of function of the endogenous C9orf72 gene, and/or a toxic gain of function of the expanded RNA. The latter may be mediated either by sequestration of RNA binding proteins into RNA foci or by production of aberrant polypeptide(s) through repeat-associated non-ATG-dependent (RAN) translation. Irrespective of the relative contribution to neurodegeneration of either RNA-mediated toxicity mechanism, a therapy reducing expanded RNA transcripts will target both RNA binding protein sequestration and RAN translation. We have generated mice modeling either a loss of C9orf72 function or a toxic gain of function to unravel the relative contributions of each mechanism. We established multiple lines of BAC transgenic mice expressing a repeat-containing human C9orf72 gene with different repeat lengths (between ~100 and ~450) and expression levels. Pathologic RNA foci containing both sense and antisense repeat RNAs and RAN dipeptides are identified in brains and spinal cords of these C9orf72 mouse models. A therapeutic strategy using antisense oligonucleotides (ASOs) that mediate degradation of RNAs carrying the C9orf72 hexanucleotide expansion is developed to target a gain of toxic function from expanded C9orf72 in ALS and FTD patients.

O.40 *C9orf72* FTLD/ALS associated Gly-Ala dipeptide repeat proteins cause neuronal toxicity and induces specific protein co-aggregation

Dieter Edbauer, Stephanie May, Daniel Hornburg, Martin Schludi, Thomas Arzberger, Kristin Rentzsch, Friedrich Grässer, Kohji Mori, Elisabeth Kremmer, Julia Banzhaf-Strathmann, Matthias Mann, Felix Meissner

German Center for Neurodegenerative Diseases (DZNE); Max Planck Institute of Biochemistry; Ludwig Maximilians University; Saarland University Medical School; Helmholtz Zentrum München, German Research Center for Environmental Health

Abstract: Hexanucleotide repeat expansion in C9orf72 is the most common pathogenic mutation in patients with amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). Despite the lack of an ATG-start codon, the repeat expansion is translated in all reading frames into dipeptide repeat (DPR) proteins, which form insoluble ubiquitinated aggregates that are most abundant in cortex and cerebellum. To specifically analyze DPR toxicity and aggregation, we expressed DPR proteins from synthetic genes containing a start codon but lacking extensive GGGGCC repeats. The five DPR species showed differential aggregation and toxicity. Surprisingly, poly-Gly-Arg and poly-Pro-Arg formed predominantly nuclear aggregates. Poly-Gly-Ala (GA) expression mimicked neuropathological findings in patients best, because it formed p62-postive cytoplasmic aggregates and induced apoptosis in primary neurons. Quantitative mass spectrometry analysis to identify poly-GA co-aggregating proteins revealed a significant enrichment of proteins of the ubiquitin proteasome system with p62 as the top hit. To reveal novel pathomechanisms we are currently validating the other identified proteins in cell culture and patient material. We are particularly testing, whether overexpression of sequestered proteins can rescue neurotoxicity of poly-GA, which would support a loss-of-function mechanism.

O.41 New mouse models of sporadic ALS/FTD with phospho-TDP-43 pathology in brain and spinal cord and a progressive motor phenotype

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University of Pennsylvania

Abstract: In frontotemporal dementia and amyotrophic lateral sclerosis, TDP-43 becomes phosphorylated and ubiquitinated and accumulates in insoluble cytoplasmic inclusions. However, it remains unclear how dysfunction of TDP-43 leads to late-onset neurodegenerative disease. A lack of valid mammalian models which recapitulate key features of human TDP-43 proteinopathies has hampered progress in understanding pathogenesis. Here we describe new mouse lines with inducible expression of cytoplasmically-targeted human TDP-43 in the brain and spinal cord which develop abundant cytoplasmic ubiquitinated and phosphorylated TDP-43-positive inclusions. We have characterized three mouse lines in detail, in which mice develop tremor and a consistent hindlimb clasping phenotype at approximately 2-3 weeks after induction of TDP-43 expression. This is followed by progressive decline in motor performance, as monitored by grip strength and rotarod test, and weight loss with brain and muscle atrophy and premature death at up to 18 weeks. TDP-43 pathology is detected in multiple regions, including motor cortex, hippocampus, striatum and spinal cord, as early as one week after induction of TDP-43 expression and accumulating over time. Furthermore, phosphorylated TDP-43 species are detected in the insoluble protein fraction by immunoblotting, which is accompanied by a decrease in endogenous mouse TDP-43 levels. Marked astrogliosis also develops in regions with TDP-43 pathology, and muscle neuromuscular junction denervation occurs prior to spinal cord motor neuron loss. These mice will allow temporal delineation of the molecular changes in TDP-43 proteinopathies, and will provide much-needed models for pre-clinical testing of therapeutics targeting TDP-43 dysfunction.

O.42 CSF FTLD biomarkers - old foes and new friends

William Hu

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Abstract: Most cases of frontotemporal lobar degeneration (FTLD) are associated with pathologic inclusions containing hyperphosphorylated TDP-43 or hyperphosphorylated Tau. The underlying pathology is predictable during life in cases with mutations or associated disorders (such as amyotrophic lateral sclerosis or progressive supranuclear palsy), but most clinically suspected FTLD patients do not have mutations or FTLD-plus syndromes. Cerebrospinal fluid (CSF) biomarkers for Alzheimer's disease, including beta amyloid 1-42 and total Tau (t-Tau), have been useful in identifying Alzheimer's disease (AD) mimicking FTLD. A decreased ratio of CSF phosphorylated to total Tau (p/t-Tau) has now been associated with FTLD-TDP in three cohorts, which makes the standardized measurements of Tau-related biomarkers critical beyond AD studies. Laboratory measures of CSF Tau phosphorylated at threonine 181 (p-Tau181) markedly underestimate the total levels of CSF p-tau181, challenging the notion that a reduced p/t-Tau ratio reflects Tau hypophosphorylation in FTLD-TDP. Other changes in FTLD CSF may account for the observed p/t-Tau ratio change, including detectable alterations in CSF cytokines and endosomal/lysosomal markers specific to FTLD-TDP. A combination of these changes may be useful in identifying patients for clinical trials targeting TDP or Tau, tracking pathologic progression in symptomatic FTLD patients, and identifying asymptomatic subjects with FTLD mutations at imminent risk of developing clinical symptoms.

O.43 Longitudinal Imaging of Sporadic FTLD

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Abstract: Ongoing efforts to develop treatments for FTD have generated interest in longitudinal measurements of disease burden. Brain imaging is a useful adjunct to clinical measures of change because brain structure and function can be measured with relatively high precision and reproducibility over time. Several imaging techniques are available, including structural MRI, perfusion MRI, diffusion tensor imaging, task-free functional MRI and FDG-PET, and the relative merits of each of these techniques in tracking FTD longitudinally have not been investigated. The FTLD Neuroimaging Initiative, which began in 2010, is a multicenter study which has enrolled over 110 patients with FTLD to undergo three longitudinal clinical and multimodal imaging assessments over one year. About 75% will be assessed with PET as well as MRI, and about 70% have completed the protocol with the remainder scheduled to finish in 2015. When complete, this dataset will provide the most comprehensive information on longitudinal change in FTLD to date, including three time-point data that is not currently available. Early analyses are demonstrating that cross-sectional maps of brain atrophy are highly reproducible across cohorts/medical centers, and that targeted regions of interest based on baseline regions of abnormality can isolate regions with high rates of change. Collection and analysis of the data are ongoing, and this presentation will highlight the latest findings emerging from the dataset.

O.44 Multimodal biomarker approaches in frontotemporal lobar degeneration

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Abstract: In recent years there has been considerable progress in improving our understanding of the molecular and genetic bases of frontotemporal lobar degeneration (FTLD). The vast majority of FTLD cases have either inclusions of tau (FTLD-tau) or a TDP-43 proteinopathy (FTLD-TDP). As these research discoveries translate to drug discovery of disease-modifying therapeutics it will be essential to improve the in vivo discrimination between FTLD-tau and FTLD-TDP. Robust and accurate biomarkers that are sensitive and specific to underlying FTLD pathology can increase the likelihood of detecting a therapeutic response and yield substantial cost-savings in the context of clinical trials. In this talk I will highlight a multimodal biomarker discovery approach that leverages data-driven multivariate informatics to integrate neuroimaging, genetic, and molecular sources of data. For example, MRI of grey matter and diffusion tensor imaging (DTI) of white matter together achieve increased statistical power and classification accuracy than a single neuroimaging modality. A combination of MRI and DTI also is more accurate that single modalities at identifying preclinical markers of genetic forms of FTLD. Also, multivariate integration of MRI, DTI, and single nucleotide polymorphisms (SNPs) demonstrates an association between neuroanatomical structure and genetic risk factors in sporadic FTLD. Together, I conclude that a multimodal biomarker approach that accounts for individual differences in neuroimaging, genetics, and underlying pathology will be essential for screening patients for entry into clinical trials and for translating research into a precision medicine approach for treatment of FTLD.

O.45 Identification of novel diagnostic CSF biomarkers for pathological subtypes of FTD with high discriminatory power

Charlotte Teunissen, Naura Elias, Marleen Koel-Simmelink, Sisi Durieux-Lu, Thang Pham, John van Swieten, Connie Jimenez, Yolande Pijnenburg

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Abstract: Frontotemporal dementia (FTD) is the second cause of early-onset dementia. Its underlying pathological spectrum can be divided in 2 main subtypes characterized by either tau or TDP-43 accumulations. Thus far, reliable biomarkers enabling the identification of FTD and its pathological subtypes are lacking. The aim of this study was to identify cerebrospinal fluid (CSF) biomarkers for accurate diagnosis of the two main pathological subtypes of FTD using unbiased in-depth mass-spectrometry proteomics. FTD patients with TDP-43 (FTD-TDP-43, n=12) or tau pathology (FTLD-tau, n=8), and controls with subjective memory complaints (SMC, n=10) were included. The proteome was analysed by abundant protein depletion by 1D gel-nano-liquid chromatography coupled to tandem mass spectrometry. Validation was performed in a larger cohort (21 FTLD-TDP; 10 FTLD-tau; 23 SMC) and of patients with other dementias (20 Alzheimer's disease (AD); 20 dementia with Lewy bodies (DLB), 18 vascular dementia (VaD)). Out of a total dataset of 1914 CSF proteins, we identified 57 proteins that were differentially regulated between the different patient groups: either between the two pathological subtypes (24 proteins), or between at least one of these FTD subtypes and controls (53 proteins). Validation in a larger cohort showed that level of YKL-40 in FTLD-tau was significantly higher compared to AD, DLB, and VaD patients. The CSF levels of FABP4 were significantly increased in FTLD-tau compared to controls, AD and DLB. We performed high resolution CSF proteomics and identified 57 CSF biomarkers that appear very promising for both FTD diagnosis as well as subtyping of pathologies.

O.46 Longitudinal diffusion tensor imaging in frontotemporal dementia

Colin Mahoney, Ivor Simpson, Jennifer Nicholas, Phillip Fletcher, Laura Downey, Camilla Clark, Hannah Golden, Nicole Schmitz, Jonathan Schott, Jonathan Rohrer, Hui Zhang, Sebastien Ourselin, Jason Warren, Nick Fox

University College London; London School of Hygiene and Tropical Medicine

Abstract: Novel biomarkers for monitoring progression in neurodegenerative conditions are needed. Measurement of microstructural changes in white matter (WM) using diffusion tensor imaging (DTI) may be a useful outcome measure. Here we report trajectories of WM change using serial DTI in a cohort with behavioural variant Frontotemporal Dementia (bvFTD). 23 patients with bvFTD (13 having genetic mutations), and 17 age-matched healthy participants were assessed using DTI and neuropsychological batteries at baseline and ~1.3 years later. Baseline and follow-up DTI scans were registered using a group-wise approach. Annualised rates of change for DTI metrics, neuropsychological measures and whole brain volume were calculated. DTI metric performances were compared and sample sizes for potential clinical trials calculated. In the bvFTD group as a whole, compared to controls, rates of change in fractional anisotropy (FA) and mean diffusivity (MD) within the right cingulum bundle (CB) were greatest (FA, -4.6%/year, pMAPT carriers had the greatest change within left uncinate fasciculus (FA, -8.8%/year, p=0.001; MD, 9.0%/year, pC9ORF72 carriers had the greatest change within right superior cerebellar peduncle (FA, -12.3%/year, p=0.005; MD 18.5%/year, p=0.02) and sporadic bvFTD had the greatest change within right CB (FA, -5.3%/year, p=0.001; MD, 2.7%/year, p=0.01). Sample size estimates using FA change were substantially lower than neuropsychological or whole brain measures of change. Serial DTI scans may be useful for measuring disease progression in bvFTD with particular trajectories of WM damage emerging. Sample size calculations suggest that longitudinal DTI may be a useful biomarker in future clinical trials.

O.47 Differential involvement of CSF P-tau181 / tau ratio in FTLD-TDP with amyotrophic lateral sclerosis

Yolande Pijnenburg, Nicolaas Verwey, Femke Bouwman, Annemieke Rozemuller, Hanne Meijers Heijboer, Rob Strijers, Wiesje van der Flier, Philip Scheltens, Charlotte Teunissen

VU University Medical Center

Abstract: The CSF P-tau181 / tau ratio was recently shown to be decreased in FTLD-TDP. Since rapidly progressive brain diseases are associated with higher CSF tau levels, we hypothesized that CSF P-tau181 / tau ratio's would be lower in FTD with amyotrophic lateral sclerosis (FTLD-TDP-ALS) compared to FTD without ALS (FTLD-TDP-no ALS). Moreover, we hypothesized that CSF P-tau181 / tau ratio would correlate with levels of CSF neurofilaments light chain (NFL), a marker of axonal degeneration. In this study levels of CSF, P-tau181 and NFL were measured in FTLD-TDP-ALS (N=14), FTLD-TDP-no ALS (N=13), Alzheimer's disease (AD, N=24) and controls with subjective memory complaints (SMC, N=24) using immunoassays. We used genetically or pathologically confirmed FTD cases or clinical FTD with EMG confirmed ALS. AD cases were either PIB positive or pathologically confirmed. The mean age of the total group was 62.3 years (SD 6.2) and did not differ between groups. Male/female ratio did not differ between groups. CSF P-tau181 / tau ratio was lowest in FTLD-TDP-ALS, followed by FTD-TDP-no ALS, AD and SMC respectively (p 181 / tau ratio and NFL was significant (r=-.446) CSF P-tau181 / tau ratio appears to be a general marker of TDP pathology in FTD, but the strongest decrease is present in the FTLD-TDP-ALS subgroup, which might be related to the faster progression in this subgroup.

O.48 Therapeutic approaches for FTLD due to progranulin (*GRN*) mutations: the low hanging fruit for FTLD treatment?

Adam L. Boxer

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Abstract: Mutations within the progranulin gene (GRN) located on chromosome 17 cause autosomal dominant familial frontotemporal lobar degeneration (FTLD) syndromes associated with underlying TDP-43 neuropathology. Progranulin is a protein that is expressed in the periphery as well as in neurons and glia within the CNS. Progranulin is enzymatically cleaved into granulins, and both the holoprotein and its cleavage products have potent effects as growth factors and regulators of inflammation. In addition to its role in FTLD, progranulin may influence the pathogenesis of Alzheimer's and inflammatory diseases. GRN mutations lead to haploinsufficiency of progranulin mRNA levels, and in turn, low progranulin protein levels that are measurable in the blood and CSF. The simplest approach to treating FTLD-GRN may be to elevate or restore progranulin protein levels into the normal range. A variety of cell culture and animal models have been developed to study FTLD due to GRN mutations (FTLD-GRN), and other genes and small molecule drugs have been identified that can regulate GRN gene expression or protein levels. Some of these drugs are already approved by the FDA for use in humans and there is considerable enthusiasm for conducting clinical trials in FTLD-GRN because blood and CSF progranulin levels can potentially be used as pharmacodynamic biomarkers to demonstrate that a particular therapy is exerting its intended biological effect in humans. Clinical approaches to FTLD-GRN therapeutic development will be presented, including examples of recent attempts to raise progranulin levels using FDA approved drugs as well as new potential therapies approaching human clinical trials.

O.49 Tau-directed therapies: microtubule modulation and passive immunization

Kurt R. Brunden

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Abstract: The neurodegeneration observed in tauopathies is thought to result from toxicity attributable to pathogenic tau oligomers or fibrils, and/or from a loss of tau-mediated microtubule stabilization subsequent to tau hyperphosphorylation and sequestration into insoluble aggregates. Accordingly, therapeutic strategies for tauopathies have been largely directed to approaches aimed at reducing tau inclusion formation or at compensating for tau loss-of-function. Over the past several years, our group has focused on the development of microtubule-stabilizing agents that might normalize microtubule function in tauopathies. These efforts led to the characterization of epothilone D as a lead drug candidate that has progressed to clinical testing in Alzheimer's disease patients. More recently, we have identified second generation microtubule-stabilizing agents that also hold promise for the treatment of tauopathies, and data will be presented which summarize our efforts in this area. In addition, the discovery that tau pathology may spread through the brain via the release of tau species that can seed subsequent tau inclusion formation in recipient neurons has led to the investigation by our group and others of the potential of tau passive immunization strategies to prevent the transmission of tau pathology, and ongoing work in this area will be presented.

O.50 Antisense oligonucleotide therapy for FTD

Timothy M. Miller

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Abstract: The microtubule associated protein tau is implicated in the pathogenesis of a class of neurodegenerative disorders known as Tauopathies, which includes some forms of Frontotemporal Dementia. Tauopathies directly result in intraneuronal accumulations of tau accompanied by cognitive decline. One therapy for these disorders may be to decrease total levels of the protein tau. To test the efficacy of a tau reducing therapy for disorders with tau inclusions, we identified antisense oligonucleotides (ASOs) that selectively decrease human tau expression throughout the entire mouse central nervous system in the TauP301S tauopathy mouse model. Total human tau mRNA levels are reduced by about 50% in Tau ASO treated P301S mice. We found that by reducing human tau to this level in younger P301S mice, hyperphosphorylated tau deposition was prevented. Even more striking was that by reducing human tau levels in aged P301S mice, pre-existing tau pathology was reversed as measured by AT8 and MC1. In addition, the Tau ASO treatment rescued hippocampal volume loss and CA1 hippocampal neuron loss. Recent experience with ASO in patients with amyotrophic lateral sclerosis suggests that CSF delivery of ASOs is well tolerated. Together, prior experience in humans and these tau data in animal models strongly support the use of a tau lowering therapy for those human patients who have tau positive neuronal inclusions, even after pathological tau species have already started to deposit in the brain.

O.51 The clinical stage HDAC inhibitor FRM-0334 induces progranulin in rodent brain and in FTLD-GRN patient-derived lymphoblasts

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FORUM Pharmaceutials

Abstract: Mutations in the progranulin gene (GRN) result in progranulin (PGRN) haploinsufficiency and cause a variant of autosomal dominant familial frontotemporal lobar degeneration (FTLD-GRN). Pharmacological interventions that restore PGRN protein to normal levels are therefore a potential therapeutic strategy for disease modification in FTLD-GRN. Histone deacetylase (HDAC) inhibitors have been shown to increase transcription of the normal GRN allele, resulting in raised levels of secreted PGRN in cells derived from carriers of pathogenic GRN mutations. We developed a series of novel highly brain penetrant HDAC inhibitors to epigenetically target brain function. In cultured primary rat neurons, the lead compound FRM-0334 induced a 5-fold increase in granulin mRNA. Induction of granulin mRNA and progranulin was also observed in patient lymphoblast- derived cell lines carrying different GRN mutations. In mouse brain, a single oral dose of FRM-0334 induced granulin mRNA peaking at 8 hours after dosing. FRM-0334 has successfully completed clinical phase 1 safety and tolerability testing in normal subjects. We are currently planning to evaluate the potential of FRM-0334 in additional clinical studies in carriers of GRN mutations.

O.52 Intranasal oxytocin for symptom treatment in frontotemporal dementia: a randomized, double-blind, placebo controlled dose-finding study of safety and tolerability

Elizabeth Finger, Julia MacKinley, Mervin Blair, Sarah Jesso, Lindsay Oliver, Stephen Pasternak, Maria Tartaglia, Isabel Dziobek, Katherine Rankin, Derek Mitchell, Andrew Kertesz, Adam Boxer

University of Western Ontario; University of Toronto; Freie Universität Berlin; University of California, San Francisco

Abstract: The lack of treatments for symptoms in FTD is a critical unmet need. A previous study in patients with FTD reported improvement in neuropsychiatric behaviours following a single dose of intranasal oxytocin compared to placebo. We aimed to determine the safety and tolerability of three doses of intranasal oxytocin [Syntocinon®, Novartis, Bern, Switzerland] administered to patients with FTD. We conducted a randomized, parallel group, double blind placebo controlled study using a dose escalation design to test three clinically feasible doses of intranasal oxytocin (24, 48 or 72 IU) administered twice daily for 1 week to 23 patients with behavioural variant FTD or semantic dementia (clinicaltrials.gov registration number NCT01386333). Primary outcome measures were safety and tolerability at each dose. Secondary measures explored efficacy across the combined oxytocin vs. placebo groups and examined potential dose-related effects. All participants enrolled completed the study and were compliant with the study medication. All three doses of intranasal oxytocin were safe and well tolerated. Exploration of secondary outcome measures of efficacy demonstrated improvement in caregiver reports on the apathy subscales on the Neuropsychiatric Inventory and the Frontal Behavioural Inventory, and an improvement in empathic concern based on the Interpersonal Reactivity Index. Effects appeared most robust in the highest dose group. In summary, one week of intranasal oxytocin treatment led to measurable improvements in social and neuropsychiatric features of FTD. A multicenter trial is warranted to determine the therapeutic efficacy of long term intranasal oxytocin for behavioural symptoms in FTD.

O.53 Increasing activity engagement and improving carer management skills in FTD: two case studies using the Tailored Activities Program (TAP)

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University of Sydney; University of New South Wales; Neuroscience Research Australia; Johns Hopkins University; University of Cambridge

Abstract: With research into pharmacological treatments yet to show any clear benefit in FTD, research into non-pharmacological management is crucial, especially in light of marked impairments in activities of daily living and severe behavioural changes. The Tailored Activities Program (TAP) is an occupational therapy (OT), community-based intervention prescribing personalised activities. Eight in-home visits are conducted over a 4-month period (assessment, activity prescription, and generalisation of strategies). The OT works closely with carers, educating them on dementia and skills in activity simplification, communication, and environmental modification. Study measures included: MoCA, ADL, NPI-C, caregiver confidence, and vigilance, which occurred at baseline and 4 months (post-intervention). A 51-year-old woman (Lara*, bvFTD) and a 63-year-old man (Michael*, semantic dementia) participated in TAP. After intervention, Lara dropped 8 points on the MoCA (12/30-4/30) but improved her ADL scores (5.3%). Additionally, there was improvement in carer confidence in using activities (49%), reduction of feeling 'on duty' (-9 hours), and reduction in distress about behaviours: apathy (-16), aberrant motor disturbance (-7) and eating disorders (-5). Michael's baseline MoCA was 2/30 (not reassessed). At program completion, decline in ADLs (-5%) and caregiver confidence were observed (-6%; of note, baseline score was at ceiling) and reduction of feeling 'on duty' (-30 minutes). Distress from behaviours increased for dysphoria (+4), however decreased for apathy (-4), disinhibition (-3) and eating disorders (-1). These cases reveal the potential benefit of TAP in FTD, while highlighting possible differences in outcomes for FTD subtypes. The ongoing randomized controlled trial in Australia will address these issues.

O.54 Communication bridge: using internet-based speech therapy to improve quality of life and access to care

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Northwestern University Feinberg School of Medicine; Memory Care

Abstract: Limited research suggests that speech-language therapy (SLT) may be helpful for maintaining communication abilities and independence for activities of daily living for individuals with aphasic dementias. Unfortunately, few speech-language pathologists receive formal training on differentiating treatment strategies for patients with dementia versus those with stroke-induced aphasia, resulting in limited access to appropriate intervention. The Communication Bridge study was designed to circumvent both geographic limitations and poor access to care by delivering SLT through a user-friendly, personalized, Internet-based portal. The portal provides participants with a platform for connecting to web-based SLT sessions, home exercises, and instructional videos. Participants with mild-to-moderate aphasia symptoms due to dementia receive an initial evaluation, eight web-based SLT sessions, and three evaluations at 2-, 6-, and 12-months post-treatment to determine the duration of therapy benefit. SLT focuses on providing individualized care, optimizing generalizability, and maximizing impact on quality of life. Participants also undergo neuropsychological testing and complete surveys to determine the effectiveness of SLT on functional communication ability and quality of life. Initial results from the 15 participants enrolled in the study suggest web-based SLT is feasible. Participants, caregivers and therapists report web-based SLT is as good as or better than traditional in-person therapy. Moving forward, the study will determine if quality of life improvements and functional gains are maintained over a 12-month period. If effective, results from this program may be used to modify existing insurance coverage for SLT and guide speech-language pathologists on effective SLT strategies for aphasic dementias.

P.1 Autonomic measures and explicit evaluation of emotional cues in behavioral variant and agrammatic variant of frontotemporal dementia

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Abstract: Previous studies reported significant deficits on emotion recognition over the Frontotemporal Dementia (FTD) spectrum. However, the basis of emotional impairment is still poorly understood, and previously tested only by face recognition approach. In order to assess the status of emotional skills in a group of patients with FTD, we investigated both conscious and explicit evaluation of emotions, by testing valence and arousal self-report measures, and the automatic and unconscious responsiveness to emotional cues, by autonomic measures (Skin Conductance Response, SCR; Heart Rate, HR). Sixteen behavioural variant of FTD patients (bvFTD) and 12 agrammatic variant Primary and Progresive Aphasia (avPPA) patients were tested. Their performance was compared to a group of 14 patients with mild probable Alzheimer's Disease (AD) and to 20 healthy controls (HC). Patients and HC were required to observe and evaluate affective pictures (IAPS) during autonomic parameters recording (Biofeedback recorder). Whereas a significant partially preserved competence in FTD groups in term of emotion rating and classification was observed, FTD patients showed significant changes in autonomic implicit response. BvFTD and avPPA patients showed lower values of SCR compared with control subjects and patients with AD. The present findings indicate that, within the FTD spectrum, an impairment of emotional recognition can be detected using autonomic measures. In particular, bvFTD showed a nonspecific and generic responsiveness to the emotional cues taking into account the autonomic measures.

P.2 Primary progressive aphasia: neuropsychological profiles of its three variants

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Abstract: Primary progressive aphasia (PPA) is a neurodegenerative disorder with primary language involvement. Three variants of PPA have been identified, including logopenic (lvPPA), often associated with Alzheimer's disease pathology, as well as semantic (svPPA) and agrammatic (agPPA), which are often associated with frontotemporal lobar degeneration spectrum pathology. Few studies have attempted to characterize the neurocognitive profile of these variants beyond the primary language disturbance. We hypothesized that the neuropsychological profile will differ among the variants of PPA. Ninety-one participants completed a thorough speech and language evaluation by a speech-language pathologist and also underwent neurocognitive testing. Clinical diagnoses were determined by consensus between two Speech Pathologists based on the language evaluation, resulting in 51 classified as lvPPA, 13 as svPPA, and 27 as agPPA. The neurocognitive evaluation included tests of memory (verbal and visual), processing speed, executive function, and visual-spatial skills. Differences were found on measures of learning and complex memory, speed, and aspects of executive function and working memory, primarily with the lvPPA group performing lower than the agPPA and svPPA groups. The agPPA group showed subtle deficits consistent with frontal lobe impairment, whereas neurocognitive function in the svPPA group was relatively preserved. Neurocognitive domains, beyond language, are differentially affected in PPA variants. The pattern of deficits in those with lvPPA suggests impairment of temporoparietal and frontal lobe functions. These results support the use of neurocognitive testing in clinical differential diagnosis of a presenting primary language concern.

P.3 Breakdown of phonology and symbolic representation in writing in semantic dementia: evidence from the Bengali script

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Abstract: The Bengali language, unlike English, is phonetically based. We wanted to examine reading and writing performance in Bengali in patients with semantic dementia (SD) and compare their performance with patients with Alzheimer's disease (AD) and healthy controls. Three patients with probable SD, 6 patients with probable AD and 10 healthy controls were compared on different aspects of reading and writing in Bengali and also for their naming abilities. The same list of words used for reading and writing assessment was taken from the most widely recognized Bengali language learning tool that systematically teaches a child or a new learner how to pronounce and write letters of the alphabet, followed sequentially by simple words, complex words, sentences and paragraphs. A detailed error analysis was conducted. Writing was significantly worse in SD patients compared to the AD patients or controls. Writing errors included (i) phonologically correct but orthographically incorrect errors; these included substitution of long vowels with short vowels and substitution of consonants with other phonologically similar consonants but with distinctive orthography (ii) both phonologically and orthographically incorrect errors leading to non-words (iii) symbolic representation errors of Bengali consonant clusters (iv) regularization errors. None of these errors was seen during reading or confrontational naming. Our findings suggest that SD patients tested in Bengali make distinctive, predominantly phonological errors in writing but not during reading and naming. They also exhibit difficulty with symbolic representation of consonant clusters during writing. The pattern is markedly different from that seen in AD patients.

P.4 Syntactic comprehension difficulties as a predictor of executive functions in the three variants of frontotemporal dementia

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Pontifica Universidad Javeriana; Université Lumière Lyon

Abstract: Patients with a clinical diagnosis of Fronto Temporal Dementia behavioral variant (FTDbv) have prominent early features of neuropsychiatry, cognitive and executive dysfunction. Language impairments, on the other hand, clearly define pertinent features of the linguistic primary progressive (PPA) and semantic dementia (SD). Language comprehension tasks are not yet studied, particularly in the FTDbv, as an important diagnosis variable. The aim of this study is to describe language difficulties and associate these difficulties with the executive functions in all variants:(bvFTD (n29), SD (n8) and PPA (n17). Bilingual Aphasia Test (BAT) was used in order to identify auditory discrimination, syntactic structures comprehension (auditory and by reading), sentences production, auditory and by reading, comprehension of narrative structures, sentences reading, as well as an analysis of errors according to the syntactic structure. Additionally we assess executive functions. Besides a descriptive analysis, a hierarchical clustering through a squared Euclidean distances was done, where patients groups were formed by similar clinical neighbors regardless the FTD variant. The analysis was run with 3 sets of variables a) BAT (100%), b) errors in BAT c) executive functions. The study showed statistical significance within the BAT tasks that allow a clinical differentiation between the three FTD variants: a tendency and selectivity on errors for the sentences, was found, that implies reversibility suggesting a relation with the executive functions. We also found that difficulties to understand complex sentences allow us to differentiate all variants and such result goes beyond language since it might be associated with executive functions.

P.5 Categorization impairment in bvFTD and PSP

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Abstract: Patients with frontal lobe dysfunction have difficulties in categorization tasks, such as the similarities task: they often fail to answer “they are fruits” to the question: “In what way are an orange and a banana alike?” Several cognitive dysfunctions may explain this impairment: 1. Deficits in similarity detection; 2. Access to general or conceptual representations; 3. Adherence to strong semantic associates or to mental representation of the items to be compared; 4. Inability to understand the instruction. The objectives of our study were to characterize the responses provided by frontal patients and to test the above hypotheses. We developed a similarity task based on 28 pairs of taxonomically related words.All words were controlled for semantic distance, imageability, length, and frequency. The instruction was: “what is the similarity between a ___ (eg:banana) and a ____(eg:orange). One of four different reformulations was randomly selected to help the patient if he failed. Thirty three patients with probable or definite behavior variant fronto-temporal dementia (bvFTD, n=13) or progressive supranuclear palsy (PSP, n=20), and 33 age, sex, and education-matched healthy controls were included. Patients were significantly impaired as compared to controls (expected answers: 40% in patients versus 89% in controls), and gave responses that controls did not: 30 % of patients’ responses were errors mentioning differences between the items: “one is yellow, the other is orange”, and 15% of patients’ responses were concrete similarities: e.g.: “they have a peel”. Rephrasing the instruction did not help patients. The cognitive mechanisms of such behaviors are discussed.

P.6 Humour processing in frontotemporal lobar degenerations

Camilla Clark, Jennifer Nicholas, Susie Henley, Laura Downey, Hannah Golden, Phillip Fletcher, Catherine Mummery, Jonathan Schott, Crutch Sebastian, Jason Warren

University College London; London School of Hygiene and Tropical Medicine

Abstract: Altered sense of humour is an early and characteristic symptom in frontotemporal dementia. However, humour deficits are difficult to assess and poorly understood. Here we investigated humour processing using a novel neuropsychological battery manipulating situational congruency and familiarity in nonverbal cartoon stimuli. We recruited 22 patients with behavioural variant fontotemporal dementia (bvFTD), 11 with semantic dementia (SD) and 21 healthy older individuals. Relative to healthy individuals, both the bvFTD and SD groups showed impaired humour recognition. Each syndromic group had a distinct profile of deficits: the bvFTD group had greater difficulty distinguishing jokes from control stimuli in the more complex, novel scenarios whereas the SD group had greater difficulty recognising jokes in slapstick scenarios. Voxel-based morphometry of brain MRI in the patient cohort revealed neuroanatomical associations of slapstick processing in temporal pole and superior temporal gyrus; and novel scenario processing and incongruency resolution in posterior temporoparietal cortex. Our findings suggest separable brain mechanisms for abstracting humour from novel scenarios and for accessing the 'lexicon' of culturally sanctioned humorous scenarios. These mechanisms may be differentially targeted by canonical syndromes of frontotemporal lobar degeneration. Humour is a candidate model system for probing incongruency and related social cognition processes in the frontotemporal lobar degenerations and impairments of humour processing may have diagnostic utility in these diseases.

P.7 Music as a model of rule encoding in frontotemporal dementia

Camilla Clark, Oliver McCallion, Hannah Golden, Jennifer Nicholas, Miriam Cohen, Catherine Mummery, Jonathan Schott, Jason Warren

University College London; Nottingham University; London School of Hygiene and Tropical Medicine

Abstract: Music is a cultural universal that codes rules and emotional reward, even in musically untrained listeners. Rule processing and reward assignment are processes that are often disrupted in frontotemporal dementia and relevant to the symptoms these patients exhibit in everyday life, but largely inaccessible to conventional neuropsychological instruments. Here we used music as a probe to address this issue. We assessed cognitive expectations generated whilst listening to music and the associated affective responses in a cohort of patients with behavioural variant frontotemporal dementia (bvFTD) and the semantic variant of frontotemporal dementia in relation to healthy older individuals. We created a set of short melodies in which cadence was manipulated such that the melodies sounded either 'finished' or 'unfinished'. Participants were asked to label each melody explicitly as finished or unfinished and to rate how pleasing they found the ending of the melody on a Likert scale. Patients with bvFTD performed comparably to healthy older individuals in the cognitive labelling of musical expectancies, but showed a different profile of affective responses to meeting versus violating those expectancies. Our findings suggest that music is a promising model system to probe implicit rule processing and associated affective valuation in frontotemporal dementia.

P.8 Regression-based error analysis in a longitudinal case study of slowly progressive behavioral variant frontotemporal dementia (bvFTD)

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Abstract: Clinical diagnostic criteria for behavioral variant Frontotemporal Dementia (bvFTD) have demonstrated utility in identifying bvFTD patients. However, a subset of patients with clinical features for diagnosis fail to meet the neuropsychological and brain imaging criteria, and they show little progression over time. This presentation has been called the FTD 'phenocopy' syndrome. Recent studies of hereditary cases with neuropathological characterization show that some of these patients have a slowly-progressive bvFTD (bvFTD-SP). Identification of these patients in the clinic remains challenging due to their normal performance on traditional neuropsychological measures and unremarkable brain scans. Our lab has previously demonstrated the utility of applying regression-based error analysis in identifying subclinical neuropsychological abnormalities. In this study, we apply this method, in conjunction with longitudinal neuropsychological analysis, to a case of bvFTD-SP recruited from the Johns Hopkins Young-Onset Dementias Clinic. At baseline, the subject presented with an 8-year history of behavioral decline in the setting of normal neuropsychological performance and brain imaging (MRI and PET). Regression-based error analysis highlighted subclinical executive dysfunction that progressed over subsequent evaluations. Longitudinal analysis of tests scores acquired in a 4-year period revealed marked decline (>2 SD) in verbal abstraction and memory. Decline (case study demonstrates the utility of regression-based error analysis and longitudinal methods in detecting progressive cognitive decline in cases of slowly progressive bvFTD.

P.9 Interest of the French version of Hayling test in behavioral frontotemporal dementia patients

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Abstract: Behavioral frontotemporal dementia (bv-FTD) is a common cause of young-onset dementia. However, because of insidious symptoms including subtle personality and behavior changes, this subtype of FTD remains difficult to differentiate from other dementias. In this context, it is important to know how different neuropsychological tests can help to achieve early diagnosis. A group of 15 bv-FTD patients was investigated using a French validated version of the Hayling test -which requires inhibition of prepotent responses- and a range of neuropsychological and behavioral tests, including executive and socio-emotional cognitive tasks. Our objective was to see how the Hayling test was correlated with other validated tests, and how this test could be sensitive for the early diagnosis. Our results showed significant correlations between Hayling test and executive tasks performance, but no correlation with social and emotional cognition tests, known to be early impaired in these dementias. However, Hayling test performance seemed to be impaired in some patients who were not significantly altered in executive and socio-emotional functions. We therefore concluded that the French version of Hayling test had an interest in addition to other validated test batteries because it could detect early some bv-DFT patients who were not deficient in other executive and socio-emotional tests. The evolution of the pattern of performance in this group and the comparison with other patients groups will specify the interest of this test in bv-FTD patients.

P.10 DAPHNE (Disinhibition-Apathy-Perseverations-Hyperorality-Neglect-Empathy): a new tool for screening and diagnosing behavioral variant of FTD (bvFTD)

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Abstract: We propose a quick and easy scale allowing quantification of behavior in bvFTD: DAPHNE. Six domains are explored by DAPHNE (adapted from Rascovsky's criteria): three positives (Disinhibition, Perseverations, Hyperorality) and three negatives (Apathy, personal Neglect and loss of Empathy).The scale is composed of 10 items with 5 possible answer categories. The aim of this study was to assess validity and reliability of this new tool in differentiating patients with or without bvFTD. DAPHNE was administered prospectively to caregivers of 36 bvFTD patients, 22 Alzheimer's patients, 16 patients with progressive supranuclear palsy (PSP) and those of 15 bipolar patients. The external validity was studied by comparing results to Frontal Behavioral Inventory (FBI), FTLD-Clinical dementia rating scale (FTLD-CDR) and frontotemporal behavioral rating scale (FBRS). We obtained a satisfactory reliability (α=0.83). Two scores are computed: DAPHNE-6 (Screening) computed from 6 synthetic binary domains with at least one symptom for each of the 6 domains and DAPHNE-40 (Diagnosis) computed as the sum of the 10 items. The mean scores of bvFTD patients (15.7±6.0/40) were significantly greater compared to all other groups (6.2±5.3/40- $p<0.0001$). A cut-off on DAPHNE-6 at 4/6 allowed to distinguish all groups (score<4) from bvFTD (score≥4), with a sensitivity of 92%. A cut off on DAPHNE-40 of 15/40 allowed to distinguish all groups (score<15) from bvFTD (score≥15), with a specificity of 92% and a PPV of 83%. DAPHNE is a quick and useful tool with excellent psychometric features that could be used in two ways: for screening but also for diagnosing bvFTD.

P.11 Theory of mind and linguistic pragmatic difficulties in behavioural-variant frontotemporal dementia

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Abstract: Frontotemporal Dementia (FTD) is the second most common form of dementia after Alzheimer's disease. Its behavioral variant (bvFTD) is characterized by a long phase of behavioural changes and social conduct disorders, associated with a progressive modification of personality. These disorders have been related to social cognition impairments which is comprised of many psychological processes that enable an individual to participate in social interactions. These include theory of mind (i.e., the ability to attribute and understand other people's desires and intentions as distinct from one's own) and linguistic pragmatic skills (i.e., social use of language), which may share common characteristics. Several studies have shown that deficits in theory of mind are one of the key features of patients with bvFTD. Deficits of pragmatic aspects of language have been rarely reported in these patients. This study evaluated theory of mind and linguistic pragmatic skills (conversational abilities, implicit language comprehension) in 11 patients with bvFTD and 12 controls matched by age and education level. Severe theory of mind and pragmatic language deficits were observed in the group of patient with bvFTD. There was no correlation between theory of mind abilities and pragmatic language ability in both groups. These results confirm past findings, but are not in favor toward overlap of these two types of social cognition skills.

P.12 Game theory decision making in behavioural variant frontotemporal dementia: the economics of fairness and social context

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Abstract: Impaired everyday decision making is a prominent feature of behavioural variant frontotemporal dementia (bvFTD), although it remains poorly understood, particularly in an ecological context. To explore this, we conducted an ecological game theory decision making paradigm (the Ultimatum Game) to assess how patients modulated their choice behaviour in response to 1) fairness of monetary offers, and 2) social context of monetary offers. Fourteen bvFTD and 16 age-matched controls participated. We found that acceptance rates did not differ when only levels of fairness were manipulated – both groups accepted fair offers and rejected unfair offers. However, when the social context was down- or up-regulated (i.e. offers were made from a poor or a rich virtual opponent, respectively) only controls adapted their behaviour by accepting more offers from poor opponents and rejecting more offers from rich opponents. By contrast, bvFTD patients showed no adaption to poorer opponents, but higher acceptance rates of offers for richer opponents. Our results demonstrate that patients do not have a fundamental deficit in economic decision making (expected utility) per se, as they modulate their behaviour in response to changes in fairness. Yet, they are impaired when required to integrate social contextual information in order to guide their decisions, particularly in regards to negative information. Interestingly, these findings provide the first objective explanation for the commonly noticed gullibility of bvFTD patients, as the patients fail to use social information to successfully guide everyday decisions.

P.13 White matter tract signatures of impaired social cognition in frontotemporal dementia

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Abstract: Impairments of social cognition are often leading features in frontotemporal lobar degeneration (FTLD) and likely to reflect large-scale brain network disintegration. However, the neuroanatomical basis of impaired social cognition in FTLD and the role of white matter connections have not been defined. We assessed social cognition in a cohort of patients representing two core syndromes of FTLD, behavioural variant frontotemporal dementia (bvFTD; n=29) and semantic variant primary progressive aphasia (svPPA; n=15), relative to healthy older individuals (n=37) using two components of the Awareness of Social Inference Test, canonical emotion identification and sarcasm identification. Diffusion tensor imaging (DTI) was used to derive white matter tract correlates of social cognition performance and compared with the distribution of grey matter atrophy on voxel-based morphometry. The bvFTD and svPPA groups showed comparably severe deficits for identification of canonical emotions and sarcasm, and these deficits were correlated with distributed and overlapping white matter tract alterations particularly affecting frontotemporal connections in the right cerebral hemisphere. The most robust DTI associations were identified in white matter tracts linking cognitive and evaluative processing with emotional responses: anterior thalamic radiation, fornix (emotion identification) and uncinate fasciculus (sarcasm identification). DTI associations of impaired social cognition were more consistent than corresponding grey matter associations.These findings delineate a brain network substrate for the social impairment that characterises FTLD syndromes. The findings further suggest that DTI can generate sensitive and functionally relevant indices of white matter damage in FTLD, with potential to transcend conventional syndrome boundaries.

P.14 Neural correlates of motivation in behavioral variant frontotemporal degeneration

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Abstract: Reduced motivation is common in bvFTD. bvFTD patients have decreased reactivity to positive (reward) and negative (penalty) signals, which contributes to their motivational disorder. The orbitofrontal cortex (OFC) is important for determining information regarding interpretation of reward and punishment. The anterior cingulate (ACC) is a region thought to compute the net value assigned to a stimulus. We investigated the neural basis of motivation. Participants with mild bvFTD (mean MMSE=27.3; n=18) and demographically-matched controls (NC; mean MMSE=29.40; n=15) completed a computerized task. We measured reaction time (RT) to press a target key in response to a stimulus presented on a computer screen. To assess motivation, participants were given an amount of money, and money is taken away as a "penalty" if they did not respond more rapidly to the stimulus relative to their previous performance. Participants also perform a "reward" condition where they received money for responding more rapidly. Motivation RT was related to gray matter (GM) using voxel-based morphometry. In the same group of participants, we compared GM in those with and without impaired motivation. bvFTD participants had slower latencies than NC ($t[33]=2.17$, $p=0.03$). Motivation RT was related to atrophy in the OFC (BA 11, 47) and ACC (BA 32). Compared to those who improved their performance in response to monetary incentive (motivated group), the unmotivated group had atrophy in the ACC. Poor motivation may result from a lack of responsiveness to either reward or negative feedback. Regions important for processing this information may have specific roles for motivational functions.

P.15 A social-interactive approach to strategic reasoning in behavioral variant frontotemporal dementia

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Abstract: Previous studies have associated social impairments that characterize behavioral variant frontotemporal dementia (bvFTD) with decision-making limitations but, to our knowledge, no prior work in bvFTD has empirically investigated reasoning in a social-interactive context. We hypothesized that bvFTD would have difficulties with strategic reasoning in an interactive context with relatively preserved reasoning in the absence of social interaction. 16 bvFTD patients and 16 demographically-matched healthy controls were presented with a game in which a marble can drop in an array following alternative paths. In a Control Game participants played alone and chose which door to open at 2 levels to drive the ball to the path that leads to the maximal amount of points. In an Interactive Game participants set the door at the first level and a competitor then sets the door at the second level. Here, patients must anticipate the competitor's move and develop an alternate strategy to maximize possible points. Only bvFTD performance were significantly worse in the Interactive Game compared to the Control Game [bvFTD: $p<.05$; Controls: $p>.5$). Voxel-based morphometry analysis (VBM) in a subgroup of 13 bvFTD related errors in the Interactive Game to atrophy in right inferior frontal gyrus (BA47) and right insula ($p<.01$; uncorrected). bvFTD have limited strategic reasoning when they must take into account a competitor's performance in a simple game. VBM related strategic limitations to atrophy in areas previously linked to risk-assessment. We also highlight the importance of interactive paradigms for advancing the understanding of social-executive deficits in bvFTD.

P.16 Degradation of subjective value judgments in patients with behavioral variant frontotemporal dementia

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Abstract: Orbitofrontal cortex (OFC) has been implicated in various aspects of decision-making, including the evaluation of value. The nature of value can be subjective (e.g., an individual prefers one item over another item) or objective (e.g., one item is more valuable than another item). In this study we evaluate the dissociation between subjective and objective value in behavioral variant frontotemporal degeneration (bvFTD) patients who have neurodegenerative disease in OFC. Subjective preference for junk foods, sports, vegetables, and flowers was assessed in comparison to objectively ordered stimuli such as circle diameter and line length. bvFTD patients (N=18) and demographically-comparable healthy controls (N=21) were asked to judge all possible pairs of seven stimuli from each of these six categories. For each pair, they were asked to select one of the images based on either their own preference (requiring the assignment of a subjective value to each stimulus). If participants can maintain a stable subjective value for each stimulus within a set, then a linear preference should emerge within each set. Patients with bvFTD performed more poorly than controls at consistently judging the subjective values ($U(37) = 31.5$, $Z = -4.485$, $p < .001$), however, they did not differ from controls in their ability to judge the relative magnitude of circle diameter and line length ($U(37) = 182.5$, $Z = -.396$, n.s.). We conclude that disease in OFC may selectively impair subjective value with relative preservation of objective value. Together these findings suggest that these two sources of value have distinct neuroanatomical correlates.

P.17 Dissecting naming impairments in the logopenic variant of primary progressive aphasia

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Abstract: Impaired naming is one of the cardinal deficits of the logopenic variant of primary progressive aphasia (lv-PPA), which is mostly attributed to unsuccessful lexical retrieval. In addition to this naming deficit, a proportion of patients diagnosed with lv-PPA, however, also display impairments in comprehension or single-word repetition, suggesting the involvement of other stages of word production. We recruited 21 individuals who fulfilled criteria for lv-PPA and had at least two clinical and language assessments, 1 year apart. All participants underwent a brain MRI scan at the first visit and surface-wise statistical analysis was conducted using Freesurfer, while 15 out of 17 participants that underwent amyloid imaging demonstrated high amyloid retention. Based on their performance on single word comprehension, repetition and confrontation naming, three subgroups of lv-PPA with distinctive linguistic profiles and distribution of atrophy were identified. The first sub-group (n=10) demonstrated pure anomia and left-sided atrophy in the inferior parietal lobule and superior temporal gyrus. The second subgroup (n=6), presenting with additional deficits in single-word comprehension, also exhibited thinning of the fusiform gyrus bilaterally. The third subgroup (n=5) showed additional impaired single-word repetition, and cortical thinning focused on the left superior temporal gyrus. The subgroups demonstrated distinctive trajectories of naming decline over time, suggesting a variable extension of the pathology throughout stages of word production. In line with previous reports, these results confirm the extensive damage to the language network and unravel the clinical heterogeneity of lv-PPA.

P.18 Determining personality and behavioral change in pre-clinical progranulin (*GRN*) gene carriers using the Iowa scale of personality change (ISPC)

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Abstract: The preclinical and earliest changes in behaviour and personality in those with genetic forms of frontotemporal dementia including progranulin (GRN) mutations have yet to be well characterized. To investigate such changes, we compared carriers to non-carriers of GRN mutations using the Iowa Scales of Personality Change (ISPC). The ISPC consists of 30 Items measured on a 7-point likert scale, grouped into five principle dimensions of personality. Cross-sectional, baseline analysis using Mann-Whitney U non-parametric tests was completed for 8 GRN carriers and 11 non-carriers enrolled in a multi-family study. Participants were similar in age, education and gender. There were no significant differences on the total aggregate ISPC scores between groups. A trend (p GRN carriers scored worse on six individual items including Irritability, Lack of Initiative, Perseveration, Depression, Lack of Persistence, and Overwhelmed. These six items were added to a factor analysis and, together, were able to significantly discriminate GRN carriers from non-carriers. Principle component analysis revealed that each of these six factors had the same weight/effect in the factor analysis, ranging from 0.794 to 0.842. Our results suggest that there are some personality and behavioural changes in GRN carriers in the preclinical and very early stages prior to overt cognitive change and dementia diagnosis. Further validation and replication of these findings are needed, but it is possible that a subset of ISPC items could be included in a battery for screening early behavioral changes in this population.

P.19 Differentiation between variants in frontotemporal dementia through a written sentence: a useful tool for the general clinician

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Abstract: The MiniMental State Examination (MMSE) is a common test used when the clinician needs to identify cognitive impairments, though this instrument limits and early diagnosis since it does not differentiate the most cortical dementia types: Alzheimer's disease (AD) and Frontotemporal dementia (FTD) (Wind et al., 1997). This study contemplates the qualitative analysis of MMSE phrase like a differential diagnosis tool. The analysis included the phrase longitude (number of words), writing mistakes (in the word or in the phrase) and the sentence complexity (cognitive resource). The test was filled out by 120 patients: 36 patients with FTD behavioral variant (FTDbv), 18 with primary progressive aphasia (PPA), 12 with Semantic Dementia (SD), 27 with Alzheimer's disease (AD) and 27 healthy controls. Results show qualitative differences in writing errors between FTD and AD; differences between FTD variants where selective to the type of errors in each variant: omission and substitution errors were common to PPA, complex phrases were lower in SD and automatic and perseverative phrases common in DFTbv.

P.20 The neuroanatomy of core neuropsychiatric symptoms

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Abstract: There is significant symptom overlap between early symptoms of bv-FTD and ideopathic psychiatric disorders, likely because they affect the same brain systems. In this study, we used a human brain-injury model to attempt to elucidate the neuroanatomy of core factors that underlie neuropsychiatric symptoms in TBI, neurodegeneration, and idiopathic psychiatric disorders. We performed structured psychiatric interviews to determine DSM psychiatric diagnoses on 254 Vietnam War veterans, 199 with penetrating brain injuries and 55 matched controls and collected cognitive measures, self-report measures of anxiety and depression (the BDI II and the HAM-A), and CT scans. Factors underlying DSM diagnoses were determined using a Principal Components Analysis (PCA) and the brain regions associated with these factors were determined with partial correlations corrected for age, education, global cognition, and total amount of brain lesioned. We replicated the factor structure underlying ideopathic psychiatric disorders previously reported by other groups, identifying 3 factors: Internalizing, externalizing, and psychosis. Damage to the left amygdala was associated with lower internalizing, damage to the right lateral orbitofrontal cortex with lower externalizing, and damage to the right posterior cingulate cortex with higher psychosis. The factor scores accounted for more of the anatomic variance than the DSM diagnoses or self-report measures. FTD patients with C9ORF72 expansions have greater involvement of the posterior cingulate than expansion - patients, which we found was associated with psychosis. This study suggests that neuropsychiatric symptoms in TBI, neurodegeneration, and ideopathic psychiatric disorders are associated with abnormalities in the same core brain systems controlling behavior and emotion.

P.21 A Swedish version of the Hayling Test – clinical validity in patients with a FTD complex disorder

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Abstract: Valid and reliable neuropsychological tests measuring inhibition, an executive function often impaired in patients suffering from FTD, are needed. The Hayling Sentence Completion Test mainly intends to measure verbal response inhibition. In the first section of the test (A), the subject is asked to quickly complete a sentence correctly with one word, measuring response initiation in seconds. In its second section (B), sentences are to be completed with an unconnected word, measuring efficiency (seconds) and response inhibition (errors). This study tested the psychometric properties of the Hayling Test – Swedish version by administering it to 76 healthy controls, aged 40-95 years (M = 67 ± 11.6). The internal consistency reliability varied from unacceptable (Cronbach's α = 0.37, A) to good (0.81; 0.81, B). Inter-rater reliability was excellent in 13/15 items (B). Associations with demographic data were assessed. The results of the control group was compared to those of 30 patients with a clinical diagnosis of a FTD complex disorder, aged 57-93 years (M = 69.3 ± 6. 2). There were no significant differences regarding age between the groups. The patient group performed significantly worse than the control group on all sub-scales, even though a slight overlap between the groups was noted. The largest difference between the groups was measured on the Hayling overall scaled score t(77.931) = 6.95, p = .0001, d = 1.38. The results indicate that the Swedish version of the Hayling Test can be of use as part of the neuropsychological assessment of inhibition in suspected FTD.

P.22 Primary empathy deficits in frontotemporal dementia

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Abstract: Loss of empathy is an early central symptom and diagnostic criterion of the behavioral variant frontotemporal dementia (bvFTD). Although changes in empathy are evident and strongly affect the social functioning of bvFTD patients, few studies have directly investigated this issue by means of experimental paradigms. The current study assessed thirty-seven bvFTD patients with early/mild stages of the disease and 30 healthy control participants multiple components of empathy (affective, cognitive and moral) using a task that involves the perception of intentional and accidental harm. We also explored whether the loss of empathy constitutes a primary deficit of bvFTD or whether it is explained by impairments in executive functions (EF) or other social cognition domains. Participants were also evaluated on emotion recognition, theory of mind (ToM), social norms knowledge and several EF domains. BvFTD patients presented deficits in affective, cognitive and moral components of empathy. However, empathic concern was the only aspect primarily affected in bvFTD that was neither related nor explained by deficits in EF or other social cognition domains. Deficits in the cognitive and moral aspects of empathy seem to depend on EF, emotion recognition and ToM. Our findings highlight the importance of using tasks depicting real-life social scenarios because of their greater sensitivity in the assessment of bvFTD. Moreover, our results contribute to the understanding of primary and intrinsic empathy deficits of bvFTD and have important theoretical and clinical implications (partially supported by grants CONICYT/FONDECYT Regular (1130920), PICT 2012-0412 and PICT 2012-1309, CONICET and INECO Foundation).

P.23 Is there a concreteness effect in semantic dementia patients?

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Abstract: Semantic Dementia (SD) is characterized by a progressive deterioration of conceptual knowledge. As well as in control subjects in SD there is a concreteness effect (more severe impairment in abstract words). However, some research has shown a reversal of this standard effect in SD patients. The aim of this study is to find a concreteness effect in initial SD patients. For this purpose we asked them to perform a synonym judgment task (SJT). We compared their performance with traumatic brain injury patients (TBI) and with control subjects. Five SD patients and five TBI patients were matched by age and education level to 30 healthy controls. The SJT consists of 60 pairs of words (40 nouns; 20 verbs) divided into four groups: (1) low concreteness synonyms; (2) high concreteness synonyms; (3) low concreteness non-synonyms; (4) high concreteness non-synonyms. All groups were matched by lexical frequency. A mixed variance analysis (ANOVA) was performed with concreteness considered as within-subjects factor (concrete words/abstract words) and group as between-subjects factor (DS/TBI/controls). The results showed a significant concreteness effect ($F(1,24=7.228; p<.05$) and a significant interrelation too ($F(2,24)=12.955; p<.001$). A second ANOVA showed that the groups differed only in abstract words. Bonferroni test indicates that SD patients differ from TBI patients ($p< .01$) and TBI from controls ($p< .001$). SD patients didn't differ from controls but differed significantly from TBI patients. TBI patients have the worst performance in abstract words. We conclude that at the initial stages SD patients have a concreteness effect in a synonym judgment task.

P.24 The role of cerebrovascular disease in behavioral variant frontotemporal dementia

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Abstract: Diagnosing behavioral variant frontotemporal dementia (bvFTD) in patients with prior history of stroke or with silent brain infarcts on neuroimaging studies can be challenging. Vascular changes in patients with bvFTD are not unusual and bvFTD is often ruled out in the presence of cerebrovascular disease (CVD). We defined CVD as the presence of large infarcts, lacunes or microinfarcts in neuropathological examination. We investigated whether bvFTD with CVD (V-bvFTD) has a specific clinical profile, different from bvFTD without CVD (NV-bvFTD). We compared demographic data, vascular risk factors, functional status, and neuropsychological functioning between neuropathologically confirmed cases of V-bvFTD (n=73) and NV-bvFTD (n=342) from the National Alzheimer's Coordinating Centre database.Patients with V-bvFTD were older (72.2±12.0 vs. 62.9±12.3, p<0.001), were more likely to be hypertensive (73.7 vs. 46.3%, p<0.001), and to have a history of stroke (21.1 vs. 5.9%, p=0.004) compared to those with NV-bvFTD. V-bvFTD patients had better performances in executive functioning (normalized Trail Making Test B -1.43±1.95 vs. -3.17±1.90, p=0.006), attention (normalized Digit Span Forward -0.66±1.53 vs. -1.40±1.38, p=0.031), and naming (animal list -1.50±1.51 vs. -2.52±0.94, p=0.005) than NV-bvFTD, although there were no differences in any of the items of the clinical dementia rating. An older age, a history of stroke or the presence of CVD on neuroimaging studies should not preclude the diagnosis of bvFTD. Our study shows that V-bvFTD constitutes a specific form of bvFTD affecting older patients, with a lesser clinical severity in terms of neuropsychological impairment but similar functional profile according to the clinical dementia rating.

P.25 Differential cognitive and affective theory of mind abilities in distinctive stages of behavioural variant frontotemporal dementia

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Abstract: ToM, a central capacity for appropriate social behavior, is critically impaired in patients with bvFTD even from the earlier stages of the disease, but no previous study has explored how the cognitive and affective components ToM may be differentially affected as disease progresses. The objective of the present study was to study affective and cognitive Theory of Mind (ToM) performance in patients with behavioural variant Frontotemporal Dementia (bvFTD) looking at a differential impairment in its components in relation to the stage of the disease. We assessed 40 patients with established diagnosis of bvFTD and 18 healthy controls using a complete neuropsychological battery that included cognitive and theory of mind tasks. We classified bvFTD patients as being in the mild (mi-bvFTD) or moderate stage (mo-bvFTD) of the disease according to their CDR scores. While both mild and moderate bvFTD patients showed deficits in the affective and cognitive components of ToM, mild patients outperformed the moderate group in cognitive ToM capacities while affective ToM was equally impaired in both bvFTD groups. The cognitive - but not the affective - component of ToM was related to executive functions. These results suggest that, even if both cognitive and affective ToM are impaired in the disease, the latter is markedly affected even during the initial stages, while deficits in cognitive ToM emerge with disease progression. We interpret our findings in the light of the pattern of cortical atrophy described for bvFTD and we discuss the association between ToM and executive functions.

P.26 Widespread emotion processing deficits are present in corticobasal syndrome compared to Alzheimer's disease

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Abstract: The presence of emotion processing deficits in frontotemporal dementia syndromes is increasingly well recognised. The extent that emotion processing is affected in atypical forms of frontotemporal dementia, such as corticobasal syndrome (CBS), however, has been surprisingly underexplored. The high rate of psychiatric symptoms, such as depression and apathy, together with documented changes in frontoparietal and subcortical brain regions, suggest that impairments in emotion processing may occur in CBS. Here, we systematically examined emotion recognition in 16 CBS patients, compared with 18 Alzheimer's disease (AD) patients and 22 healthy controls. Behavioural analyses revealed that the CBS group was impaired on basic, as well as complex, cognitively demanding, emotion processing tasks, with recognition of negative emotions tending to be disproportionately impaired. In contrast, the AD group showed impaired performance on complex tasks only (Ekman 60, TASIT). Neuroimaging analyses revealed divergent neural regions associated with emotion processing performance according to diagnosis. In CBS, worse emotion recognition was associated with cortical thinning in the posterior cingulate/precuneus bilaterally and the left inferior frontal gyrus, together with volume loss in the left basal ganglia. In AD, however, reduced emotion recognition was associated with cortical thinning in the right anterior cingulate, bilateral insulae, and volume loss in the hippocampus and nucleus accumbens bilaterally, as well as the right amygdala. These findings have important clinical implications for the treatment and management of CBS patients and suggest that psychiatric disturbances present in CBS may be in part due to widespread changes in emotion processing abilities.

P.27 Amygdala atrophy and emotion effects in face-responsive regions in bvFTD

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Abstract: In the healthy brain, emotional relative to neutral facial expressions enhance activity in face-responsive areas. This effect is commonly explained by modulatory influences from the amygdala. In behavioral variant FTD (bvFTD), facial emotion recognition is impaired and this has been associated with atrophy of the amygdala. By using combined structural and functional magnetic resonance imaging in 19 bvFTD and 20 matched controls, we studied the effect of emotions in face-responsive regions and its relationship with gray matter volume of the amygdala. We used voxel-based morphometry to study gray matter volume. During the event-related fMRI, we presented dynamic facial expressions (fear and chewing) as well spatiotemporally scrambled control stimuli. Gray matter volume was significantly decreased in antero-medial temporal cortex including amygdala in patients with bvFTD compared to controls. We found significant emotion effects in face-responsive occipitotemporal cortex and superior temporal sulcus in controls, but not in patients with bvFTD. Furthermore, in patients with bvFTD, we found a positive correlation between gray matter volume of the left amygdala and differential activity between fearful and chewing expressions in left fusiform face area. Our data suggest that anterior temporal atrophy in bvFTD affects emotion effects in posterior face areas.

P.28 Cognitive test scores in pathologically verified frontotemporal dementia

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Abstract: Differences in cognitive profile between frontotemporal dementia (FTD) and the most common neurodegenerative disease, Alzheimer's disesae (AD) are well known, but rarely verified with large numbers of pathologically-verified (pv) samples. This is important since there remains a high rate of misidiagnosis during life, with approximately 20% of clinically diagnosed behavioral variant FTD cases receiving pathological diagnoses of AD. The National Alzheimer's Coordinating Center (NACC) dataset allows for investigation of large numbers of pathologically verified cases. We were interested differences in cognitive test scores, particularly in tests of memory and executive functions, between groups with ultimate diagnoses of AD or FTD. It is important to understand how test scores given as part of the diagnostic process relate to the ultimate diagnosis given at autopsy. All cases with valid MMSE were included, to capture only subjects that were able to complete testing. We compared a group of 403 patients with pvFTD, with 3368 pvAD samples from the NACC dataset. Comparisons of tests from the Uniform Data Set completed at their first visit were carried out. Most tests differentiated the two groups significantly, with pvFTD getting higher scores, as would be expected given the comportmental, rather than cognitive, presentation of many bvFTD patients; Logical Memory Part I (initial recall of a story), Trailmaking Parts A and B and the MMSE failed to differentiate groups. The results of the current study are important with regard to how we interpret cognitive test scores. The relationship to clinical diagnosis and subtypes of pathological diagnosis in FTD will be discussed.

P.29 Recognition of negative facial emotions differentiates between behavioral-variant frontotemporal dementia and major depressive disorder

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Abstract: Features typical of behavioral-variant frontotemporal dementia (bvFTD), such as apathy, loss of empathy, impaired social interactions, and changes in dietary habits are also observed in major depressive disorder (MDD). Consequently, bvFTD patients are frequently misdiagnosed as suffering from MDD early in the disease process. New clinical tools are needed to address this challenge and improve diagnostic accuracy between these two diseases. Whilst emotion processing is affected in bvFTD and MDD, growing evidence indicates that the pattern of emotion processing deficits varies between the disorders. As such, emotion processing paradigms have substantial diagnostic potential to distinguish bvFTD from MDD. The current study compared 19 patients with bvFTD, 15 patients with MDD, and 31 healthy control subjects on an emotional intensity rating task. The stimuli comprised morphed faces from the Ekman and Friesen stimulus set containing faces of each gender with two different degrees of emotional intensity for each basic emotion. Analyses uncovered a strong dissociation between bvFTD and MDD patients in rating the intensity of negative emotions: bvFTD patients rated all negative emotions (anger, disgust, fear, sadness) significantly less intensively than MDD patients. Our findings confirm that bvFTD patients are impaired in recognizing negative emotions, whereas MDD patients tend to overrate negative emotions. An easily applicable emotion recognition test such as ours focussing on negative emotions can contribute to the differentiation of bvFTD and MDD patients and consequently help improve diagnostic accuracy and management of these patients.

P.30 Functional MRI of musical emotion processing in frontotemporal dementia

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Abstract: Music is a novel and relevant stimulus for probing brain mechanisms of emotion, reward and social cognition in frontotemporal lobar degeneration. Here we assessed the brain mechanisms that represent fundamental emotional properties of music using fMRI in a cohort of patients fulfilling consensus criteria for the behavioural variant of frontotemporal dementia (bvFTD; n=15) in relation to healthy older individuals (n=11). Experimental contrasts were created by manipulating the amount of variation in two dimensions of musical emotion coded in short chord sequences – consonance-dissonance and major-minor mode – and in a parallel contrast, an analogous manipulation was applied to nonverbal vocal expressions (happy – sad). In both the bvFTD and the healthy control groups, music processing was associated with extensive bilateral superior temporal lobe activation. Compared with the healthy control group, the bvFTD group showed reduced activation of left putamen for processing consonance – dissonance but enhanced activation of right superior temporal sulcus for processing musical mode; and reduced activation of left anterior superior temporal sulcus for processing vocal emotion. The findings delineate separable neuroanatomical mechanisms for coding different kinds of emotion information in musical and vocal sounds, and suggest these mechanisms may contribute to the complex derangements of emotional behaviour that define bvFTD.

P.31 Acquired personality disturbances in behavioral variant frontotemporal dementia: comparison with focal prefrontal and nonfrontal lesions

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Abstract: Systematic investigation of personality disturbances associated with bvFTD has been constrained by limitations of assessment instruments. The Iowa Scales of Personality Change (ISPC) address several of these limitations. Premorbid characteristics and acquired personality disturbances (APDs) of 10 patients with probable bvFTD by consensus criteria were compared with 102 participants with stable, chronic focal brain lesions: 31 involving the ventromedial sector of prefrontal cortex (vmPFC), and 71 with lesions outside of prefrontal cortex (so for the purposes of this study they may be considered brain-damaged controls; BDC). The premorbid personality characteristics of the groups were normal, and highly similar across groups. The base rate of APDs among BDC was typically 10% - 25% across characteristics. In contrast, bvFTD had very high rates of APDs (mean, 66.4%, up to 100%) on several scales reflective of executive dysfunction, disturbed social behavior, and hypoemotionality/apathy — but bvFTD did not show elevated rates of disturbance for other personality characteristics. The comparison group with stable vmPFC lesions also developed disturbances in most of the same characteristics as bvFTD, but at rates and severity intermediate between bvFTD and BDC. Study findings indicate that patients with bvFTD do not show widespread, nonspecific personality disturbances, but are reliably found to have very high rates of disturbances in characteristics previously shown to be associated with vmPFC damage. Personality deterioration from progressive neurodegeneration of prefrontal cortices associated with bvFTD is similar in nature but of considerably greater severity than the consequences of stable, focal prefrontal lesions.

P.32 A tensor based morphometry study of socioemotional communication features in behavioral variant frontotemoral dementia

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Abstract: Behavioral variant frontotemporal dementia (bvFTD) is a neurodegenerative disease that is characterized by a disturbance in elements of social and emotional communication. Degeneration in particular neural regions may compromise production of expressive features required for sharing social emotions and establishing interpersonal connectivity. Examples of these elements include prosody, eye contact, and appropriate variation in facial expressions. Previous literature suggests that patients with different dementias exhibit a lack of pitch modulation, mutual eye contact, and facial expressivity during social interactions. However, previous studies have mainly focused on recognition of expressive prosody in others (i.e., emotional recognition of faces). As such, the neural correlates of disrupted behavioral outputs in these patients have yet to be identified or investigated. This study used tensor-based morphometry (TBM) in conjunction with a novel clinician rating scale, called the Frontotemporal Observational Inventory, to identify brain regions of interest associated with clinical assessment of decreased or atypical expressive prosody (i.e., eye movements, facial expression, and voice variations) in patients with bvFTD and early-onset Alzheimer's disease (EOAD). Our results from the rating scale showed that patients with bvFTD had greater deficits in their output of expressive prosody in all domains compared to EOAD patients. These data were significantly correlated with lower right frontal lobe volume, in particular in the right dorsolateral prefrontal cortex (DLPFC). These results illustrate the differences in symptomatology between bvFTD and EOAD patients and advance our knowledge of the neural underpinnings of socioemotional deficits in bvFTD.

P.33 Nonverbal semantic memory in behavioral variant frontotemporal dementia and early onset alzheimer's disease: a tensor based morphometry analysis

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Abstract: Nonverbal semantic memory is associated with the anterior temporal region, a primary area of involvement in behavioral variant frontotemporal dementia (bvFTD). A cognitive measure of semantic memory, Pyramids and Palm Trees, has demonstrated value in distinguishing semantic dementia from Alzheimer's disease (AD) and may also have value in distinguishing bvFTD from AD. Thirteen patients with bvFTD and 16 matched patients with early-onset AD were characterized with neuropsychological and neuroimaging measures. Participants were administered the Pyramids and Palms Trees Test (PPT) in which participants select one stimuli from two pictures that semantically and conceptually best matches a target. Tensor based morphometry was applied to 3D T1-weighted MRI scans and Jacobian maps were computed from each individual's Jacobian brain map. Regional volumes were correlated with the PPT task, controlling for age, education, and diagnosis. Results revealed, the bvFTD group performed worse than the AD group ($p = .03$) on the PPT which correlated with reduced right frontal ($r = .46$, $p = .03$) and temporal lobe ($r = .44$, $p = .04$) volume. In conclusion, both bvFTD and AD patients exhibit semantic decline; however, the bvFTD patients exhibited poorer nonverbal semantic memory (PPT) than the AD group, which was associated with reduced right frontotemporal volume. The identification of degradation in nonverbal semantics in bvFTD warrants further exploration.

P.34 Rating patient symptoms in behavioral variant frontotemporal dementia: clinician versus caregivers

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Abstract: Behavioral variant frontotemporal dementia (bvFTD) presents with insidious changes in social and emotional communication. Clinicians may have difficulty recognizing these manifestations of bvFTD; hence, the diagnosis of bvFTD relies heavily on caregiver reports of socioemotional symptoms. It is unclear how well reporting of these symptoms differs between family caregivers and clinicians. Identifying this discrepancy may facilitate bvFTD diagnosis. The objective of the study was to examine clinician rating of bvFTD symptoms by comparing their ratings with those of family caregivers. Family caregivers and physician clinicians independently rated 13 patients with Clinically Probable bvFTD as “abnormal” or “normal” on 50 clinical symptoms based upon the patient’s current status. These symptoms comprised 12 clusters commonly observed in bvFTD (e.g., socially inappropriate behavior, diminished social interest, perseveration). Discrepancies between clinician and caregiver ratings were compared using frequency counts, discrepancy scores, and nonparametric analysis. A significant discrepancy was identified between family caregiver and clinician ratings of patients’ symptoms. Caregivers endorsed greater abnormal voice pragmatics, social restraint, focus of attention, discourse, self-conscious behaviors, mental energy/persistence, interpersonal connectivity, and emotional attachment than clinicians. Caregivers and clinicians were similar in their rating of patients’ motor and affect symptoms (i.e., gait, facial affect, eye/gaze, and gait/posture, and motor behaviors). In conclusion, while clinicians and family caregivers converge in their assessment of overt nonverbal and motor symptoms, caregivers endorse far greater socioemotional behavioral disturbances than do clinicians. In the diagnosis of bvFTD, direct clinician ratings of socioemotional symptoms cannot substitute for a detailed interview and report from caregivers.

P.35 Utility of the FTLD-NACC neuropsychology module in the differential diagnosis of behavioral variant frontotemporal dementia and Alzheimer's disease

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Abstract: The FTLD-NACC module was designed as a standard clinical evaluation to foster multicenter research in Frontotemporal Lobar Degeneration (FTLD). The present study assessed the utility of the FTLD-NACC neuropsychology module in the differential diagnosis of behavioral variant frontotemporal dementia (bvFTD) and Alzheimer's Disease/Mild Cognitive Impairment (AD/MCI). As a proxy for underlying AD pathology, we used a total-tau:amyloid-beta threshold (>0.34) previously found to be 95% accurate across two autopsy series [Irwin et al., 2012]. All patients had CSF profiles concordant with their clinical syndrome and presumed underlying pathology: 15 AD/MCI patients had a CSF profile consistent with AD and 26 bvFTD patients had CSF inconsistent with AD (presumed FTLD). The FTLD-NACC neuropsychological battery includes measures of verbal generation (F-L letter fluency), visuospatial abilities and visual memory (Benson Figure copy/recall), language (Word Reading, Sentence Reading/Repetition, Noun/Verb Naming), grammar (Northwestern Anagram Test) and semantics (Semantic Word-Picture Matching Test, Semantic Associates Test). Despite comparable MMSE scores (bvFTD MMSE=24.5, AD/MCI MMSE=22.5, $p>.05$), bvFTD patients performed significantly worse than AD/MCI patients on letter fluency (bvFTD=13.3, AD/MCI=19.0, $p<.05$), but significantly better on delayed recall of the Benson figure (bvFTD=9.0, AD/MCI=3.2, $p<.05$). A logistic regression model that included letter fluency and Benson recall correctly classified 84% of patients with bvFTD and 80% of patients with AD/MCI. ROC curves using the combined predicted probability of Benson recall and letter fluency provided excellent discrimination between groups (AUC=0.92). In conclusion, the letter fluency and visual memory components of the FTLD-NACC module are able to adequately discriminate between CSF-consistent bvFTD and AD/MCI.

P.36 Temporal discounting of future rewards in behavioral variant frontotemporal dementia and Alzheimer's disease

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Abstract: Although patients with behavioral variant frontotemporal dementia (bvFTD) are known to make impulsive social and financial choices, few systematic studies have measured impulsivity in bvFTD using objective patient-based tasks. We administered the Delay Discounting Task (DDT) to evaluate temporal discounting of future rewards in patients with mild bvFTD (n=17, MMSE=24), Mild Cognitive Impairment / Alzheimer's disease (AD/MCI) (n=22, MMSE=24) and 20 matched elderly controls. Participants were asked to make 51 hypothetical choices between small immediate and larger delayed monetary rewards (e.g., "would you prefer $18 today or $30 in 67 days?"). Temporal discount rates (k) were estimated, with larger k values indicating greater discounting of future rewards. Mann-Whitney tests revealed that bvFTD patients had higher discount rates (k median=0.257) compared to elderly controls (k median=0.009, p.05). 10 bvFTD and 10 AD/MCI patients had high-resolution structural imaging within 1-year of the DDT. A non-parametric permutation analysis (RANDOMISE) constrained to regions of reduced GM in bvFTD related high discount rates to bilateral atrophy in orbitofrontal cortex, right insula, anterior cingulate and lateral prefrontal cortex. In conclusion, bvFTD patients showed greater discounting of future rewards compared to elderly controls and AD/MCI patients. These findings are consistent with the functional neuroimaging literature relating temporal discounting to a fronto-striatal network associated with value-based decision-making. Further studies should explore whether high discount rates in the DDT relate to real-life impulsive behaviors in bvFTD.

P.37 Neuropsychiatric symptoms in primary progressive aphasia and apraxia of speech

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Abstract: A prospective analysis of the neuropsychiatric symptoms(NPS) across the three categories of primary progressive aphasia(PPA) and apraxia of speech(PPAOS), the prevalence and nature of the symptoms, and symptoms that could be helpful to better differentiate these PPA and PPAOS categories. 106 consecutive patients with a diagnosis semantic variant{svPPA}(13), logopenic variant{lvPPA}(37), agrammatic variant{agPPA}(15) or PPAOS(41), were included in this prospective study. The classification of patients was achieved after thorough neurologic, speech and language assessments. All PPA patients who were not able to be classified were not included for this study. The NPS were measured by the Neuropsychiatric Inventory Questionnaire(NPI-Q).There were 65 patients with PPA and 41 with PPAOS diagnosis. The most distinguishing features between PPA and PPAOS were anxiety, apathy, aberrant motor behavior and appetite, while among the subtypes of PPA were disinhibition and appetite changes. Patients with both PPA and PPAOS initially exhibited irritability and depression but with increase in disease duration, the PPAOS patients showed apathy(55.5%) while the PPA patients showed disinhibition(28.6%), appetite changes(28.6%) and aberrant motor behavior(14.3%). Mood symptoms like anxiety and appetite changes are more likely to be present in initial stages of PPA whereas behavioral symptoms like aberrant motor behavior and apathy are likely to occur in PPAOS. The NPS seems to evolve with the progression of the disease in both PPA and PPAOS. A better understanding of the NPS among these groups of patients helps to better outline a treatment strategy for both the patient and the caregiver.

P.38 Impulsivity and reduced sensitivity to negative consequences in behavioral variant frontotemporal dementia

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Abstract: Poor monetary decision-making is a hallmark of behavioral variant frontotemporal dementia (bvFTD), but the cognitive bases of this deficit are still poorly understood. We sought to characterize poor decision-making in FTD using formal laboratory measures. In experiment 1, patients with bvFTD (n=9), Alzheimer's disease (AD, n=12) and healthy controls (HC, n=24) performed a delay discounting task involving hypothetical choices between smaller immediate rewards ($3-90) and larger delayed rewards ($5-100 1-25 weeks later). In experiment 2, a partially overlapping group of patients with bvFTD (n=14), AD (n=15) and HC (n=22) performed a mixed gambles task to assess sensitivity to financial losses. Participants were endowed with $30 and chose whether to accept or reject 36 two-outcome gambles with win/loss ratios between 0.6 and 2.2. In experiment 1, a general linear model with age, gender, MMSE and CDR sum of boxes as covariates yielded a trend (p=0.067) for bvFTD choosing the smaller immediate reward (57% of the time) more often than AD (41%) and HC (43%). In experiment 2, the mean win/loss ratio threshold for mixed gambles in bvFTD patients was 1.10, as compared with 1.64 in AD patients and 1.58 in HC (p=.009). Follow-up analyses in a subset of subjects with executive function scores (n=27) showed that the difference between bvFTD and AD remained significant after controlling for executive functioning. Poor decision-making in bvFTD may be explained, in part, by an impulsive preference for short-term over long-term rewards, and by reduced sensitivity to negative consequences.

P.39 Differentiating the frontotemporal dementias using the Montreal Cognitive Assessment

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Abstract: The Montreal Cognitive Assessment (MoCA) is a screening tool used by many Canadian practitioners. Little information is known on how effectively the MoCA screens for Frontotemporal Dementia (FTD) subtypes. Our objectives were to 1) determine whether FTD and AD can be accurately parsed using the MoCA; 2) to determine whether AD and FTD sub-types can be parsed using the MoCA; and 3) describe longitudinal MoCA performance by FTD subtype. To do this select demographic and testing data were extracted from a database of research participants who met probable diagnosis for AD or FTD. Logistic regression was used to determine if dementia subtypes were associated with overall scores, subscores, or combinations of subscores on the MoCA. Differences between baseline and MoCA scores at 13-24 months were compared. Our results showed that FTD (n=94) performed better than AD subjects (n=98) on overall MoCA (18.1 vs 16.3; p=0.02) and several subscores. Subscores were useful in parsing between many, but not all, FTD subtypes. Subjects with FTD had significantly larger decline in performance on the MoCA within 13-24 months than AD subjects (p=0.01). This difference was significant for only for Semantic Dementia and Corticobasal Degeneration of the five subtypes included in the longitudinal comparison. The results indicate that the MoCA may be a useful tool to track progression of cognitive symptoms in FTD. Further, the data will inform future research on scoring models for the MoCA to enhance screening and detection of patients with FTD.

P.40 Frontotemporal dementia is associated with globally impaired cognitive empathy and deficient emotional empathy for negative stimuli

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Abstract: Behavioural variant frontotemporal dementia (bvFTD) is a neurodegenerative disorder primarily affecting social cognition and emotion, including loss of empathy. Many consider empathy to be a multidimensional construct, including cognitive empathy (the ability to adopt another's perspective) and emotional empathy (the capacity to share another's emotional experience). Cognitive and emotional empathy deficits have been associated with bvFTD; however, little is known regarding performance on behavioural measures of emotional empathy, and whether empathic responses differ for negative versus positive stimuli. Presently, 24 patients with bvFTD and 24 healthy controls completed the performance-based Multifaceted Empathy Test (MET), which taps cognitive and emotional empathy, and allows for the discrimination of responses to negative versus positive realistic images. MET scores were also compared with caregiver ratings of patient behaviour on the Interpersonal Reactivity Index Perspective Taking and Empathic Concern subscales. Patients with bvFTD were less accurate than controls at inferring mental states for negative and positive stimuli. They also reported lower levels of shared emotional experience, more positive emotional reactions, and diminished arousal to negative social stimuli. Patients showed reduced emotional reactions to negative non-social stimuli as well. Lastly, the MET and IRI measures of emotional empathy were found to be correlated. Our results demonstrate that the MET is a valid and objective measure of empathic performance in patients with bvFTD. They also suggest that patients show a global deficit in cognitive empathy, and deficient emotional empathy for negative, but not positive, experiences. This may be partially due to a generalized negative emotional processing impairment.

P.41 Is the emotion recognition deficit associated with frontotemporal dementia caused by inattention to diagnostic facial features?

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Abstract: Frontotemporal dementia (FTD) is a debilitating neurodegenerative disorder characterized by severely impaired social and emotional behaviour, including emotion recognition deficits. Though fear recognition impairments seen in some neurological and developmental disorders featuring amygdala dysfunction can be ameliorated by reallocating attention to diagnostic facial features, the possibility that similar benefits can be conferred to patients with FTD remains unexplored. Presently, 24 patients with FTD and 24 healthy controls completed a task which examined the impact of presenting distinct regions of the face (whole face, eyes-only, and eyes-removed) on the ability to recognize angry, fearful, disgusted, and happy expressions. A recognition deficit was demonstrated across emotions by patients with FTD relative to controls. Crucially, emotion recognition accuracy did not disproportionately improve as a result of isolating diagnostic facial features in patients with FTD relative to controls; furthermore, the removal of critical facial features resulted in a relative decline in performance for both groups. Negative facial expressions were also mislabelled as happy by patients with FTD more often than controls, providing further evidence for abnormalities in the representation of positive affect in FTD. Thus, unlike particular neurological and developmental disorders, the emotion recognition deficit observed in FTD is not likely driven by selective inattention to critical facial features. This work suggests that the emotional expression recognition deficit associated with FTD is unlikely to be rectified by adjusting selective attention to diagnostic features, as has proven useful in patients with amygdala lesions and youth with high psychopathic traits.

P.42 The relationship between abstract attitude and stereotyped behavior in patients with frontotemporal lobar degeneration

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Abstract: ~Stereotyped behavior is one of the defining characteristics of frontotemporal lobar degeneration (FTLD), manifesting in both behavioral variant of frontotemporal dementia (bvFTD) and semantic dementia (SD) subtypes. Abstract attitude “also called categorical attitude” is a concept to denote the ability to use conceptual categories in order to classify things according to their attributes and to think symbolically rather than concretely. Abstract attitude has been considered as one of the important background mechanisms under the semantic memory system. However, we hypothesize that the concept might be the mental process whose impairment leads to behavioral change seen in FTLD as well as the semantic disturbance. Originally designed tasks to assess abstract attitude were given to 13 FTLD patients (six bvFTD and seven SD patients) and a comparison group of Alzheimer’s disease (AD) patients (n=13). In addition, neuropsychiatric symptoms and the magnitude of stereotyped behavior were assessed by the Neuropsychiatric Inventory (NPI) and the Stereotypy Rating Inventory (SRI), respectively. Patients with FTLD had more severe impairment of abstract attitude compared with those with AD. We found a significant correlation between the performance of abstract attitude assessing tasks and the SRI score (r=0.59, p=0.032) in the FTLD group. On the other hand, there was no significant correlation between the performance of abstract attitude assessing tasks and the NPI score (r=0.03, p=0.92). These results suggest that patients with FTLD have obvious damage of abstract attitude, and damage of abstract attitude may play a key role in the development of stereotyped behavior in FTLD.

P.43 Heart rate responses to social stimuli in frontotemporal dementia compared to Alzheimer's disease and healthy controls

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Abstract: Patients with behavioral variant frontotemporal dementia (bvFTD) have prominent alterations in social behavior that may be evident as psychophysiological changes. We examined heart rate (HR) changes, which are sensitive to the social versus non-social nature of stimuli, as well as their degree of unpleasantness. We hypothesized that patients with bvFTD would fail to exhibit HR responses to social stimuli compared to patients with Alzheimer's disease (AD) and healthy controls (HCs). Among10 bvFTD patients, 15 AD patients, and 18 HCs, HR was measured while participants viewed pleasant-social, pleasant non-social, unpleasant social and unpleasant non-social pictures from the International Affective Picture System (IAPS) that were presented for six seconds. HR changes were calculated for each category with arousal reflected in HR acceleration and an orienting response in HR deceleration. Piecewise linear random-effects regression model with a series of linear segments and corresponding breakpoints was used to characterize the non-linear trajectory of HR change.During the first two second interval, both HCs and AD patients, but not the bvFTD patients, showed HR changes to pleasant social stimuli; acceleration or arousal in HCs and deceleration or orienting in AD patients. Moreover, both HCs and AD patients, but not the bvFTD patients, showed significant HR deceleration, or orienting, to unpleasant pictures. Together, these findings in bvFTD suggest a quantitative decrease in basic autonomic reactivity to all stimuli. Future work is needed to further characterize the psychophysiological manifestations of altered social behavior in bvFTD.

P.44 Behavioral and autonomic reactivity to moral dilemmas in frontotemporal dementia

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Abstract: Aberrations in moral behavior are characteristic of behavioral variant frontotemporal dementia (bvFTD). Prior research in this disorder has shown a disproportionate impairment in moral behavior that depends on an emotional or empathic responsiveness to others. This study investigated the behavioral and autonomic nervous system correlates of moral decision-making and judgment among patients with bvFTD. We presented two moral dilemmas (one "personal" or emotional and empathic; one “impersonal” or dispassionate and rational) to 8 patients with bvFTD, 11 with Alzheimer’s disease (AD) and 10 healthy controls (HC) and obtained measures of their behavioral responses and skin conductance responses (SCR). Consistent with prior studies, the bvFTD respondents had impaired moral judgment on the “personal” dilemma, compared to AD patients and HC. Verbal self reports indicated that bvFTD participants had decreased or absent discomfort with their decisions, whereas AD patients and HC expressed clear distress and guilt. Furthermore, the response times for bvFTD patients were shorter than for AD patients and HC, suggesting less hesitation and discomfort during deliberation. In sharp contrast with these behavioral responses, SCR revealed increased reactivity of the sympathetic system among the bvFTD participants when viewing the “personal” dilemma, compared to AD patients and HC. This discordance between blunted behavioral responsiveness and unexpected autonomic hyperreactivity offers insights into the basis of altered moral behavior in bvFTD. We hypothesize that bvFTD affects the integration of psychophysiological reactivity to emotions with the appreciation and expression of emotion, a process necessary for forms of moral behavior that depend on emotion and empathy.

P.45 Assessment of semantic memory with the SMT-42

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Abstract: In a memory clinic there is still no short easy way to assess semantic memory (SM). The aim of this prospective study was to validate a scale called - Semantic Memory Test 42 -(SMT-42) comprising 42 items (7 categories with 6 questions in each category): for example « does this animal (duck, wolf, whale .etc..) have 0, 2 or 4 legs? ». 21 high and 21 low frequency items were chosen in a random manner .SMT-42 was administered to 109 healthy controls with the Pyramid and Palm Trees Test (PPTT), oral naming 80 and the Stroop test. Conceptual validity was analyzed in the whole sample with sex, age, level of education, lexical frequency and category, length of completion and PPTT score. The variability of results depended on the frequency of items (high and low $p < .001$), categories (manufactures /naturals $p < .001$), level of education (≥ 12 years, 40/42 versus 36/42 < 12 years, $p < .01$). To assess its sensitivity, the SMT-42 was administered to 15 semantic variant of progressive primary aphasia (Vs-PPA) compared with 15 matched controls. Compared to controls the median SMT- 42 score in the Vs-PPA was lower (31 versus 41, $p < .001$) and the length of completion longer (241 s versus 111 s, $p < .001$).The SMT-42 could be a useful tool, able to detect SM impairment in less than 5 minutes in a memory clinic. The study is on going in the Alzheimer's disease and the other PPA groups.

P.46 Impaired recognition of static and dynamic emotional body expressions in early bvFTD

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Abstract: Progressive deterioration of social cognition and emotion processing are core symptoms of the behavioral variant of frontotemporal dementia (bvFTD). These deficits have been documented primarily through assessment of facial expression recognition. Here we investigate if bvFTD is also associated with impaired recognition of static (Experiment 1) and dynamic (Experiment 2) emotional body expressions. In addition, we compared body expression processing with static (Experiment 3) and dynamic (Experiment 4) facial expression processing, as well as to face identity processing (Experiment 5). The task was always a two-alternative forced-choice simultaneous match-to-sample format, in order to minimize the influence of language processes. The results reveal that bvFTD is associated with impaired recognition of static and dynamic emotional body expressions and that this is not associated with general cognitive decline nor executive task demands. No differential impairments were observed regarding motion (static vs. dynamic) or category (body vs. face). These findings indicate that deficits in recognition of emotions conveyed by visual cues in bvFTD are not specific for faces but equally apply to at least one other object category, i.e. bodies.

P.47 Divergent neural correlates for false recognition in behavioural variant frontotemporal dementia and Alzheimer's disease

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Abstract: While memory impairment is a predominant symptom of Alzheimer's disease (AD), patients with behavioural variant frontotemporal dementia (bvFTD) can also show memory deficits. Although both patient groups perform poorly on measures of free recall, their performance on forced-choice recognition tests is more variable. One reason might be the variability of false-positive recognition and whether these errors are due to medial temporal dependent memory impairment, or prefrontal cortex dependent over-endorsement of items regardless of memory. The current study analysed recognition performance on the Rey Auditory Verbal Learning Test (RAVLT) in 39 bvFTD, 77 AD and 61 control participants from two centres (India, Australia). While both AD and bvFTD patients were impaired on delayed recall, bvFTD patients showed intact recognition performance when considering the number of correct hits. However, both patient groups endorsed a large number of false-positives, and performed equally poorly when a difference score (correct hits - false-positives) accounted for these errors. More importantly, voxel-based morphometry analyses revealed divergent regions of atrophy associated with false-positive errors, with ventromedial prefrontal areas implicated in bvFTD, and parahippocampal, posterior cingulate and thalamic regions implicated in AD. These findings suggest that false-positive errors relate to prefrontally-mediated strategic retrieval deficits in bvFTD, in contrast to episodic memory impairment in AD. This supports the notion that poor performance on memory tests is driven by different neural mechanisms in bvFTD and AD. This further highlights the need to develop better memory tests that distinguish between memory impairments in bvFTD and AD, thereby improving diagnosis and disease management.

P.48 Degradation of multiple frontal systems controlling response speed in frontotemporal dementia

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Abstract: Debate persists over whether executive function comprises a collection of related, but fundamentally dissociated cognitive processes (Norman and Shallice, 1986; Stuss and Alexander, 2007), or a unitary entity/resource related to general intelligence (Roca et al., 2010; 2013). To address this question, 51 affected FTLD patients (27 bvFTD, 15 SD, 9 PNFA) and 36 healthy controls completed multiple reaction time-based tasks. The Complex reaction time test (Stuss et al., 2005) required a button press to letter A but not B-D. Controls responded more quickly with longer inter-trial intervals (6-7s vs 3-4s), as did bvFTD patients. The Switch task (Aron et al., Brain, 2004) required a 'left' or 'right' button press following word ("LEFT"), arrow () combined stimuli. A cue (e.g. [respond to] "WORD") preceded stimuli by 200ms (short warning) or 1500ms (long warning). bvFTD patients were less able to make use of preparation time (associated with bilateral orbitofrontal atrophy), react quickly to compatible stimuli (R middle frontal gyrus), inhibit incompatible information (right ventromedial frontal) or switch response mode (right superior medial frontal). Externally- and self-paced finger tapping, requiring 50 regular, suprasecond taps, elicited greater variance in bvFTD (associated with fronto-cerebellar-brainstem structural changes). All behavioural and neuroimaging results survived correction for WASI Matrix Reasoning score as an estimate of 'g'. These results provide evidence for multiple frontal systems controlling response speed, and indicate impairments of general intelligence cannot account for the patterns of executive dysfunction observed in FTD.

P.49 Decoding emotion from abstract art in behavioural variant frontotemporal dementia

Miriam Cohen, Camilla Clark, Crutch Sebastian, Jason Warren

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Abstract: Impaired processing of emotions is a well recognised feature of frontotemporal lobar degeneration, particularly the behavioural variant of frontotemporal dementia (bvFTD). However, deficits have been described chiefly for canonical emotions conveyed via biological and social channels such as facial and vocal expressions, and more recently, music. It is not clear whether analogous problems extend to other, more abstract kinds of emotion coding, such as emotions embodied in non-representational art – an issue of clinical relevance, in light of recent reports of enhanced artistic interest and creativity in some patients with bvFTD. To address this issue, we designed a novel neuropsychological test requiring two-alternative-forced-choice matching of emotional valence between non-representational paintings controlled for perceptual and stylistic characteristics; the test was administered to a cohort of patients fulfilling consensus criteria for bvFTD and to healthy older individuals. Overall, the patient and control groups performed comparably and individual patients with bvFTD scored highly on the test. The findings suggest a possible basis for differentiating mechanisms of abstract and social emotion decoding in bvFTD and may help to explain the sometimes paradoxically preserved artistic abilities of these patients.

P.50 The neural signature of autobiographical memory disruption in frontotemporal dementia

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Abstract: Autobiographical memory (ABM) refers to the recollection of personally relevant events from the past and relies upon the integrity of a distributed brain network. Compromised ABM retrieval has been reported in frontotemporal dementia (FTD); however, the neuroanatomical signature of these ABM deficits remains unclear. This study aimed to establish the neural correlates of ABM disruption in FTD. Recent and remote ABM was assessed using the Autobiographical Interview in 11 behavioural-variant FTD (bvFTD), and 10 semantic dementia (SD) patients, and compared to 15 Alzheimer's disease (AD) and 14 healthy Control participants. Consistent with previous studies, global ABM impairments were observed in bvFTD and AD, which correlated with verbal fluency performance in both groups. In contrast, SD patients displayed relatively preserved recent memory, but striking alterations in remote memory. Notably, these remote memory deficits correlated exclusively with semantic processing. Voxel-based morphometry analyses revealed distinct neural correlates for ABM retrieval in each patient group. Irrespective of time period, ABM retrieval was associated with integrity of left temporal, orbitofrontal, and frontopolar regions in bvFTD, and bilateral frontopolar, medial temporal, and occipital regions in AD. Remote memory deficits in SD related predominantly to atrophy in left temporal regions known to support semantic processing. Our results reveal prominent ABM dysfunction in FTD syndromes, attributable to degeneration of dissociable regions in the brain. These findings advance our understanding of the neural bases of ABM and highlight a central role for semantic memory in remembering personal events from the past.

P.51 Social cognitive dysfunction in semantic dementia - behavioural and neural correlates

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Abstract: Semantic dementia (SD) is traditionally conceptualized as a language disorder, however, recent reports point to marked alterations in social cognition in this syndrome. The precise neurocognitive mechanisms driving social dysfunction in SD remain unclear. Here, we sought to clarify the extent to which three processes essential for social functioning are disrupted in SD. Patients with predominantly left-lateralized SD (n=11), behavioural-variant frontotemporal dementia (bvFTD, n=10) and healthy older Controls (n=14) completed a Theory of Mind task requiring mental state attribution and a structural MRI. Informants of participants completed the Perspective Taking and Empathic Concern subscales of the Interpersonal Reactivity Index. Prominent deficits were evident in all patient groups for Theory of Mind, Perspective Taking, and Empathic Concern. Notably, the magnitude of social cognitive impairment in SD was comparable to that observed in bvFTD. Controlling for semantic processing ameliorated Perspective Taking and Empathic Concern deficits in SD. Theory of Mind impairments, however, remained present. Voxel-based morphometry analyses revealed that Theory of Mind impairments in SD were associated principally with atrophy in right anterior temporal regions (temporal fusiform cortex, inferior temporal gyrus), as well as bilateral amygdalae and temporal poles. Our results confirm the presence of marked disruption across multiple domains of social cognition in SD, with Theory of Mind deficits not exclusively attributable to a primary semantic impairment. These findings highlight the importance of right temporal regions in supporting social cognition and indicate that the emergence of social dysfunction in SD reflects the encroachment of pathology into the right anterior temporal lobe.

P.52 Abbreviated Pyramids and Palm Trees Test effectively discriminates semantic-variant progressive aphasia from other variants of primary progressive aphasia

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Abstract: Primary progressive aphasia (PPA) is a pathologically heterogeneous neurodegenerative disease that affects language. PPA is classified into three variants: semantic (svPPA), logopenic (lvPPA), and nonfluent/agrammatic (naPPA), which are diagnosed on the basis of converging clinical, imaging, and genetic/neuropathological evidence. Although clearer diagnostic criteria for PPA variants have been defined (Gorno-Tempini et al., 2011), objective clinical tests are needed to better distinguish language deficits between variants so more reliable diagnoses can be made. We used a modified nonverbal semantic task, Pyramids and Palm Trees (PPT) (Howard & Patterson, 1992), to examine semantic memory of concrete object concepts between groups of each variant. The task is administered across two modalities, pictures and words, and includes 14 cross-culturally validated items. Pathology-confirmed PPA patients, svPPA (n=22), lvPPA (n=20), and naPPA (n=8), completed the task. Because some participants completed all 14-items across trials that included a combination of both modalities, or only one modality, the scores used for the analysis were prioritized: (1) pictures, (2) words, or (3) mixed - a combination of picture and word items. A Kruskal-Wallis analysis across all groups was significant ($X2=11.57$; $p<0.003$). svPPA patients were significantly impaired in the abbreviated 14-item PPT compared to lvPPA ($U=107$; $p=0.003$) and naPPA ($U=34.5$; $p=0.01$) patients, while lvPPA patients do not differ from naPPA ($U=75$; $p=0.77$). Thus, svPPA patients had significant semantic memory impairments compared to lvPPA and naPPA patients. The abbreviated 14-item PPT task provides an efficient and objective clinical test to discriminate svPPA patients from other PPA variants.

P.53 Longitudinal naming decline in primary progressive aphasia

Kathy Ran, Murray Grossman, Corey McMillan

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Abstract: Primary progressive aphasia (PPA) is a neurodegenerative condition that causes progressive language deficits. We examined the longitudinal decline of confrontation naming in three recognized variants of PPA: semantic variant primary progressive aphasia (svPPA, n=25), nonfluent agrammatic primary progressive aphasia (naPPA, n=19), and logopenic variant primary progressive aphasia (lvPPA, n=31). We administered an abbreviated (n=30) version of the Boston Naming Test (BNT), which consists of black-and-white line drawings that are presented to a subject individually to name. We assessed progressive disease effects on high, middle, and low frequency words. We evaluated the scores at an initial visit and about one year later. After covarying for duration between assessments and MMSE at the time of assessment, we found a significant group by time by frequency effect (p=0.004). Subsequent analyses showed that all patients were worse than controls at both sessions. Naming in each patient group generally declined over time, although this varied depending on word frequency: svPPA patients were at floor on low-frequency words at both assessments (7% correct), lvPPA also did not decline in naming low-frequency words, although they were not at floor (34% correct), and naPPA patients did not decline in naming high-frequency words (73% correct). These findings indicate unique longitudinal profiles of confrontation naming in PPA.

P.54 Verbal inhibition in frontotemporal dementia: executive deficit versus language impairments

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Abstract: First stages in frontotemporal dementia (FTD) are predominantly characterized by changes in behavior and loss of selective cognitive abilities where executive functions and language are present. This study aims to evaluate the ability to restrain an automatic word through a task named The Hailing Sentence Completion Test. This test assesses automatic verbal inhibition and consists of two sets of 15 sentences each having the last word missing. Subjects must complete, as fast as possible, the phrase (first set) and in the second set with a non-sense word. The test was filed out by 38 Colombian patients: 11 with primary progressive aphasia (PPA) and 27 with behavioral variant (FTDbv). All subjects had more than 5 years of education and ages were between 61 and 78 years old. Results show low punctuation in all subjects, without statistically significant difference between PPA and FTDbv. Nonetheless, there were a notable qualitative differences when the type of answers where analyzed. Patient's (APP and FTDbv) errors were similar, though subjects with PPA showed a high number of responses without semantic and morphological relationship. We found a response pattern for some Hayling Test items than can provide clinic information for early diagnosis. In conclusion, the type of Hayling responses can differentiate between FTD variants (PPA and FTDbv): the linguistic impairment facilitates, when responding, a non-sense word in the APP group, whereas the FTDbv patients error depends on the executive function since no responding or given a near by semantic error is more common.

P.55 Memory and emotion processing performance can improve classification between nonfluent PPA syndromes

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Abstract: The nonfluent variants of primary progressive aphasia (PPA), nonfluent PPA (nf-PPA) and logopenic variant PPA (lv-PPA), are difficult to distinguish for non-language experts. They share similar language features despite their different underlying pathology. The objective of this study was to investigate non-language cognition and emotion processing in order to improve diagnostic accuracy of nf-PPA and lv-PPA. We recruited 38 dementia patients meeting diagnostic criteria for PPA (nf-PPA = 20, lv-PPA = 18), with in vivo confirmation of pathology using PiB-PET, a putative biomarker of Alzheimer's disease, and 21 matched healthy Controls. All participants underwent a comprehensive assessment of cognition and emotion processing, as well as a high-resolution structural MRI. Task performances were compared between the groups and those found to differ significantly were entered into a logistic regression analysis. Analyses revealed a double dissociation between nf-PPA and lv-PPA. Patients with nf-PPA exhibited significant emotion processing disturbance compared to lv-PPA patients and Controls. In contrast, only the lv-PPA group was significantly impaired on tasks of episodic memory. Logistic regression analyses showed that 87% of patients were correctly classified using emotion processing and episodic memory composite scores, together with a measure of visuospatial ability. In summary, investigations of the non-language presenting features in patients diagnosed with nonfluent PPA can help differentiate between nf-PPA and lv-PPA syndromes, with a double dissociation observed on tasks of episodic memory and emotion processing. These findings have important clinical implications, with identification of patients who may potentially benefit existing therapeutic interventions currently available for Alzheimer's disease.

P.56 Comparing longitudinal neuropsychological profiles in behavioural-variant FTD and Alzheimer's disease

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Abstract: Current consensus diagnostic criteria indicate that executive dysfunction with relatively sparing of episodic memory defines the neuropsychological profile of the behavioural variant of frontotemporal dementia (bv-FTD). Nevertheless, the clinical differentiation of bv-FTD from Alzheimer's disease (AD) remains difficult since executive dysfunction is common in AD, and bv-FTD can present with marked episodic memory deficits early on. This contention, however, is based on cross-sectional studies, and little is known about the stability and progression of these cognitive deficits over time. Using mixed-model regressions, we investigated the trajectory of performances on general cognition, memory, executive tasks and functional scales over a mean follow-up of 2 years in 22 probable bv-FTD and 31 typical AD patients. Analyses demonstrated that bv-FTD experienced a more rapid functional deterioration and, despite equivalent baseline performance, a steeper decline in global cognition than AD. At baseline, both groups were significantly impaired on executive function and memory tasks compared to controls, but these deficits were more marked in the bv-FTD group. Bv-FTD showed significantly larger annualised decline than AD on the ACE-R memory domain (-2.9 vs -1.3 z score change) and digit span forwards (-0.4 vs -0.1 z score score change). Despite the different magnitude of impairments, these finding suggest that neither the initial neuropsychological assessment nor projected performances can reliably distinguish the totality of bv-FTD and AD individuals. In turn, tasks that measure social cognition and emotional processing appear to be useful complements to assist with the differential diagnosis between these two dementia syndromes.

P.57 Social cognition in FTD-3 - a pilot study

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Abstract: Dementia due to a truncating mutation in the CHMP2B gene has been described in a large Danish family (Skibinski et al., 2005). Studies on the clinical presentation suggest that changes in behaviour and personality are among the earliest and most prominent symptoms (Gydesen et al., 2002). CHMP2B related dementia has therefore been classified as a subtype of frontotemporal dementia (FTD-3). Recent studies suggest that the changes in personality and social conduct seen in FTD patients are caused by impairment in social cognitive functions, for instance in the ability to identify emotional expressions. We administered a short version of the Emotion Hexagon Test (Calder et al., 1996) to five early symptomatic CHMP2B mutation carriers. The test involves judging expressions based on computer morphed images of a model from the Ekman and Friesen series. For each picture, the subject is asked to choose which of six basic emotions (happiness, surprise, fear, sadness, anger, or disgust) that best matches the expression depicted. A maximum of 24 points can be obtained. Two of the five mutation carriers gave arbitrary answers (in both this and other tests). Their scores were considered invalid. The other three subjects, who all had profound cognitive impairment on neuropsychological tests, obtained 14, 15 and 17 points. These scores are within the expected values based on a sample of 30 healthy elderly Danes (Mean:16,4. SD:2,9). Our preliminary data thus suggest, that impairment in social cognition might not be a core feature in FTD-3.

P.58 Clock hand placement: frontotemporal dementia versus Alzheimer's disease

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Abstract: The clock drawing test (CDT) is widely used in clinical practice to diagnose and distinguish patients with dementia. It remains unclear, however, whether the CDT can distinguish among the early-onset dementias. Accordingly, we examined the ability of both quantitative and qualitative CDT analysis to distinguish behavioral variant frontotemporal dementia (bvFTD) and early-onset Alzheimer's disease (eAD), the two most common neurodegenerative dementias with onset < 65 years of age. We hypothesized that executive aspects of the CDT would discriminate between these two disorders. The study compared 15 bvFTD and 16 eAD patients on the CDT using two different scales and correlated the findings with neuropsychological testing and magnetic resonance imaging (MRI). The total CDT scores did not discriminate bvFTD and eAD; however, specific analysis of executive hand placement items successfully distinguished the groups, with eAD exhibiting greater errors than bvFTD. The performance on those executive hand placement items correlated with measures of naming as well as visuospatial and executive function. On tensor-based morphometry of the MR images, executive hand placement correlated with right frontal volume. These findings suggest that lower performance on executive hand placement items occurs with involvement of the right dorsolateral frontal-parietal network for executive control in eAD, a network disproportionately affected in AD of early onset. Rather than the total performance on the clock task, the analysis of specific errors, such as executive hand placement, may be useful for early differentiation of eAD, bvFTD, and other conditions.

P.59 CERAD neuropsychological battery in patients with frontotemporal lobar degeneration

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Abstract: The objective of the study was to evaluate the use of the Consortium to Establish a Registry for Alzheimer's Disease – Neuropsychological Battery (CERAD-NB) among the patients with frontotemporal lobar degeneration (FTLD). The study consisted of 95 patients with FTLD and 91 age and gender matched Alzheimer's disease (AD) patients diagnosed in the memory outpatient clinic of Kuopio University and Oulu University Hospitals. The mean age at the onset of the symptoms of FTLD patients was 65 years and the mean age at the time of examination was 67 years. The CERAD-NB scores were under the cut-off values in two or more subtests in most of the FTLD patients even at the early stage of the disease (Mini-Mental State Examination score ≥ 24 points). Using cut-off scores based on normative data impairments were most frequently detected in the performance of verbal fluency, clock drawing and wordlist learning, whereas the best scores were in the constructional praxis recall and wordlist recognition subtests. The patient with AD had considerable difficulties in the subtests of delayed recall. The profile of weak performance in the verbal fluency and relatively high scores in the delayed recall subtests in patients with FTLD may help to distinguish FTLD from AD.

P.60 Impairment in sentence comprehension in patients with the behavioral variant of frontotemporal degeneration (bvFTD)

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Abstract: Deficits in sentence comprehension have been observed in non-aphasic patients diagnosed with the behavioral variant of frontotemporal degeneration (bvFTD). Grammatical comprehension and performance on language, working memory, and executive measures were analyzed, in an effort to elucidate the basis for these impairments. The scores on these measures in patients with bvFTD (n=23) were compared with the scores of patients with amnestic Mild Cognitive Impairment (aMCI) (n=13) and healthy elderly controls (n=20). To assess sentence comprehension, a two-alternative sentence-picture matching task was administered, in which patients chose the picture best described by a sentence, the meaning of which depends on grammatical interpretation. Pyramids and Palm Trees (PPT) and Boston Naming Test (BNT) were used to assess semantic memory; Trails B (TB), FAS Category Fluency (CF), and the Visual Verbal tests were administered to evaluate executive functioning; and Digit Span backwards (DB) was used as a measure of working memory. Significant impairment was found in the sentence comprehension task in the bvFTD cohort compared to controls ($p < .001$), and a trend toward significance was found when compared to aMCI subjects ($p=.052$). BvFTD patients' sentence comprehension performance correlated with scores on both PPT ($r=.68$, $p<.002$) and FAS ($r=.54$, $p<.01$). These findings suggest that grammatical comprehension is impaired in non-aphasic bvFTD subjects, and contributing factors to this impairment appear to include deficits in executive functioning and semantic memory.

P.61 Difference between patients with frontotemporal dementia and Alzheimer's dementia on a test of practical judgment

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Abstract: In FTD executive deficits and specifically poor judgment are a hallmark of the disease. Patients with AD also often have executive deficits during the disease progression. Given that impaired judgment can occur in FTD and AD; the current study investigates if there are any differences between the two groups when judgment is measured with a standardized test. The test of practical judgment (TOPJ) is an objective measure of everyday judgment. Patients have a hypothetical scenario presented to them and they are asked to explain what they would do in that situation. The TOPJ was administered in a clinical setting during a standardized neuropsychology battery. At the time of testing the patients did not have a clinical diagnosis. In this initial analysis, Later, nine patients diagnosed with probable FTD were matched on the MOCA test score, with nine patients with suspected AD. Correlation analysis was conducted to compare the scores of the FTD patients and AD patients. It was found that a statistically significant difference exists in the TOPJ scores of the two groups. Specifically, while the the FTD patients performed significantly worse than the AD patients. The results demonstrate that although judgment is affected in both groups poor decision making is more pronounced in patients with FTD.

P.62 "Knowing what you don't know" – language insight in semantic dementia

Sharon Savage, Olivier Piguet, John Hodges

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Abstract: Reduced insight commonly occurs in dementia and can be specific to certain domains of functioning, such that a person may be aware of declines in one area (e.g., memory), but not in another (e.g., personality change). Recent models have identified semantic memory as playing a role in the capacity for insight. Despite this, little investigation of insight has been conducted in Semantic Dementia (SD), with patients often described as being aware of their language problems. Twenty-two SD (n = 11 severe, n = 11 mild-moderate) and 9 nonfluent primary progressive aphasic patients completed 3 experimental tasks of language insight. Skills in evaluating language were tested by comparing performance ratings on the Cookie Theft task with objective scoring. Awareness regarding the existence and previous use of certain words was tested using 2 additional tasks. While SD patients were as accurate as nonfluent patients in rating their own performance on the Cookie Theft immediately following the task, they were significantly poorer at evaluating the same content re-recorded, or other examples of poor language. Compared to nonfluent patients, severe SD patients also made more errors identifying past exposure to low frequency words and non-words. Lastly, when tested on labels for specific aspects of an object, SD patients were prone to errors regarding both the existence, or their past knowledge, of certain words. Thus results showed that while SD patients demonstrate a general awareness of their language impairments, they have difficulty evaluating language content, which impacts upon their language insight.

P.63 Spatial orientation discriminates behavioural variant FTD from Alzheimer's disease

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Abstract: Behavioural variant FTD (bvFTD) can show episodic memory deficits and associated hippocampal atrophy similar to Alzheimer's disease (AD), which can create diagnostic uncertainty. Nevertheless, AD show additional atrophy changes to the retrosplenial cortex, a region which has been associated with spatial orientation processes. Thus, retrosplenial changes and associated spatial disorientation might be a better discriminator for bvFTD and AD than episodic memory. The current study addresses this point by measuring spatial orientation via a novel virtual environment task in 3 patient cohorts (bvFTD n=13, AD n=11, semantic dementia (SD; n=12), and 21 age- and education-matched controls. Participants were shown short video clips (20-40 seconds) from a first person perspective travelling through a virtual supermarket. At the end of the video, participants were explicitly asked to point towards the direction of the starting point from the finishing location. On standard delayed recall episodic memory tasks (e.g., word list), all patient groups were impaired compared to controls with AD showing the worst performance. In contrast, bvFTD and SD performed similar to controls on the virtual supermarket orientation task, whereas AD performed at chance level denoting severe disorientation in this group only. These findings indicate that spatial orientation is differentially affected in bvFTD and AD, unlike other aspects of episodic memory. Use of spatial orientation tasks, such as the current virtual supermarket task, may therefore be a promising clinical diagnostic tool to dissociate bvFTD from AD, particularly in the presence of concurrent episodic memory impairments.

P.64 Distinct learning patterns mark underlying neuropathology in primary progressive aphasia

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Abstract: Primary Progressive Aphasia (PPA) can be caused by frontotemporal lobar degeneration (FTLD) or by Alzheimer's disease (AD). This study sought to determine if performance on a learning test could differentiate PPA patients with autopsy-confirmed AD (PPA-AD, N=14) from those with FTLD (PPA-FTLD, N=8) and from patients with AD neuropathology and amnestic dementia (DAT-AD, N=8). Learning of words and shapes was tested under two conditions: 1) *effortless* recall immediately following stimulus presentation without forewarning to remember and 2) *effortful* recall following multiple learning trials. ANOVAs compared the groups with respect to learning condition (effortless, effortful) and material (words, shapes). Additional analyses compared effortless to effortful recall within each group. Between-group comparisons revealed that PPA-FTLD had better effortless recall of words than PPA-AD, whereas PPA-AD had better effortless recall of shapes than DAT-AD (*p*s < .05). PPA-FTLD showed near-ceiling effortless recall that did not significantly differ from effortful recall of words or shapes. In PPA-AD, effortful recall of both was significantly better than effortless recall (*p*s < .05). In DAT-AD, effortless recall of both was poor and only significantly worse than effortful recall of words (*p* < .05). In conclusion, FTLD neuropathology was associated with a high capacity for online storage (effortless encoding) of words and shapes. Among PPA patients, AD neuropathology was associated with improvement in word and shape recall following effortful learning trials. By contrast, AD neuropathology in amnestic patients was associated with poor effortless and effortful recall, particularly for shapes.

P.65 Bilingualism influences differentially behavioural and language variants of FTD

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Abstract: Recent evidence suggests that bilingualism is associated with a delay in the age at onset of dementia, possibly due to an advantage in executive control. However, studies from healthy adults suggest a bilingual cost to verbal skills. Frontotemporal Dementia (FTD) syndromes are characterised by clinical subtypes that affect differentially domains of behaviour, cognition, language and praxis and therefore provide an opportunity to explore the effect of bilingualism on different cognitive functions in disease. We compared the age at onset and prevalence of FTD subtypes in 160 FTD patients (98 bilingual, 62 monolingual). Overall, bilinguals presented with dementia 3.6 years later than monolinguals (p=0.024). A significant difference in age at onset between monolinguals and bilinguals was found in the behavioural variant FTD (bvFTD) (54.9 vs 60.9 years, p=0.034), but not in progressive nonfluent aphasia (60.1 vs 62.8 years), semantic dementia (57.0 vs 59.6 years), corticobasal degeneration (60.3 vs 60.4 years), FTD MND (51.7 vs 59 years), and PSP (60.8 vs 63.1 years). In terms of prevalence, the proportion of bilingual patients in SD group (80%) was higher than in the overall cohort (62%). No significant difference was found in all other subgroups. Our results, demonstrating a delay in the age at onset of bvFTD, but not in language and motor variants of FTD, support the role of bilingualism in enhancing executive control. On the other hand, the higher prevalence of semantic dementia among bilinguals could hint at possible costs of bilingualism to language functions in disease.

P.66 An fMRI study of facial expression processing in individuals at-risk for developing frontotemporal dementia

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Abstract: Patients with behavioural variant Frontotemporal Dementia (bvFTD) have well characterized emotion recognition deficits, particularly for negative emotions including anger and disgust. We previously demonstrated that in patients with FTD, functional magnetic resonance imaging (fMRI) during a emotional facial expression task revealed emotion specific blood-oxygen-level-dependent (BOLD) signal deficits in neural regions involved in normal facial expression processing. Furthermore, these BOLD signal abnormalities persisted after corrections for atrophy. As atrophy can be difficult to detect in many patients during early or prodromal stages of the disease, we sought to use task-based fMRI in biological family members of patients with FTD to determine whether BOLD signal changes may be sensitive to detect early neural dysfunction in emotional processing before the onset of atrophy. To date, 16 family members and 13 healthy controls have completed an fMRI facial emotional processing task and an emotion recognition task. FTD heritability was quantified for family members based on the criteria outlined in Goldman et al (2005), and by genotyping for MAPT, progranulin and C9ORF72. Preliminary results reveal that relative to aged-matched controls, FTD biological family members show increased activity in the left inferior frontal gyrus and the right insula when viewing angry and disgusted faces, respectively. These results suggest that increased BOLD signal may represent a prodromal FTD neural signature, possibly related to inefficient processing and increased neural recruitment when viewing emotional expressions. This approach may be applied to establish new tools for early disease detection and tracking disease progression.

P.67 Predictive mechanisms and speech perception in progressive non-fluent aphasia

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Abstract: Progressive Non-Fluent Aphasia (PNFA) is an adult onset neurodegenerative condition characterised by apraxia of speech and/or agrammatism. Object knowledge and comprehension of single words is spared, but many patients complain that perceiving speech is effortful, even in optimal listening environments. PNFA typically leads to subtle neuroimaging changes, but changes in cortical thickness in inferior frontal gyrus correlate with grammatical processing, while those in inferior frontal sulcus correlate with fluency. In normal individuals, activity in these areas is modulated by the congruency of prior knowledge with incoming degraded speech, implying a role in predictive mechanisms that integrate sensory information with prior expectations. Furthermore, deficits in basic auditory processing have recently been documented in individual patients with PNFA. This study assessed the relative contribution of top-down and bottom-up processes to the anecdotal complaint of speech perception difficulties. Eleven patients performed a battery of tests assessing: 1) sensitivity to pitch changes, frequency modulation, and differences in spectro-temporal modulation; 2) the influence of prior stimulus knowledge on the perceived clarity of degraded speech; 3) ability to report degraded speech; and 4) ability to discriminate small differences between spoken words. Compared to age-matched controls, patients with PNFA demonstrated significant but diverse deficits in basic auditory processing, and were much more affected by the congruency of prior knowledge when rating speech clarity. These results inform our understanding of this frequently reported yet poorly understood symptom in PNFA, and have more general implications for the role of the left frontal lobe in predictive models of speech perception.

P.68 Neuropsychiatric symptoms of patients with behavioral variant frontotemporal dementia compared with patients with Alzheimer's disease: frequency, correlation and caregiver distress- Brazil

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Abstract: Neuropsychiatric symptoms are more prevalent in certain types of dementia. Frontotemporal Dementia (FTD) is an umbrella term for a group of dementia syndromes that present clinically without amnesia, especially in the early stages. It interferes significantly in the patient's autonomy and it causes high physical, financial and emotional tribulation to the family nucleus, leading to early institutionalization. The objectives of this study were: to identify the most frequent and more severe neuropsychiatric symptoms in patients with behavioral variant FTD compared to patients with Alzheimer disease (AD) and to evaluate which disease causes more distress to the caregiver. Sixty-two caregivers, aged 55 or older, with at least two years of formal education, were invited to participate. 31 provided care for patients with bvFTD and 31 for those with AD. bvFTD and AD patients were matched according to the severity of the disease, based on the Clinical Dementia Rating (CDR). The NPI and NPI-D were applied to the caregivers and the symptoms were analyzed with exploratory factor analysis. bvFTD caregivers reported higher frequency and severity of neuropsychiatric symptoms, as well as higher distress, when compared to AD caregivers. Significant differences were found between these groups for: delusions, agitation, apathy/indifference, disinhibition, irritability/lability, total score of behavioral and neuropsychiatric symptoms, and total caregiver distress. The results reinforce the need for studies regarding the neuropsychiatric manifestations in bvFTD, as they seem to be associated with high degree of caregiver distress.

P.69 Biochemical identity of von Economo neurons

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Abstract: An atypical layer 5b projection neuron with distinct bipolar morphology, the Von Economo neuron (VEN), is found primarily in frontoinsular (FI) and anterior cingulate cortex (ACC). VEN functions remain unknown, but their regional topography and selective vulnerability in the behavioral variant of frontotemporal dementia (bvFTD), schizophrenia and autism suggest they are involved in sophisticated social-emotional functions. Identifying the biochemical phenotype and morphology would aid in understanding of the selective vulnerability of VENs and provide novel targets for therapy. In this study, we aim to identify mRNA and protein expression patterns that elucidate the biochemical phenotype(s) of VENs in ACC and FI. The Allen Brain Atlas (ABA) contains gene expression data from over 150 neurotransmitter genes which have been visualized by in situ hybridization (ISH) throughout the brain in several control subjects. We have systematically assessed the ABA for VEN-containing regions and studied the ISH for VEN-positive patterns. Positive findings were validated using immunohistochemistry in ACC and FI post-mortem human material. The ABA showed layer 5 specific staining for a GABA subunit theta (GABRQ) in ACC for VEN-shaped and surrounding pyramidal neurons. Immunohistochemistry revealed that GABRQ is indeed expressed in VENs and a minority of layer 5 pyramidal cells in the ACC. Future studies will define the proportion of VENs expressing this and other proteins identified through the ABA atlas. The findings will enhance our understanding of this important cell type and aid in future anatomical studies of bvFTD.

P.70 The tauopathy associated with mutation +3 in intron 10 of Tau: an update on the MSTD family

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Abstract: Familial Multiple System Tauopathy with Presenile Dementia (MSTD) is associated with a (g) to (a) transition at position +3 in intron 10 of MAPT gene. Spina et al. (2008) reported neuropathologic data from 14 mutation carriers. Seven additional brains of individuals, symptomatic for 3-13 years before death, have been examined. Brain atrophy varied according to disease duration. Neuronal and/or glial tau-immunoreactive deposits, consisting of 4-repeat tau are found in all cases within telencephalon and brainstem; argyrophilic grains are present in hippocampus. Quantitative neuroimaging had been used to analyze progression of atrophy in living affected individuals and for predicting disease onset in an asymptomatic mutation carrier that displayed a trend toward impairment of memory, verbal fluency, conceptual shifting and response inhibition, as evidenced by scores either approaching or below the 5th percentile of healthy controls, as observed four years before her death. Longitudinal changes in 5 symptomatic patients showed average whole brain volume (WBV) change -2.47%/year. For the asymptomatic mutation carrier, WBV changes were -0.47%/year in the first 2 years of assessment and -1.83%/year in the following 5 years, therefore indicating an acceleration of the rate of brain atrophy and suggesting the approaching threshold of a clinically recognizable symptomatology. This subject became symptomatic at age 50, with disinhibition, loss of executive functioning, word finding difficulty, and short term memory deficit. She died at age 53. Neuropathologic examination showed severe tau pathology throughout the telencephalon and brainstem. This study provides additional insights to the understanding of the natural history of inherited tauopathies.

P.71 Does the APOE genotype modify the neuropathologic phenotype associated with the *MAPT* IVS10+16C>T mutation?

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Abstract: The proband (Subject A), a male, manifested behavioral changes and intellectual deterioration at age 52 and died at 69. His daughter (Subject B) is reported to have had a change in behavior and onset of depression at age 42. Her memory and verbal skills declined and died at age 52. The proband's sister (Subject C) developed dementia at age 58 and was subsequently diagnosed with Alzheimer disease (AD). She died at age 74. Brain tissue of these subjects was studied by histology, immunohistochemistry and molecular genetics. Tau-immunoreactive neuronal and glial deposits were present in all cases. Argyrophilic grains (AG) were observed in the hippocampus and neocortical regions in all cases. Subject C met also the neuropathologic criteria for AD. In the hippocampus of subject C, tau-immunoreactive neuritic elements of plaques appeared as thick clusters. Analyses of the MAPT and APOE genes revealed a single nucleotide (C to T) substitution located sixteen base pairs (+16) outside of exon 10 (IVS10+16C>T) in all cases. The APOE genotype was ε2/ε3 for Subject B and ε4/ε4 for C. Immunohistochemistry was carried out to determine the relative participation of 3- and 4-repeat tau in the pathologic process of AD and the hereditary tauopathy. In Subjects B and C, AG consisted of 4-repeat tau. However, 3-repeat tau was present only in Subject C and associated with neurites of hippocampal plaques. In these cases, AG are associated with 4-repeat tau. In one patient, APOE ε4/ε4 is associated with AD pathology and presence of 3- and 4-repeat tau.

P.72 The prevalence of TDP-43 inclusions is much higher in control Asians older adults than Caucasians : a population-based clinicopathological study

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Abstract: Abnormal deposition of TDP-43 protein is key in the majority of frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Several factors including educational level, language and cultural aspects may influence the clinical expression of TDP-43 pathology. Susceptibility to disease also depends on ethnicity. Our group previously demonstrated that African ancestry protects against the accumulation of β-amyloid plaques. In this study, we examined non-demented subjects from the Brain Bank of the Brazilian Aging Brain Study Group of the University of Sao Paulo Medical School for the presence of abnormal TDP-43 deposition. Ethnicity was ascertained by DNA markers, in most of the cases. We included 202 non-demented subjects, older than 50 years: either Caucasians (n=176) or Asians (n=26). Presence of abnormal TDP-43 was assessed in brain slides immunostained against phospho-TDP (MAb409/410 Cosmo Bio, Japan, 1:1000). Positivity required identification of inclusions in, at least, one of the regions of interest (inferior temporal gyrus, hippocampal formation and amygdala). Chi-square test showed a significant difference in TDP-43 positivity between Caucasians (17%) and Asians (31%) (p=0.04). Logistic regression analysis showed higher prevalence of TDP-43 in Asians compared to Caucasians subjects, after adjusting for confounding factors, such as age, gender, education and Braak stage (OR=0.34, 95% CI 0.12-0.94, p=0.04). Our results suggest that Asians are more prone to exhibit TDP-43 inclusions than Caucasians, although it is not clear if this deposition results in clinical decline. Studies using different ethnic group dwelling in the same city may help to identify genetic protective factors against the expression of clinical dementia.

P.73 *C9orf72* mutation screening in neuropathological patient cohorts from Sweden confirms a high prevalence

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Abstract: The prevalence of C9orf72 mutations is variable across different populations and the prevalence in clinically diagnosed FTD and ALS patients from Sweden is among the highest in the world. In this study we used immunohistochemical staining of formalin fixed paraffin embedded (FFPE) sections from cerebellum for detection of repeat-associated non-ATG translation products of the pathological G4C2 expansion (C9RANT) from Ash et al 2013. The method was validated in an independent autopsy series of 12 known Swedish C9orf72 mutation carriers detected by repeat primed PCR. The results showed that 16 of 99 (16%) neuropathologically confirmed FTLD, FTLD-MND and ALS cases were immunoreactive for the C9RANT antibody: 6 out of 47 (13%) FTLD cases were positive, 2 out of 11 (18%) FTLD-MND cases were positive and 8 out of 41 (19,5%) ALS cases were positive. In an independent and blinded DNA-based repeat primed PCR analysis in those cases where blood DNA or DNA from frozen brain tissue were available (N=27) the mutation status was confirmed (4 positive for the expansion and 23 were negative for the expansion mutation). We are currently optimizing the repeat primed PCR method for analysis of DNA extracted from FFPE brain tissue. Quantitative analysis of the relative load of aggregates is ongoing together with genotyping of 68 tagged single nucleotides (SNPs). This will allow us to examine the potential correlation between the distribution and severity of C9RANT immunoreactivity with the genetic background of the expansion mutation as well as the correlation to clinical phenotypes.

P.74 Quantitative digital image analysis of Pick's disease neuropatholgy

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Abstract: Neuron-to-neuron spread of pathogenic proteins is hypothesized in tauopathies. There is minimal study of this non-random distribution of tau pathology in Pick's disease. We examined three regions (mid-frontal cortex,MFC; superior-temporal cortex, STC; cingulate gyrus, CG) from 10 Pick's disease cases using a novel method of digital image analysis. Slides were simultaneously immuno-stained for phosphorylated-tau (PHF-1) and whole-slide digital images obtained at 10x magnification using identical exposure. 10 non-overlapping 1.0 mm2 regions of interest in grey matter were randomly selected per slide for analyses. Cases were randomly divided into a test (n=5) and training set (n=5). Automated quantification of pick-body inclusions were obtained through creation of a thresholding algorithm. To determine optimal thresholding parameter, we applied a range of incremental size and shape threshold settings to the training set and used manually-detected counts as the dependent variable in linear regression. To validate the optimal threshold in the training set, we applied this setting to the independent test set and found high accuracy to detected tau inclusions (R2=0.79,residual=15.3%). We then compared auto-detected mean Pick-body counts between regions and found a higher burden in MFC (mean=75.2,SE=5.8) than STC (mean=30.6,SE=3.3;MWU=2.2,p=0.03) but not CG (mean=69.5,SE=5.8;MWU=0.4,p>0.1). There was a trend for higher counts in CG compared to STC (MWU=1.9,p=0.06). Disease duration robustly correlated with STC counts (ρ=0.8,p=0.005) but not MFC (ρ=0.3,p>0. 1) or CG (ρ=-0.3,p>0. 1). This suggests Pick's disease may initially involve frontal neocortical and limbic regions and then spread to temporal neocortex. Digital image analysis provides a reliable fine-grained quantitative approach for FTLD histopathology.

P.75 Primary progressive apraxia of speech associated with progressive supranuclear palsy pathology

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Abstract: Primary progressive apraxia of speech (PPAOS) is a disorder characterized by relatively isolated and progressive dysfunction of motor speech planning and programming. Features of apraxia of speech include slow speech rate, sound distortions or substitutions, and lengthened intersegment duration between sounds, syllables and words. PPAOS is distinguished from other neurodegenerative disorders, particularly the non-fluent/agrammatic variant of primary progressive aphasia, by the absence of language impairment or other neurologic signs especially early in the course. While the clinical syndrome has been well-described, its neuropathological correlate is lacking. We aimed to report the pathology in three patients who carried the initial clinical diagnosis of PPAOS. Tau pathology was found in all the patients investigated, interestingly in a pattern consistent with progressive supranuclear palsy (PSP). It has been recognized that PPAOS and PSP share similar neuroanatomical characteristics. These findings provide support to the theory that PPAOS and the clinical syndrome of PSP may be on the same spectrum of neurodegenerative disorders.

P.76 Clinicopathological phenotypes associated with *SQSTM1* gene mutations

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Abstract: There is a strong genetic influence on the clinicopathological phenotypes associated with frontotemporal lobar degeneration (FTLD) and frontotemporal dementia (FTD). Intracellular deposition of TDP-43 is the hallmark of a frequent subgroup of cases with FTLD. Mutations in the sequestosome 1 (SQSTM1) gene have rarely been found in individuals with FTD. It is not clear whether SQSTM1 mutations consistently associate with p62 or TDP-43 pathologies. Here we provide a comprehensive clinicopathological description of two cases. The clinical phenotype of patient 1 was compatible with the behavioural variant (bv) of FTD. In the framework of the EU EOD consortium, genetic analysis revealed a nonsense mutation NP_003891.1:p.(Glu396*) in SQSTM1. TDP-43 pathology was compatible mostly with the features of type B, however, neuronal granular cytoplasmic TDP-43 immunoreactivity was numerous and abundant oligodendroglial inclusions were seen in the white matter. TDP-43 pathology was seen to a greater extent as p62 immunoreactivity in neurons but in a similar extent in oligodendrocytes. The clinical phenotype of patient 2 was compatible with bvFTD associated with parkinsonism and bulbar symptoms in the later stage. Genetic testing of patient 2 identified a C9orf72 repeat expansion mutation together with a missense mutation NP_003891.1:p.Arg212Cys in SQSTM1. TDP-43 pathology was characterised by neuritic profiles and oligodendroglial cytoplasmic inclusions compatible mostly with type A of FTLD-TDP pathology. In contrast to patient 1, p62 pathology was seen to a greater extent as TDP-43 immunoreactivity in neurons similar to cases with the C9orf72 mutation. Our study expands the neuropathology spectrum of genes associated with FTLD-TDP.

P.77 Oligodendroglial response in the spinal cord in TDP-43 proteinopathy with motor neuron involvement

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Abstract: TDP-43 proteinopathies represent a spectrum of neurodegenerative disorders. Variable clinical presentations, including frontotemporal dementia, amyotrophic lateral sclerosis, and mixed forms are associated with the spatial heterogeneity of the TDP-43 pathology. Recent studies emphasize the role of oligodendrocytes in the pathogenesis of amyotrophic lateral sclerosis. In the present study we evaluated whether TDP-43 proteinopathies associate with an oligodendroglial response. We performed a study on 7 control and 10 diseased cases with spinal cord involvement. Using the oligodendroglia-specific antibody, TPPP/p25, we assessed oligodendrocyte density in the lateral corticospinal tracts along with the presence of perineuronal oligodendrocytes in the anterior horns. We performed densitometry of myelin basic protein (MBP) immunoreactivity. The numbers of TDP-43 and p62 immunoreactive inclusions were counted in both lateral corticospinal tracts and anterior horns. Double immunolabeling confirmed that oligodendrocytes harbor TDP-43 inclusions. In the lateral corticospinal tracts MBP density, but not the number of oligodendrocytes, was decreased in the diseased group. However, oligodendrocyte counts in the lateral corticospinal tract correlated positively, while the density of MBP inversely, with the number of neuronal inclusions in the anterior horn suggestive of a compensatory response of oligodendrocytes. The number of neurons with perineuronal oligodendrocytes correlated with the amount of inclusions.In conclusion, our study further emphasizes the importance of oligodendroglia in the pathogenesis of TDP-43 proteinopathies with spinal cord involvement.

P.78 New intraneuronal component in NIFID

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Abstract: Neuronal Intermediate Filament Inclusion Disease (NIFID) is a rare cause of frontotemporal dementia characterized clinically by psychiatric disturbances and cognitive impairment in early-onset cases, and by complex neurologic symptoms including dementia in cases with late onset. NIFID is characterized neuropathologically by intraneuronal hyaline inclusions containing phosphorylated neurofilaments, α-internexin and FUS (fused in sarcoma) RNA binding protein (FUS) which are immunoreactive with antibodies directed against residues 200 and 250 in early-onset and late-onset cases, but negative with antibodies against amino acids 90 and 220 of human FUS in cases with late onset. Genetic studies consistently show no mutations in FUS. Here we report an additional component of hyaline inclusions co-localizing with α-internexin. This component is a member of the cadherin superfamily which encode calcium-dependent adhesion proteins largely present in fibroblasts. In the CNS, this protein is weakly expressed in the cytoplasm of normal neurons and massively condensed in NIFID intraneuronal inclusions. Mutations in genes related to the same pathway are causative of abnormal brain development.

P.79 Survival in the laguage variants of FTD

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Abstract: We recently showed that the revised criteria for frontotemporal dementia (FTD) syndromes identified a relatively high proportion of patients with Alzheimer disease (AD) pathology, particularly among the language variants (40% have AD compared with <10% of those with behavioural variant FTD). There are now three language variants (semantic, non-fluent and logopenic) with AD concentrating in the newly described logopenic variant (>75%). Survival for FTD is on average shorter than that for AD. This study assesses the survival of cases diagnosed using the new criteria for the language variants of FTD. 69 cases were included (31 semantic, 16 non-fluent, 22 logopenic). Kaplan-Meier survival analyses revealed that patients diagnosed with semantic variant survived longer from symptom onset compared with the other two groups (median 13±1y versus 9±1 for the other two language groups, p=0.003). Assessment of those patients with or without AD within each group revealed that patients with AD survived for a similar time regardless of their clinical diagnosis (median 9±1y, p=0.79), whereas those with FTD pathologies had variable survival (semantic=13±1y, non-fluent=9±1y, logopenic=6±1.5y, p<.0001). In particular, semantic cases with AD had a shorter median survival from symptom onset of ~4 years, while logopenic cases with FTD pathologies had a similar shorter survival compared to those with AD. This study shows that AD pathology influences survival in cases reaching clinical diagnostic criteria for a language variant of FTD.

P.80 TDP-43 pathology and cognition in ALS and ALS-FTD: a clinico-pathological correlation study

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Abstract: Roughly 50% of patients with ALS show cognitive changes; of these, 5-10% suffer from FTD. In this clinico-pathological study, we investigated the histopathological substrate of disturbed cognition in 18 neuropsychologically well characterised ALS patients who were divided into the following three cognitive subgroups: cognitively not impaired (ni, N=7), cognitively impaired (ci, N=5), and demented (ALS-FTD, N=6; one with a C9orf72 repeat expansion). The extent of TDP-43 pathology was assessed semiquantitatively in ten supratentorial brain regions (score 0-4). In addition, each patient was classified into ALS stages I-IV in accordance with Brettschneider (2013). The revised NIA criteria (ABC-score) was utilised to assess potential Alzheimer´s pathology (Montine 2012). An analysis of covariance was applied, adjusted for age and Braak´s neurofibrillary tangle stages. The average age of our patient group was 66 years (52-75). The TDP-43 score, averaged across the ten supratentorial brain regions, was significantly higher in FTD than in the ni and ci groups (means in ni, ci, FTD: 1.2, 1.3, 3.1; p=0.01 and 0.02, respectively). No significant differences were found between the ni and ci groups (p=0.89). The Brettschneider stage correlated strongly with the averaged TDP-43 score (r=0.86) though only to a weak extent with the cognitive stage as defined by the grouping ni, ci, ALS-FTD (r=0.39). A minor correlation was found between the cognitive stage and age and Alzheimer´s pathology (r=0.32, 0.27). Our findings regarding a significant difference between demented and non-demented ALS patients underline a close relationship between cognition and the amount of cortical TDP-43 pathology.

P.81 Case reports of two patients with comorbidity of FTLD-TDP and progressive supranuclear palsy

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Abstract: Frontotemporal lobar degeneration with transactive response DNA binding protein 43 (FTLD-TDP) and progressive supranuclear palsy (PSP) are two distinct neurodegenerations with different clinical presentation. We report two cases with FTLD-TDP and PSP in comorbidity confirmed neuropathologically. Case one: 59-year-old man presented with progressive amnestic dementia suggesting Alzheimer's disease. Subsequently he developed impairment of executive functions, low verbal fluency, and apathy, together with increasing parkinsonism. Later appeared downward gaze palsy, frequent falls and incontinence with severe frontal lobe impairment and he died at age of 62 years. Case two: 58-year-old man presented with ataxia, tremor and nystagmus, with impaired verbal fluency and constructional apraxia. Progressively he developed akinesia, rigidity, frequent falls, and verbal aggressivity. He became bedridden and deceased at 63 years. Neuropathological examination in both cases revealed neuronal and glial tau pathology (AT8, DR4) in the hippocampus, striatum, mesencephalon, and cerebellum and to lesser extent in the frontal cortex. Moreover ubiquitin, p62, and phospho-TDP-43-immunoreactivities in neurons and neuropil were found mainly in the hippocampus, mesencephalon, and frontal and temporal cortices. Genetic analysis for microtubule-associated protein tau (MAPT) and progranulin (PRGN) gene mutations was negative. In conclusion, we present two cases with neuropathologically confirmed comorbidity of FTLD-TDP and PSP, with very different initial leading symptoms. Clinical and neuropathological correlations in atypical cases of neurodegenerative dementias are crucial to describe new entities of overlapping syndromes, which might help us to understand the pathophysiology of the known dementia hallmarks.

P.82 Neuropathologic phenotype associated with the ΔK280 *MAPT* gene mutation

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Abstract: Pick disease (PiD) is usually a sporadic frontotemporal lobar degeneration-tauopathy although hereditary forms are described. The proband was a 54 year-old man with a progressive dementia clinically suspected to be either Alzheimer disease (AD) or a frontotemporal dementia (FTD). Family history includes a 49 year-old sister with dementia. At autopsy, the proband's brain weighed 1140 grams. The left hemibrain showed severe frontal and moderately severe temporal lobar atrophy, moderate to severe striatal atrophy, and severe lateral ventriculomegaly. The hippocampal formation and parietal and occipital lobes showed no obvious atrophy. Neuronal loss, gliosis, and spongiosis were severe in the frontal cortex and moderate in the temporal and entorhinal cortex. Tau-positive round neuronal inclusions typical of Pick bodies, immunopositive for 3-repeat tau, were most frequent in frontal cortex yet appeared in multiple cortical areas and entorhinal cortex, amygdala, and hippocampal formation. The white matter contained tau-positive threads and glial inclusions, accompanied by moderate gliosis and myelin pallor. Ballooned neurons were frequent in amygdala, claustrum, and insular cortex. No ß-amyloid deposits were identified. DNA analysis revealed a three-nucleotide deletion in exon 10 in one allele of the MAPT gene. The pathogenic nature of this mutation, predicted to lead to deletion of amino acid K280, remains inconclusive as it has been described in a case of FTD and in a case of late-onset AD. Characterization of additional family members, both affected and unaffected, may lead to clarification of the pathogenic role of the ΔK280 MAPT gene mutation in PiD.

P.83 Alzheimer's disease in clinical versus pathological frontotemporal dementia cohorts - how big is the clinicopathological mismatch?

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Abstract: A relatively high proportion of patients with Alzheimer disease (AD) pathology are identified in cases diagnosed using the revised criteria for frontotemporal dementia (FTD) syndromes, particularly in the language variants (40% have AD compared with <10% of those with behavioural variant FTD). A neuropathology audit of patients with clinical AD at NIA Alzheimer Disease Centers revealed FTLD and not AD pathologies in ~20% of cases. We therefore assessed the clinical diagnoses of dementia patients participating in longitudinal research programs at tertiary referral centres in Sydney and Cambridge that reached pathological criteria for FTLD. 169 consecutive neuropathologically-ascertained cases were included, 51% with TDP pathologies and 40% with tau pathologies. Direct comparison between using these different strategies for identifying FTD cohorts for clinicopathological analyses through the same centres revealed less cases with clinical certainty of diagnosis of an FTD syndrome (135 cases but ~20% have AD pathology) versus those with pathological FTLD (169 cases but ~5% had clinical AD). Only 102 cases overlapped between these different cohorts (~75% of clinical FTD versus 60% of pathological FTD). These differences impacted on the proportion of cases with different dementia syndromes (47% versus 59% with behavioural variant, 53% versus 36% with language variants, 0 versus 5% with clinical AD), as well as the prevalence of TDP (35% versus 51%) and tau (31% versus 40%) in the clinical versus pathological cohorts. The method of case ascertainment of FTD cohorts significantly impacts on the types of FTD cases analysed in clinicopathological correlation studies.

P.84 Clinicopathological correlation in frontotemporal dementia

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Abstract: The diagnostic process in patients with cognitive decline is often challenging. Frontotemporal dementia (FTD) is the second most common form of presenile dementia and is most often caused by frontal temporal lobar degeneration (FTLD). However, there is an overlap with other underlying pathologies. With emerging therapeutic options for dementia it is important to distinguish the various pathologies during life. We studied the clinicopathological correlation in our existing prospective cohort (n=562) of possible and probable FTD patients with a definite diagnosis (n=202; clinically 163 probable and 39 possible FTD). A definite diagnosis was based on pathological findings (n=119) and/or known mutations (n= 126; 50 MAPT, 31 GRN and 45 C9orf72). The clinical picture of definite FTD was in 73.8% behavioral FTD, 8.4% semantic dementia, 6.4% progressive non-fluent or logopenic aphasia, 6.4% FTD motor neuron disease, progressive dementia with parkinsonism (n=4), psychiatric disorder (n=2), Alzheimer's disease (n=3) and progressive supranuclear palsy (PSP) (n=1). Pathological findings confirmed FTLD in 108 cases (81 probable and 27 possible) with accumulation of tau in 21.3%, transactive response DNA-binding protein 43 in 27.2%, fused in sarcoma protein in 3.5% and not classifiable in 1,5%. Three probable and 8 possible FTD had a definite diagnosis not consistent with FTLD: 6 Alzheimer's disease, 2 Creutzfeldt-Jacob disease, 1 corticobasal degeneration, 1 PSP and 1 no brain disease. These results illustrate there exists a considerable clinicopathological heterogeneity of FTD which may hamper the prediction of underlying pathology in living patients.

P.85 Region-specific changes in C9orf72 protein isoform levels in brains of *C9orf72* patients detected using isoform-specific antibodies

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Abstract: A noncoding hexanucleotide repeat expansion in C9orf72 is the most commonly known cause of frontotemporal dementia and amyotrophic lateral sclerosis (ALS). The repeat expansion has been shown to cause a downregulation of C9orf72 transcripts, suggesting that haploinsufficiency may contribute to disease pathogenesis. From 3 transcript variants, two C9orf72 protein isoforms are generated: a long form (C9-L) and a short form (C9-S). To investigate C9orf72 proteins we generated rabbit polyclonal antibodies against peptide sequences of C9-L and C9-S proteins. Antibody specificity was confirmed using constructs encoding tagged C9-L or C9-S proteins. Following sequential protein extraction from frontal cortex tissue, we noted distinct biochemical profiles of C9-L and C9-S: C9-L was found to be poorly soluble and was present in the insoluble fraction whereas C9-S was found to be highly soluble and present in the low salt fraction. Quantification of C9-L levels in frontal cortex tissue showed significantly lower levels in C9orf72 cases compared to sporadic ALS cases (n=8 per group, pC9orf72 and sporadic ALS cases in either region examined (n=8 per group). Thus, we have generated antibodies which specifically recognize C9orf72 isoforms, demonstrated distinct biochemical profiles of the isoforms in brain tissue, and shown that the repeat expansion in C9orf72 leads to region-specific downregulation of C9-L levels, providing support that haploinsufficiency of C9orf72 is a contributing factor to disease pathogenesis.

P.86 The presence of heterogeneous nuclear ribonucleoproteins in frontotemporal dementia with FUS positive inclusions

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Abstract: Fused in sarcoma (FUS) has been identified as the major protein in the pathological lesions in frontotemporal lobar degeneration with FUS-positive inclusions (FTLD-FUS). The disease pathogenesis of FTLD-FUS remains poorly understood. However transportin1 (TRN1) is abundantly found in FUS-positive inclusions. TRN1 is responsible for shuttling proteins containing an M9 nuclear localisation signal between the nuclear and cytoplasmic compartments. FUS is a member of the FET protein family, which also includes Ewing's sarcoma and TATA-binding protein-associated factor 15, both of which are present in the pathological lesions in FTLD-FUS, suggesting a disturbance of transportin-mediated nuclear import of the FET proteins. FUS is also known to belong to the heterogeneous nuclear ribonucleoprotein (hnRNP) protein family. Therefore we wished to investigate whether this family of proteins is associated with FUS pathology and could be implicated in the pathogenesis of these diseases. We studied the localization of proteins of the hnRNP family in affected brain regions in patients with FTLD-FUS and normal control brains by immunohistochemistry and biochemical analysis. Here we demonstrated the presence of several hnRNP proteins in a proportion of pathological inclusions including neuronal cytoplasmic inclusions and dystrophic neurites. Dense cytoplasmic staining was also evident containing several hnRNP proteins. Biochemical analysis also revealed a shift in the location of the hnRNP proteins from the nucleus to the cytoplasm which was not apparent in normal controls. These results implicate a wider dysregulation of TRN1 associated nuclear import between intracellular compartments, than mechanisms only affecting the FET proteins.

P.87 Does frontotemporal dementia associated with chorea suggest the diagnosis of frontotemporal lobar degeneration with fused in sarcoma positive inclusions of the basophilic inclusion body disease subtype?

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Abstract: Choreoathetotic involuntary movements occur very occasionally in patients with frontotemporal lobar degeneration (FTLD). We had an autopsy case of young onset FTLD with chorea. She was diagnosed neuropathologically as FTLD with fused in sarcoma (FUS)-positive inclusions (FTLD-FUS) after her death. We then reviewed the clinical records of 72 neuropathologically confirmed FTLD cases archived in our laboratory and found two more cases of FTLD with chorea. All 3 cases were FTLD-FUS and the subtype was basophilic inclusion body disease (BIBD). The clinical and neuropathological features of these 3 cases were compared with the other cases of BIBD without chorea. The average age at onset was about 44 years in both BIBD with and without chorea. The chorea was complicated with athetosis in two cases and with ballism in one. The clinical diagnosis of all 6 cases was the behavioral variant of frontotemporal dementia (bvFTD). Parkinsonism was absent in BIBD with chorea but was present in those without chorea. We could not find any neuropathological feature that distinguishes those with and without chorea. We conclude that, in the clinical setting, the occurrence of choreoathetosis in bvFTD suggests the diagnosis of FTLD-FUS of the BIBD subtype.

P.88 Ultrastructure of oligodendroglial, neuronal and astrocytic inclusions in globular glial tauopathy

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Abstract: Globular glial tauopathy (GGT) is a recently recognized subtype of frontotemporal lobar degeneration. GGT remains incompletely characterized, especially at the ultrastructural level. Globular oligodendroglial inclusions (GGI) immunoreactive for 4-repeat tau are the sine qua non of GGT. GGI are Gallyas-positive, while neuronal cytoplasmic inclusions (NCI) and globular astrocytic inclusions (GAI) are negative. We performed immunoelectron microscopy on brain samples of a 59 year-old woman with 4 year history of corticobasal syndrome. The brunt of the cortical atrophy was in frontal lobe, particularly the premotor and motor cortices. There was also corticospinal tract degeneration. The medial temporal lobes and basal ganglia were affected. GGI and coiled body-like oligodendroglial inclusions were found. The hypothalamus had many round NCI that were positive for 4R tau and weakly positive for 3R tau. The basal ganglia had numerous 4R tau-positive, Gallyas-negative GAI. Ultrastructurally, similar tau filaments/tubules were detected in affected neurons and glia. They were mostly straight and had a diameter of 10-20 nm. Tau-positive GAI were often perivascular. Serial sections showed that tau and glial fibrils did not intermix in GAI. The present of filaments/tubules of similar morphology in Gallyas-positive GCI and NCI, as well as Gallyas-negative GAI is difficult to reconcile. Other factors, such a different post-translational modifications or conformation of tau, or different associated proteins, must account for the variable argyrophilia, which is an important diagnostic characteristic of astrocytic lesions in GGT. Our ultrastructural findings add to the characterization of the neuropathology of this emerging tauopathy.

P.89 Clinicopathological correlations in behavioral variant frontotemporal dementia

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Abstract: Accurately predicting the molecular pathology of patients with behavioral variant frontotemporal dementia (bvFTD) poses a daunting challenge for clinicians and will become increasingly important with the development of disease-modifying therapies. We sought to improve pathological prediction by exploring clinicopathological correlations in a large bvFTD cohort. Of 438 patients in whom bvFTD was either the top or an alternate possible diagnosis, 117 had available autopsy data, including 98 with a primary pathological diagnosis of frontotemporal lobar degeneration (FTLD), 15 with Alzheimer's disease (AD), and 4 with amyotrophic lateral sclerosis without neurodegenerative pathology outside of the motor system. The FTLD cases were distributed between FTLD-tau (34 patients – 10 corticobasal degeneration, 9 progressive supranuclear palsy, 8 Pick's disease, 3 FTDP-17, 3 unclassifiable, and 1 argyrophilic grain disease), FTLD-TDP (55 patients – 9 type A including one with motor neuron disease (MND), 27 type B including 21 with MND, 8 type C with right temporal presentations, and 11 unclassifiable including 8 with MND), FTLD-FUS (8 patients), and one patient with FTLD-ubiquitin positive not otherwise specified. AD was uncommon (6%) among patients whose only top diagnosis during follow-up was bvFTD. Seventy-nine % of FTLD-tau, 86% of FTLD-TDP, and 88% of FTLD-FUS met "possible" bvFTD diagnostic criteria at first presentation. The frequency of the 6 core bvFTD diagnostic features was similar in FTLD-tau and FTLD-TDP, suggesting that these common symptoms may not help separate patients by major molecular class. Symptom profiles differ among pathological subtypes, suggesting distinct anatomical vulnerabilities and informing the clinician's pathological prediction.

P.90 Nitrative stress and oxidative stress in amyotrophic lateral sclerosis/parkinsonism-dementia complex of the Kii peninsula of Japan

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Abstract: Background: Amyotrophic lateral sclerosis/parkinsonism-dementia complex of the Kii peninsula of Japan (Kii ALS/PDC) is a unique tauopathy. The purpose of this study is to reveal the pathological role of nitrative and oxidative stress on the patients with Kii ALS/PDC. Objective: Seven patients with Kii ALS/PDC (men 3:4 women, average age: 70.7 y.o., average duration of the illness: 7.0 years, 3 ALS, 2 ALS with dementia and 2 PDC) were submitted for the study. Method: Immunohistochemical study was performed on the folmaline-fixed, paraffin-embedded temporal lobe sections using AT8, anti-8-NG antibody, anti-OHdG antibody, anti-NFκB antibody and anti-iNOS antibody. Results: Most of hippocampal neurons were stained with anti-8-NG antibody, anti-OHdG antibody, anti-NFκB antibody and anti-iNOS antibody and most of AT-8 positive neurons were co-stained with anti-8-NG antibody. Discussion: Nitrative stress and oxidative stress may precede tau accumulation and neurodegeneration in Kii ALS/PDC. Conclusion: Nitrative stress and oxidative stress play an important role o the pathomechanisms of Kii ALS/PDC.

P.91 Senile complex tauopathy; a pathological subtype of frontotemporal lobar degeneration with behavioral variant frontotemporal dementia and parkinsonism as clinical phenotype

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Abstract: Senile complex tauopathy (SCT, Kovacs et al., 2011) is a rare pathological entity characterized by diffuse glial AT8 positive tau with negative silver staining. One of its hallmarks are so called 'dust-cloud astrocytes'. The clinical spectrum of SCT has not been described in detail, whereas only a small number of clinical cases have been identified thus far. Here we describe the case history of a 75-year-old female with a diagnosis of bvFTD during life. Her brain was donated to the Netherlands Brain Bank (NBB). Autopsy of her brain surprisingly revealed CST. This led us to identify CST in other NBB cases and determine clinico-pathological correlations. A systematic search identified 10 other cases. Five out of these had dust cloud astrocytes. Excluding cases with pathological comorbidities, 2 cases were added to our study. Unfortunately, clinical information on one case was insufficient. CST case 1 had an onset with memory problems, followed by behavioral disinhibition, apathy and compulsive behavior. Parkinsonism and falls occurred later in the course of the disorder. Her MRI showed symmetric frontoparietal atrophy. CST case 2 died at the age of 81 and had a 12 year history of disinhibition, aggression, apathy, and loss of empathy. There were memory and orientation disturbances and he developed parkinsonism and falls. His CT of the brain showed bifrontal atrophy. Since the clinical picture of SCT fulfills the clinical criteria of bvFTD, it might be considered to add CST to the FTLD-spectrum, but future research in larger patient groups should underpin this.

P.92 The progranulin cleavage products, granulins, impair stress response and exacerbate toxicity in a model of TDP-43 proteinopathy

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Abstract: Mutations in progranulin have been implicated in autosomal dominant forms of FTLD with TDP-43 pathology but the mechanism by which progranulin haploinsufficiency leads to neurodegeneration is unclear. Attention has been focused on the normal function of progranulin; however much less is known about granulins, the bioactive cleavage products of progranulin. C. elegans progranulin (PGRN-1) is cleaved into three granulins. We investigated whether increased levels of cleaved granulins, rather than progranulin haploinsufficiency per se, could drive disease development. We expressed individual granulin fragments in a pgrn-1(-) null background strain. We found that granulins conferred sensitivity to unfolded protein stress in pgrn-1(-) animals. Alone, the granulins had no effect on lifespan or coordination. However, when expressed in a pgrn-1(-); humanTDP-43 background, granulin-expressing animals were shorter-lived, progeric and incoordinated compared to animals expressing either granulin or TDP-43 alone. Granulins conferred selective vulnerability to acetylcholine neurons. Co-immunoprecipitation experiments show that granulins interact with lysosomal membrane proteins known to regulate necrotic cell death. When the necrotic cell death cascade is initiated, intracellular pH decreases. Using a ratiometric pHluorin, we found that granulins lowered the intracellular pH of neurons compared to controls and pgrn-1(-) animals. Our findings suggest a novel mechanism for neurodegenerative disease related to progranulin haploinsuffuciency, that is, aberrant activation of the necrotic cell death pathway. These findings are significant, because current therapies for FTLD are focused on increasing progranulin levels, rather than decreasing granulin levels. Improved understanding of granulin function and toxicity may lead to targeted therapies in FTLD and other neurodegenerative diseases.

P.93 Role of progranulin in lysosome biology: Implications in the pathophysiology of frontotemporal dementia

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Abstract: Genetic linkage studies identified loss of function mutations in the progranulin (grn) gene as a major cause of Frontotemporal Dementia (FTD). Progranulin is a secreted glycoprotein that is involved in multiple cellular functions from cell proliferation to inflammation. In the nervous system, it is expressed in microglia and neurons; full-length Progranulin has neurotrophic and anti-inflammatory properties. However, the exact molecular mechanism by which Progranulin exerts its cellular function is not yet clear. Intracellular Progranulin has been shown to localize to the endoplasmic reticulum, golgi and lysosomes. Characterizing the role of Progranulin and its signaling mechanism represents an opportunity to gain insight into FTD pathogenesis and will help identify therapeutic targets. Here we investigate the contribution of Progranulin to lysosome activity and the consequences of lysosomal modulation on the inflammatory state of microglial cells. We show that Progranulin is expressed in mouse microglia and its knock-down results in lower threshold to inflammatory stimuli and enhanced release of proinflammatory cytokines. We also present evidence suggesting that cells derived from FTD patients with progranulin mutations have reduced levels and activity of lysosomal enzymes, including Cathepsin D and β-glucocerebrosidase. Taken together, our results suggest that Progranulin plays an anti-inflammatory role in the brain, and propose a potential link between lysosomal dysfunction upon loss of Progranulin in microglia and induction of neuroinflammation in FTD. This study will shed light on the cellular mechanisms of Progranulin physiology and pathophysiology underlying FTD and neurodegenerative diseases, and broaden our perspectives on potential means of intervention to treat FTD.

P.94 Efficacy study of sortilin-progranulin axis targeting reagents

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Abstract: Progranulin (PGRN) haploinsufficiency is a cause of frontotemporal lobar dementia with pathological Tar-DNA protein 43 (TDP-43) inclusions (FTLD-TDP). Given that the majority of GRN mutations associated with FTLD-TDP are null mutations, which generate unstable transcripts subjected to nonsense-mediated mRNA decay or missense mutations, which generate proteins that cannot be secreted, GRN mutations are believed to mediate FTLD-related neurodegeneration via a loss-of-function mechanism. As such, we have recently proposed targeting the sortilin-progranulin (SORT1-PGRN) axis as a means to discover PGRN-enhancing therapeutics. We have shown biochemical reagents that reduce SORT1 expression or block SORT1-PGRN interactions can efficiently inhibit SORT1-mediated PGRN endocytosis. To further understand how the SORT1-PGRN axis might regulate extracellular PGRN levels, we have evaluated the efficacy of various SORT1-PGRN axis targeting reagents, including MPEP (a SORT1 suppressor), BVFP (a PGRN carboxyl-terminal binder) and neurotensin (NT) analogues (SORT1 ligands) utilizing a SORT1 overexpression cell model to enhance assay sensitivity. We found that MPEP possesses the highest maximum efficacy (Emax) to increase extracellular PGRN levels followed by neurotensin and BVFP (i.e. Emax: MPEP > NT > BVFP). Additive effects were observed when MPEP was dosed in combination with either BVFP or NT as expected given their distinct mechanisms. Of note, one of the stable, CNS-permeable NT analogues increases extracellular PGRN in vitro and increases brain PGRN levels in a mouse model of PGRN haploinsufficiency. Taken together, our data further demonstrate the SORT1-PGRN axis is a promising target for the discovery and development of PGRN-enhancing therapeutics for FTLD-TDP associated with GRN mutations.

P.95 Profiling of ubiquitination pathway genes in peripheral cells from *C9orf72* and *GRN* mutation carriers with frontotemporal lobar degeneration

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Abstract: The aim of this study was to analyze the expression profile of 84 key genes involved in the degradation of cellular protein by the ubiquitin-proteasome system in peripheral cells from C9 Open Reading Frame 72 (C9ORF72) and progranulin (GRN) Frontotemporal Lobar Degeneration (FTLD) mutation carriers as compared with non-carriers and age- matched controls (n=6 per group). A generalized trend towards a down-regulation of the ubiquitination pathway genes was observed in C9ORF72 expansion carriers as compared with controls. In particular, statistically significant decreased levels of ARIH1, UBE2E1, UBE2I, UBE2N and UBR1 genes were observed in C9ORF72 carriers as compared with controls (-1.31, -1.52, -1.28, -1.16 and -1.44 fold regulation, respectively, PCBL, MUL1, RNF123 and RNF148 genes (3.82, 2.05, 1.59 and 3.71 fold regulation, respectively, PGRN mutation carriers as compared with controls, except for UBE2Z gene (21.32 fold regulation, P=0.004). ARIH1, UBE2E1, UBE2I, UBE2N and UBR1 genes encode for members of the E2 ubiquitin-conjugating enzyme family, whereas CBL, MUL1, RNF123 and RNF148 genes display E3 ubiquitin ligase activity. According to our preliminary results, ubiquitin genes deregulation could represents one of the possible pathogenic mechanisms underneath C9ORF72 expansion, while it does not seem to be implicated in pathogenesis of FTLD in GRN mutation carriers.

P.96 Misfolded wild-type SOD1 induced by pathological FUS or TDP-43 transmits intercellularly and is propagated misfolding-competent

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Abstract: Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) represent a continuum of brain neurodegeneration disorder, where FUS or TDP-43 pathology is often detected. Clinically indistinguishable cases of ALS can be caused by either inheritable mutation in the genes encoding SOD1, TDP-43, FUS, among others, or can occur sporadically. Misfolded SOD1 has been detected in both familial and sporadic ALS patients, despite SOD1 mutations accounting for only ~2% of cases. We previously reported that pathological FUS or TDP-43 kindles misfolding of human wtSOD1 in living cells. Here, we used human cell cultures and mouse primary neural cultures expressing human wtSOD1, to establish that FUS or TDP-43-induced misfolded SOD1 can traverse between cells through incubation of untransfected cells with conditioned media, triggering conversion of endogenous SOD1. This spread is arrested by pre-incubating the conditioned media with SOD1 misfolding-specific antibodies, demonstrating their therapeutic potential. We find that recipient cells pre-treated with SOD1-siRNA do not contain misfolded SOD1, implying that endogenous SOD1 is required as substrate for active conversion. Furthermore, transfection of TDP-43 into cells triggers its cleavage, mislocalization and hyperphosphorylation; these properties are not observed in untransfected cells incubated with conditioned media from TDP-43 transfected cells, further confirming that the transmission of SOD1 misfolding occurs independently of TDP-43. It is interesting to speculate that since nearly half of all FTD patients contain inclusion of TDP43 or FUS, there could be induced misfolding of endogenous SOD1, which may play a role in up to 15% of FTD patients which meet ALS criteria.

P.97 Neuronal endo-lysosomal trafficking defects in a *CHMP2B* mouse model of FTD

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Abstract: Charged multi-vesicular body protein 2B (CHMP2B) is part of the endosomal sorting complex required for transport-III (ESCRT-III), a large multimeric complex which is involved in endo-lysosomal trafficking and autophagy. Mutations leading to C-terminally truncated CHMP2B are responsible for causing familial frontotemporal dementia (FTD). We have previously reported that transgenic mice expressing mutant truncated CHMP2B show decreased survival, and formation of inclusions which are ubiquitin- and p62-positive, but tau- TDP-43- and FUS-negative, equivalent to the composition of the inclusions observed in CHMP2B mutation patients. Electron microscopy showed the presence of axonal swellings, which contained an accumulation of both autophagic and endosomal/lysosomal vesicles. These defects were not seen in transgenic mice expressing WT CHMP2B, or in Chmp2b knockout mice, suggesting that the defects seen in the mutant CHMP2B mice occur due to a gain of function mechanism. To further investigate the molecular mechanism by which C-terminal truncation of CHMP2B leads to neurodegeneration, we have cultured primary cortical neurons from CHMP2B transgenic mice. We have used a combination of fixed and live cell confocal imaging techniques to investigate components of the endo-lysosomal pathway. Live cell imaging of endo-lysosomal structure trafficking has revealed a defect in mutant CHMP2B cortical neurons, with a specific reduction in the motility of dendritic endo-lysosomes. These data implicate compromised endo-lysosomal trafficking in neurodegeneration caused by CHMP2B mutation.

P.98 Adapting microglial function by pharmacological modulation of the triggering receptor expressed on myeloid cells 2

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Abstract: The Triggering receptor expressed on myeloid cells 2 (TREM2) is a type-I transmembrane glycoprotein that is selectively expressed on microglia within the central nervous system (CNS). TREM2 functions to regulate the differentiation of a variety of myeloid cells and has been shown to modulate the phagocytic activity and inflammatory responses of microglial cells. Recently, TREM2 has been reported as a risk factor for several neurodegenerative diseases including Alzheimer's disease (AD) and frontotemporal dementia (FTD). Interestingly, even in sporadic AD and FTD patients the concentrations of soluble TREM2 (sTREM2) in the cerebrospinal fluids was significantly reduced. Furthermore, homozygous TREM2 missense mutations, which result in undetectable sTREM2 concentrations, lead to a FTD-like syndrome further strengthening the role of TREM2 in maintaining CNS homeostasis. In a proof of principle study we show a positive correlation of TREM2 cell surface expression with the phagocytic activity of microglial cells. We now report the establishment of a cellular assay used to quantify cell surface expression and sTREM2 generation. These assays were subsequently used in a drug screening effort using libraries of FDA-approved drugs and other known bioactive compounds. The identification of compounds that selectively and specifically enhance TREM2 activity without interfering with other essential signaling pathways will be a first crucial step towards new therapeutic strategies for neurodegenerative diseases like FTD.

P.99 A phenotypic screen of a mouse microglial cell line reveals novel mechanisms to modulate levels of progranulin

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FORUM Pharmaceuticals

Abstract: Mutations in the progranulin gene (GRN) result in progranulin (PGRN) haploinsufficiency and cause autosomal dominant familial frontotemporal lobar degeneration (FTLD-GRN). Pharmacological interventions that restore PGRN protein to normal levels are therefore a potential therapeutic strategy for disease modification in FTLD. A phenotypic assay was developed to monitor PGRN levels in a mouse microglial cell line, BV-2, in order to identify modulators of PGRN. A custom collection of compounds with known pharmacological activity targeting a wide spectrum of biological pathways was screened. Compounds that increased PGRN in either intracellular, extracellular, or both compartments were identified, and maps of discrete pathways were constructed. Active compounds were subsequently profiled in a dose response assay in primary mouse microglia, to validate that targeting such mechanisms may translate to therapeutic relevance in the brain. A subset of these screening hits was also shown to increase secretion of PGRN from primary neurons, while the activity of other compounds remained exclusive to microglia. Compound activities found to modulate PGRN levels included: cytoskeletal regulators, lysosomal alkalizing agents, cholesterol synthesis inhibitors, kinase inhibitors, and modulators of other signaling pathways. Our findings demonstrate that a phenotypic screen can yield insights into PGRN biology and regulation.

P.100 Depletion of cellular cholesterol levels results in increased progranulin secretion and altered progranulin glycosylation

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Abstract: Increasing net progranulin (PGRN) secretion is a potential therapeutic strategy for frontotemporal lobar degeneration (FTLD) caused by mutations in the granulin gene that result in PGRN haploinsufficiency (FTLD-GRN). A phenotypic screen was conducted to identify novel modulators of PGRN levels in a mouse microglial cell line, BV2 (see accompanying abstract). Two antifungal inhibitors of the enzyme lanosterol 14 alpha-demethylase, itraconazole and posaconazole, caused increased PGRN secretion in both BV2 cells and primary mouse microglia. Cholesterol supplementation reduced the effect of itraconazole and posaconazole on extracellular PGRN levels, suggesting that the observed increase in PGRN is indeed caused by depletion of cellular cholesterol levels. This was confirmed through depletion of membrane cholesterol by treatment with methyl-b-cyclodextrin, which caused an increase in secretion of PGRN in both BV2 cells and primary microglia. Posaconazole and bafilomycin A also caused altered migration of secreted PGRN by SDS-PAGE, which was determined to be due to differences in PGRN glycosylation. These data suggest that there is a pool of PGRN that is released under a variety of conditions including cholesterol depletion. While the biological activity of altered PGRN glycoforms has yet to be determined, further elucidation of signaling pathways or regulatory events that can promote release of this PGRN pool may present a novel therapeutic strategy for FTLD-GRN.

P.101 Investigating the role of filamin C as a novel player in the pathogenesis of FTLD-ALS spectrum disorders

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Abstract: Neuronal accumulation of the TAR DNA-binding protein 43 (TDP-43) is a pathological hallmark of patients with FTLD and ALS. TDP-43 is a multifunctional RNA-binding protein involved in multiple RNA-related processes including transcription and splicing regulation. Recently, an unexpected requirement for TDP-43 in vessel patterning and perfusion was found upon loss of both TDP-43 orthologs in zebrafish. Loss of TDP-43 also resulted in increased levels of Filamin C (FLNC), an actin cross-linking protein involved in cellular architecture and signaling, which was similarly observed in the frontal cortex of FTLD-TDP patients. To further elaborate the pathogenicity of FLNC in FTLD disease etiology, we performed a mutational screening of FLNC in the Belgian FTLD cohort using next-generation sequencing based on multiplex PCR panels developed with MASTR technology (www.multiplicom.com). Preliminary analysis of 179 patients of the Belgian FTLD cohort identified eleven loss-of-function missense mutations in FTLD patients that were absent in control individuals. In addition, we performed an FLNC expression analysis of FTLD patients with different genetic etiologies and found that elevated FLNC levels were mainly attributable to progranulin (GRN) haploinsufficiency. These results were confirmed in a Grn knock-out mouse model, providing a possible link between elevated FLNC levels and GRN loss with concomitant formation of TDP-43 pathology. Together, these findings suggest that aberrant FLNC expression is closely related to GRN deficiency in FTLD and might be an underlying disease mechanism in FTLD patients.

P.102 Ribosomal protein L11 mediated neuronal apoptosis

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Abstract: Impairments to nucleolar function have been implicated in several neurodegenerative diseases, including polyglutamine diseases and most recently in familial ALS caused by mutations in the C9ORF72 gene. In many systems including neurons cell death is a consequence of persistent nucleolar stress. While the p53 pathway appears to be the effector cell death pathway in neurons that are exposed to nucleolar stress, it is unclear what the signals that lead to its activation are. Here we report that shRNA mediated knockdown of ribosomal protein L11 blocked cortical neuron apoptosis in response to nucleolar stress. The protective effect was present when nucleolar stress was induced by knockdown of the RNA Polymerase-1 co-factor TIF1A or 5-Fluorouracil. Moreover, shRPL11 partially protected against apoptosis that was induced by the DNA damaging agents etoposide and camptothecin that are known to affect the nucleolus. Lastly, overexpression of RPL11 was sufficient to induce neuronal apoptosis. Taken together our data suggest that RPL11 is required for the neuronal cell death response to nucleolar stress.

P.103 Anti-inflammatory transforming growth factor β signaling increases microglial progranulin levels

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FORUM Pharmaceuticals

Abstract: Mutations in the granulin (GRN) gene result in progranulin (PGRN) haploinsufficency which causes frontotemporal dementia (FTD). Increasing PGRN levels in the CNS is a potential therapeutic strategy. Progranulin is expressed by both neurons and microglia in the CNS where it is believed to be a growth factor and inflammatory-mediator. It is currently unclear which signaling pathways are responsible for PGRN regulation in the CNS. We identified elements in the GRN promoter which are predicted to respond to transforming growth factor β (TGFβ). TGFβ is a growth factor and cytokine involved in inflammatory resolution and repair. We hypothesized that TGFβ signaling could increase PGRN levels, allowing for potential crosstalk of TGFβ and putative immune functions. We treated murine primary microglia with recombinant TGFβ1 resulting in a dose-dependent increase in secreted PGRN and a modest increase in intracellular levels, which was reversed with TGFβ inhibitors. Similarly, a small molecule TGFβ agonist induced a modest increase in secreted PGRN. The magnitude of the response was dependent on the activation state of the cells. A time course of TGFβ1 treatment revealed that the protein increase was delayed, thereby suggesting a transcriptional mechanism. Quantitative PCR revealed an increase in Grn transcript following TGFβ1 treatment. Our data link PGRN and TGFβ signaling, which supports the hypothesis that PGRN may play a role in regulating CNS inflammation. Selectively increasing TGFβ signaling in CNS microglia may provide a therapeutic approach for treating FTD-GRN.

P.104 *C9orf72* expression in amyotrophic lateral sclerosis and frontotemporal dementia

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Abstract: GGGGCC repeat expansions in the C9orf72 gene are a common cause of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD) and ALS-FTD. Haploinsufficiency caused by loss of expression from the mutant allele has been proposed as a potential disease mechanisms. C9orf72 isoform-specific gene expression analysis with quantitative and digital PCR was performed to study C9orf72 expression in brain and blood and to assess any associations with disease parameters. In brain and blood samples no significant difference in total C9orf72 expression was observed between patients carrying GGGGCC expansions and controls. Repeat expansion carriers showed an altered transcript preference with reduced V2 ratios, but elevated V3 ratios. Aging reduced total C9orf72 expression from healthy individuals, while total C9orf72 expression tended to increase with age in repeat expansion carriers. In sporadic ALS and FTD an age-independent elevation in C9orf72 expression was observed. Lower C9orf72 levels were associated with increased survival in sporadic ALS patients. Interestingly, the C9orf72 V3 transcript, which is elevated in GGGGCC expansion carriers and gives rise to RNA foci and dipeptide repeat proteins, was inversely correlated with survival. Our findings indicate that GGGGCC expansions do not significantly affect total C9orf72 transcript levels. The abundance of V2 is reduced, whereas the expression of the V3 transcript containing the expanded GGGGCC repeats is enhanced. V3 correlated negatively with survival. Our findings indicate that C9orf72 expression is an age-independent blood marker of sporadic ALS and FTD and higher C9orf72 levels are associated with a survival disadvantage in sporadic ALS patients.

P.105 Colocalization of HDAC6 and TDP-43 in heat stress evoked stress granules in patient derived EBV-transformed B lymphocytes

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Abstract: In earlier studies we showed that immortalized patient B lymphocytes can be used to examine TDP-43 translocation after heat stress and localization to stress granules as determined by double staining with TIA-1. Because there is evidence for an involvement of the histone deacetylase (HDAC) 6 in cytoplasmic TDP-43 accumulation and stress granule regulation we aimed in the present study to determine if HDAC6 can be analyzed in B cells of patients with and without TDP-43 mutation. Three B cell lines from a familial ALS patients TDP-43-G348C mutation, from a sporadic ALS patients without TDP-43 mutation and from a healthy control person were heat-stressed, allowed to recover for 5h and then subjected to ICC or Western Blot. Colocalization of TDP-43, TIA-1 and HDAC6 was determined by confocal laser microscopy. We found that the control line is characterized by increased HDAC6 and TDP-43 colocalization after recovery from stress, while the Pearson's coefficient are almost the same for TIA-doublestaings. Cells from the patient with sporadic ALS do not show a colocalization of TDP-43 and HDAC6 but an increase in the coefficient for TDP-43 and TIA-1. In contrast, the cells from the patient with TDP-43 mutation exhibit a colocalization of HDAC6 and TIA-1 after recovery from stress. These data point to differences in the processing of stress in B cells dependent on TDP-43. Analysis of larger B cell line numbers and different TDP-43 mutations will be the next step as well as the recapitulation of the experiments in untransformed patient B lymphocytes.

P.106 Characterizing molecular pathogenesis in early *C9orf72* associated FTD

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Abstract: A GGGGCC hexanucleotide repeat expansion in the non-coding region of C9ORF72 is the most frequent known genetic cause of frontotemporal dementia and amyotrophic lateral sclerosis. Disease onset is usually in midlife, but age at onset and disease duration are variable, even within a single family. Multiple pathogenic mechanisms have been proposed, including loss of protein expression, accumulation of repeat containing mRNA foci, aggregation of proteins generated by abnormal repeat associated non-ATG (RAN) translation, and TDP-43 aggregation. We studied two unique patients with C9ORF72 expansion. Case 1 is a 65 year old woman with bvFTD who showed minimal focal degeneration in subgenual anterior cingulate cortex, medial pulvinar nucleus of thalamus, and amygdala. In these and other regions, RAN translated protein aggregates and RNA foci were abundant, whereas TDP-43 pathology ranged from scarce to absent. Case 2 is a 74 year old woman with FTLD-TDP type B who suffered severe head trauma during childhood and developed refractory epilepsy in her 50s. Left anterior temporal lobectomy and amygdalohippocampectomy was performed at age 61 with remittance of seizures and full cognitive recovery. By age 66, she developed non-epileptic spells followed by progressive behavior, language, and visuospatial decline. RAN translated protein aggregates and RNA foci but not TDP-43 inclusions were present in the surgically resected temporal lobe, whereas well-developed TDP-43 pathology was seen at autopsy 13 years later. In conclusion, TDP-43 inclusion formation may not be necessary for degeneration in C9ORF72 mutation carriers, and C9ORF72-specific pathological phenomena occur prior to symptom onset and TDP-43 aggregation.

P.107 Induction of DNA double-strand breaks mimics FTLD-FUS neuropathology

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Abstract: Fused in Sarcoma (FUS) is a multi-functional RNA/DNA binding protein. FUS is a member of the FET protein family including EWS and TAF15. FET proteins are primarily nuclear, where they bind RNA and DNA to modulate transcription, mRNA splicing, and DNA repair. In ALS cases with FUS inclusions (ALS-FUS), mutations in the FUS gene cause disease, whereas FTLD cases with FUS inclusions (FTLD-FUS) do not harbor FUS mutations. Notably, in FTLD-FUS, all FET proteins accumulate with their nuclear import receptor Transportin 1 (TRN1). ALS-FUS inclusions are exclusively positive for FUS. It is unclear what causes disease in FTLD-FUS and the mechanism causing FET proteins to accumulate exclusively in this disease. We find that induction of DNA double-strand breaks (DSBs) cause the FET proteins to accumulate in the cytoplasm and become highly phosphorylated. Intriguingly, oxidative DNA damage and DNA single-strand breaks do not cause phosphorylation or cytoplasmic redistribution of FET proteins. Additionally, we find that endogenous FUS in mouse neurons does not respond in the same fashion to DSBs compared to human neurons or glia. These findings suggest that DSBs may be the initiating factor that causes FTLD-FUS. Research to identify environmental or genetic factors in FTLD-FUS that may cause DSBs is ongoing. Finally, we find the mouse CNS does not accurately reflect the biology of human FET proteins or the DNA damage response. Thus, primates or human iPS-derived neurons may be better models for studying the function of FUS, pathogenesis of FTD sub-types, and for drug discovery.

P.108 Thr175 phosphorylated tau induces pathological fibril formation via GSK3β mediated phosphorylation of Thr231 in vitro

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Abstract: We have previously demonstrated that amyotrophic lateral sclerosis with cognitive impairment (ALSci) is associated with pathological inclusions of microtubule associated protein tau (tau) phosphorylated at Thr175 (pThr175) and that pThr175 is associated with increased GSK3β activation in vivo. We have examined whether the presence of pThr175 leads to the activation of GSK3β and phosphorylation of Thr231 as a determinant of pathological fibril formation. Neuro2A cells were transiently transfected with wild-type (WT) GFP-tagged 2N4R tau or one of 2 mutant constructs: pseudophosphorylated (Thr175Asp) or phosphorylation inhibited (Thr175Ala). GSK3β activation was examined by western blotting for phospho-GSK3β (Tyr216) and normalized by densitometry to total GSK3β and GFP-tagged tau expression. Live cell confocal imaging was conducted for fibril quantification. Cell death was assessed by MTT and Trypan blue assays. 72 hours post transfection, GSK3β activation was increased, along with fibril formation and cell death in Thr175Asp transfected cells relative to WT and Thr175Ala tau. Treatment with each of 4 GSK3β inhibitors (LiCl, AR-A014418, TWS-119, Tideglusib) or shRNA knockdown of GSK3β decreased fibril formation and cell death to baseline levels. Inhibition of phosphorylation at Thr231 (Thr231Ala) prevented pathological fibril formation in response to Thr175Asp. Pseudophosphorylation and inhibition of Ser235 phosphorylation had no effect on Thr175Asp fibril formation, indicating an unprimed mechanism of Thr231 phosphorylation. We conclude that pThr175 induces GSK3β-mediated phosphorylation of Thr231 leading to pathological fibril formation, suggesting a potential therapeutic avenue for the treatment of ALSci.

P.109 Progranulin transcripts with short and long 5'-UTRs are differentially expressed via translational repression

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Abstract: Haploinsufficiency of progranulin (GRN) is a major genetic cause of Frontotemporal lobar degeneration (FTLD) associated with TAR DNA-binding protein of 43 kDa (TDP-43) deposition. Therefore understanding the mechanisms, which control cellular expression of GRN, is required not only to understand disease etiology but also for the development of potential therapeutic strategies. We identified different GRN transcripts with short (38-93 nucleotides) or long (219 nucleotides) 5'-untranslated regions (UTR) and demonstrate a cellular mechanism, which represses translation of GRN mRNAs with long 5'-UTRs. The long 5'-UTR of GRN mRNA contains an upstream open reading frame (uORF), which is absent in all shorter transcripts. Since such UTRs can be involved in translational control, we compared the expression of GRN mRNA with long, short or no 5'-UTRs. Our investigation revealed a selective repression of GRN translation by the 219 nucleotide long 5'-UTR. The specific ability of this GRN 5'-UTR to repress protein expression was further confirmed by its transfer to a reporter. Mutagenesis of the two AUG codons within one uORF rescues translational repression. These findings suggest uORF-dependent mechanism, which leads to reduced initiation of translation of the GRN protein. As shown by an in frame fusion of the uORF and GFP, ribosomes can initiate at both uORF-AUG codons, which might result in stalled ribosomes or in impaired re-initiation at the downstream start codon. "Leaky" initiation at the uORF might allow a fraction of ribosomes to reach the downstream AUG and translate low levels of GRN.

P.110 The effects of progranulin depletion on neuronal cell lines

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Abstract: Haploinsufficiency of GRN with concomitant loss of 50% of PGRN protein levels causes frontotemporal lobar degeneration (FTLD). PGRN-mediated neurodegeneration belongs to the TAR-DNA binding protein-43 (TDP-43) proteinopathies. To investigate how PGRN influences neuronal biology we used immortalized NSC34 neuronal cells to establish lines that stably over-express human PGRN (NSC34-PGRN) or have depleted PGRN (NSC34-SHPGRN) or control cells that express vector only. The PGRNshRNA constructs result in approximately 40-60% reduction of endogenous PGRN levels, similar to that seen in GRN haploinsufficient FTLD neurons. High progranulin expressors, (NSC34-PGRN) show greater cell body area, a flattened shape and have longer neuritic extensions compared to the controls. NSC34-SHPGRN cells have a rounded cell body, multiple shorter neuritic extension and long, tortuous flattened processes that appear to be failed neurite extensions. Thus PGRN dramatically influences cell morphology and cytoskeleton. RNA was subjected to Illumina MouseWG-6 v2.0 Expression BeadChip microarray analysis. Genes showing statistically significant changes in expression were identified by Flex array analysis, and selected genes expressions confirmed by qRTPCR and Western blot. The microarray analysis identified altered expression of regulatory genes (GAPS and GEFs) in the Rho-Rac-CDC42 cytoskelatal rearrangement pathways. These changes may contribute to the morphological defects of NSC34-SHPGRN cells. Gene networks were analyzed using the Ingenuity Pathway Analysis software. The most statistically significant alterations in gene networks in the NSC34-SHPGRN cells are linked to neurological disease. Other pathways that are altered by low PGRN levels are associated with synaptic structure and function, and calcium ion channels, lipid/sterol metabolism, and histone activity.

P.111 Targeting tau-mediated NMDA receptor hypofunction corrects abnormalities in a mouse model of frontotemporal dementia

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Abstract: Frontotemporal dementia (FTD) is a rapidly progressive and lethal disease, with no effective treatments. It is known that tau mutations cause FTD, but the underlying neurobiology is undefined. We sought to identify how tau affects the neurobiology in order to find potential treatment targets. Here, we address this question using a mouse model expressing human tau with an FTD-associated mutation (V337M). We studied behavior, physiology, biochemistry, and neuropathology in several cohorts of mice at different ages. These mutant tau mice had abnormal repetitive behavior characteristic of FTD and synaptic deficits selectively in regions associated with FTD (ventral striatum and insula). There, mutant tau depleted PSD-95, resulting in smaller PSDs and fewer synaptic glutamate receptors, including NMDA receptors (NMDAR). Recordings from ventral striatum neurons revealed deficits in NMDAR-mediated synaptic transmission, resulting in impaired network activity. Pharmacologically targeting NMDAR hypofunction in vivo with cycloserine, an FDA-approved NMDAR co-agonist, reversed network impairments and repetitive behavior. These results indicate that mutant tau impairs NMDAR trafficking, causing NMDAR hypofunction in vulnerable brain regions, and that this process can be therapeutically targeted. These findings have important treatment implications, including the possibility of repurposing cycloserine for treating FTD.

P.112 Investigating molecular mechanisms of VCP/p97 associated neurodegeneration through patient induced pluripotent stem cells and neurons

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Abstract: Mutations in Valosin-containing protein (VCP, also known as p97) lead to inclusion body myopathy, Paget's disease of the bone and frontotemporal dementia (IBMPFTD, Watts et al 2004)) as well as amyotrophic lateral sclerosis (ALS, Johnson et al 2010). VCP is a widely expressed AAA+ ATPase with roles in multiple pathways including protein turnover and degradation, mitochondrial function and stress granule formation. Cell models that allow VCP mutations to be studied in the context of human neurons will be a useful tool for the study of disease mechanisms and the screening of novel therapeutics. We have generated induced pluripotent stem cells (iPSCs) from two patients with the disease-linked mutations R155C and R191Q in VCP. These cells were fully characterised for expression of pluripotency factors, karyotype stability and lack of transgene integration. VCP and control iPSC were differentiated into cortical glutamatergic neurons, characterised by the expression of the deep layer markers TBR1 and upper layer marker SATB2.Investigations into mitochondrial biology, stress granule clearance and DNA damage repair are currently underway to define VCP-linked phenotypes in the mutant cells. A better understanding of the cellular mechanisms of VCP-driven neurodegeneration will not only enhance our understanding of disease progression (in neurons and other tissues), but also help define therapeutic targets in the future. Linking VCP mutations with other gene defects that lead to FTD, may help define a common pathway and a better understanding of the disease as a whole.

P.113 Generation of cell culture models for investigating disease mechanisms in C9orf72 frontotemporal dementia and amyotrophic lateral sclerosis

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Abstract: Frontotemporal dementia (FTD) is a neurodegenerative disorder characterised by progressive defects in behaviour, language and personality, which exhibits concomitance with amyotrophic lateral sclerosis (ALS), a disease typified by motor neuron degeneration, muscular atrophy and loss of voluntary movement. A GGGGCC repeat in the first intron of C9orf72 is expanded in patients, and is the most common known genetic cause of familial FTD and ALS. Repeats are transcribed in both sense and antisense directions and aggregate into RNA foci, which sequester RNA-binding proteins. Additionally, expanded repeats initiate repeat-associated non-ATG (RAN) translation, forming potentially toxic dipeptide repeat (DPR) proteins. To investigate these RNA and DPR protein gain-of-function mechanisms, we generated a range of different length repeat constructs up to 103 repeats. We also generated 'RNA-only' constructs with interruptions containing stop codons in all sense and antisense reading frames within the repeat sequence, preventing all RAN translation. The increased stability of these constructs allowed 1152 repeats to be maintained. Pure and 'RNA-only' constructs exhibit length-dependent formation of sense and antisense RNA foci when expressed in neuroblastoma cells, with equivalent length constructs forming RNA foci to the same extent. In addition, constructs encoding all five DPR proteins were made using alternative codons, yielding DPR protein when expressed, but no RNA foci. These constructs provide important tools for dissecting the relative roles of RNA and DPR protein gain-of-function pathologies within C9orf72 ALS/FTD.

P.114 Stem cell models of *C9orf72*-linked frontotemporal dementia

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Abstract: The expanded GGGGCC repeat in an intronic region of C9orf72 is the most common genetic cause of Frontotemporal Dementia and Amyotrophic Lateral Sclerosis. Recent studies show a role of expanded RNA and dipeptide aggregates as pathological features, supporting a toxic gain of function disease mechanism, while others show that loss of C9orf72 function can also lead to disease. In our effort to understand the underlying disease biology, we are studying cortical neurons from patient-derived induced pluripotent stem cells (iPSC). iPSC were differentiated into cortical neurons using a dual SMAD inhibition protocol followed by an extended period of in vitro neurogenesis. Cortical identity was confirmed by immunofluorescence to both deep layer (Tbr1) and upper layer (Satb2) markers. To generate a neuronal model for C9orf72 haploinsufficiency, we have generated CRISPR constructs to disrupt we have targeted exon 2 of C9orf72 gene thus creating a functional C9orf72 knock-out iPS cell line. The temporal expression and splicing of C9orf72 has been investigated by analysis of C9orf72 protein and RNA levels throughout cortical development in both control and patient-derived neurons. Studying these stem cell models will increase our understanding on C9orf72 function as well as its role in Frontotemporal Dementia pathogenesis.

P.115 Problems and solutions when analyzing tau pathology in mice models of FTD

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Abstract: Aggregates of hyperphosphorylated tau protein are found in a group of diseases called tauopathies, and are present in about 50% of Frontotemporal dementia (FTD) cases. In FTD, the causes and consequences of tau hyperphosphorylation and aggregation are not well understood and are often investigated in laboratory animals. Mice are the models of choice as they are easily amenable to transgenic technology. However, the analysis of tau pathology in mice poses unique challenges not always obvious to tackle. Here, we address the problems inherent to the analysis methods, from immunohistochemistry, to analysis of insolubility and to Western blots, and illustrate how each of them can be a source of false results. We show that paraformaldehyde is a poor fixative for tau (except when aggregated), and that other methods of fixation are preferable. We also show that the different methods of isolation of insoluble tau are not always reliable. Moreover, we demonstrate that when analyzing tau by Western blotting with some mouse monoclonal anti-tau antibodies, strong unspecific signals due to the endogenous immunoglobulins can interfere with genuine tau signal. We propose the use of secondary antibodies light-chain specific or specific to non-denatured immunoglubulins to avoid this important source of false results. Lastly, we show that the physiological parameters of the mice such as temperature, can be a source of experimental artifacts. As there is an increasing interest about tau, we hope that this work will help the community avoid common pitfalls when analyzing tau pathology, especially in mice models of FTD.

P.116 A new inducible transgenic mouse model for *C9orf72* linked ALS and FTD

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Abstract: Frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) are two devastating neurodegenerative disorders that share clinical, genetic and pathological overlap. A hexanucleotide repeat expansion in the C9orf72 gene was identified as a frequent cause of FTD and ALS (Renton et al., 2011; DeJesus-Hernandez et al., 2011). Since then, many different theories about the possible pathogenic mechanisms of this repeat have been proposed, including haploinsufficiency leading to a loss of function of the endogenous C9orf72 protein product, RNA toxicity caused by the sequestration of RNA-binding proteins or production of toxic dipeptide repeat proteins (DPR) by non-ATG initiated translation (RAN) of the repeat. To investigate the RNA gain-of-function mechanism in vivo, we generated a new inducible mouse model for the C9orf72 repeat expansion. We will show the first characterization of this mouse model. This mouse exhibits 80 GGGGCC repeats, is doxycycline(dox)-inducible and expresses GFP in different tissues of the body upon 12 weeks of dox administration. Our model shows ubiquitin-positive inclusions, which is a pathological hallmark of C9orf72 ALS and FTD patients.

P.117 Transgenic mice expressing a pathological variant of TDP-43 develop neurodegenerative and behavioral phenotypes characteristic of FTD

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Abstract: Abnormal alternative splicing and downstream translation initiation generates a pathological variant of TDP-43, called TDP-35, in FTLD/ALS. TDP-35 is a component of TDP-43 positive inclusions, and causes neurotoxicity when expressed ectopically in primary neurons. To explore the contribution of TDP-35 to disease pathogenesis, we generated transgenic mice expressing TDP-35 under the control of the hamster prion promoter. A prominent pathological finding was the presence of large, aggregate-like accumulations of TDP-35 in neuronal cytoplasm accompanied by a loss of endogenous TDP-43 in specific neuronal populations. Despite broad neuronal expression of TDP-35 throughout all regions of the brain, age-dependent neuronal loss and associated neuroinflammation were observed only in selectively vulnerable brain regions: the amygdala, entorhinal cortex, and hippocampus, which are in consensus with the regions most affected with TDP-43 pathology in FTLD brains. Behavioral testing using novel object recognition, Barnes maze, and cued and contextual fear conditioning indicated the presence of an age-dependent decline of non-spatial memory and cued memory, while spatial memory remained intact. This selective cognitive phenotype mimics the presence of emotional and behavioral abnormalities and the absence of spatial deficits in FTD patients. In conclusion, we have generated a transgenic mouse model that recapitulates the progressive neuronal loss, some aspects of the neuropathological features, and selective behavioral deficits reminiscent of FTD. This mouse model may be useful for investigating disease mechanisms underlying FTD and for testing therapeutics aimed at improving cognition in FTD.

P.118 *C9orf72*-associated nucleolar stress is caused by dipeptide repeats

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Abstract: The wild type C9orf72 gene contains a hexanucleotide (GGGGCC) sequence in the first intron, expansion of which is a common cause of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). The expansions, typically limited to around 30 repeats in healthy controls, can range into the thousands in FTD and ALS patients. The mechanism of disease is still a focus of major investigation for the FTD-ALS community. RNA foci have recently been pinpointed as a cause of nucleolar stress in cells containing C9orf72 repeat-expansions (CRE). Meanwhile, it has been shown that aberrant proteins are translated from the CRE RNA via an ATG-independent mechanism producing five different dipeptide repeat proteins (DPRs). To address the effect of CRE-generated proteins we produced expression constructs bearing C9orf72 DPRs of varying length using alternative codons in a randomized fashion. This produces the DPRs without repetitive RNA. This study focuses on the affect of the arginine-rich dipeptide repeats of proline-arginine (PR) and glycine-arginine (GR). Transfection of both GR and PR DPRs in T98G cells leads to expression purely in the nucleolus (PR) and nucleolus and cytoplasm (GR) and produces a nucleolar stress phenotype. These data suggest that arginine rich DPRs contribute directly to nucleolar stress in the absence of toxic RNA.

P.119 Loss of progranulin leads to lysosomal abnormalities

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Abstract: Heterozygous loss-of-function mutations in the progranulin (GRN) gene cause GRN haploinsufficiency and increase the risk for developing frontotemporal lobar dementia (FTLD) with TAR DNA-binding protein (TDP) -43 inclusions. Strikingly, a complete loss of GRN leads to a lysosomal storage disease, an adult variant of neuronal ceroid lipofuscinosis (NCL). Brains of Grn knockout mice show some features of FTLD pathology such as pathological phosphorylation of TDP-43, but also an age dependent increase of lysosomal proteins. We have now investigated whether the accumulation of the lysosomal membrane protein TMEM106B, a risk factor for FTLD-TDP associated with GRN mutation carriers, is CNS specific. In addition, the increase of lysosomal proteins cathepsin D and Lamp1 as well as a typical storage component in NCL patients, namely saposin D was examined regarding tissue specificity. Preliminary results show a tissue dependent change of expression levels for most analyzed proteins in Grn knockout mice. To understand if clearance and endocytosis of GRN is responsible for the observed lysosomal phenotypes, we investigated Sortilin (SORT1) mediated lysosomal transport of GRN. Analysis of the Sort1 knockout mouse brain failed to reveal altered levels of lysosomal proteins like TMEM106B, cathepsin D and Lamp1. These findings suggest that reduced endocytosis and lysosomal transport of GRN is not the major pathway responsible for the accumulation of lysosomal proteins. However, the accumulation of lysosomal proteins in the Grn knockout mouse suggests that GRN may play a role in the integrity and function of lysosomes in brain tissue.

P.120 Modelling *C9orf72* loss of function

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Abstract: The GGGGCC intronic repeat expansion within C9ORF72 is the most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Reduced C9ORF72 protein levels and diminish expression of c9orf72 mRNA has been observed by several groups. Although the mutation may also cause a toxic gain of function, these results suggest a protein loss of function mechanism. To investigate the role of C9ORF72 haploinsuffiency in ALS and FTD disease pathogenesis, we have generated C9ORF72 knock-down mice by targeting the RNA mouse homologous of C9ORF72. In this study, we showed that C9ORF72 knock-down mice display increased depression-like behavior, as well as deficits in social recognition from a relatively young age. The C9ORF72 deficient mice do not present impaired spatial learning and memory loss in the Morris water maze. Thus, C9ORF72 deficiency induced FTD-like behavioral deficits. This phenotype is consistent with the behavioural symptoms observed in patients. While further histological and molecular characterization is still in progress, these mice may serve as an important tool for deciphering underlying mechanisms in C9 ALS/FTD.

P.121 Using C. elegans to understand frontotemporal dementia

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Abstract: Understanding pathogenic mechanisms causing frontotemporal dementia (FTD) has been a difficult journey. While many cases are reported with aggregates of TDP-43 or FUS protein, only a small fraction of the cases are linked to genetic mutations in MAPT, GRN, C9ORF72 or VCP. The link between the aggregated proteins and the genetic causes of FTD is still an unresolved question in the field. Interestingly, TDP-43, FUS, GRN, MATP, C9ORF72 and VCP all have orthologues in the nematode C. elegans. Our laboratory aims to understand the function of these genes and their impact on neurodegeneration using simple genetic models. We have developed several models to study these genes among which we have characterized loss of function mutants to understand the impact of a loss of expression of GRN and C9ORF72 and we have developed a model based on the transient RNA expression of a pathogenic GGGGCC repeat. Using theses models, we aim to identify genetic interactions among these genes and other FTD and ALS genes. We are also conducting a drug screening to identify molecules specifically targeting the motility defect caused by the loss of function of C9ORF72 in worms. We believe that using these models we could unravel pathogenic pathways related to FTD and identify new therapeutic avenues. An update of our work will be presented.

P.122 The poly-glycine-alanine RAN-Translation product of the *C9orf72* expansion mutation forms toxic insoluble peptides

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Abstract: The most common genetic cause of both Frontotemporal Dementia (FTD) and Amyotrophic Lateral Sclerosis (ALS) is a hexanucleotide repeat expansion in a non-coding region of C9ORF72. The cellular mechanism of disease was primarily suggested to be an RNA-mediated toxicity resulting from the formation of intranuclear inclusions called RNA foci. Recently, these non-coding repeat expansions were found to produce long homopolymeric dipeptides through a novel mechanism called Repeat-Associated Non-ATG Translation (RANT). In diseased patient brains, these RANT products form insoluble neuronal aggregates that colocalize with p62 pathology. However, it remains to be determined if these RANT peptides actually initiate neuronal toxicity or have a secondary role in disease pathogenesis. Here we show that only one of the possible RANT products of the C9ORF72 repeat expansion, Glycine-Alanine (GA), forms high-molecular weight, detergent-resistant aggregates when overexpressed in 293T cells. Expression of this poly-GA peptide in human induced pluripotent stem cell-derived neurons also formed insoluble cytoplasmic inclusions that impaired neuronal physiology. Furthermore, these poly-GA inclusions induced and colocalized with p62 pathology. TDP-43 inclusions were also induced but did not colocalize with the poly-GA aggregates, reflecting the pathology seen in -C9ORF72--related FTD/ALS. Although our results do not rule out the possibility of RNA-toxicity, they suggest the RANT products alone, particularly poly-GA, have the ability to disrupt neuronal function and recapitulate some of the pathology seen in diseased human brains. It follows then that C9ORF72 repeat expansion may contribute to disease similarly as other neurodegenerative disorders, through the production and accumulation of insoluble toxic peptides.

P.123 Neurons directly converted from fibroblasts of c9ALS/FTD patients recapitulate pathology seen in the brain

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Abstract: The discovery of an expanded non-coding GGGGCC repeat expansion in the c9orf72 gene as the most common genetic cause of ALS and FTD (c9ALS/FTD) spurred the recent development of novel cellular and animal models recapitulating key disease features. However, the majority of models currently available have limitations. For example, overexpressing the expansion produces two disease hallmarks, RNA foci formation and repeat-associated non-ATG (RAN) translation, but not reduced expression of c9ORF72 mRNA and protein as seen in c9ALS/FTD patients. Potentially important events resulting from the expansion of the repeat within genomic DNA may be not present in the overexpression models. Moreover, it is technically difficult to clone a repeat sequence that would be similar in length to those observed in patients. To overcome such challenges, we present a method to transdifferentiate patients` dermal fibroblasts using a previously published vector encoding short hairpin RNA targeting polypyrimidine-tract-binding protein 1 (PTB1). PTB1 has been shown to inhibit neuronal differentiation triggered by miR-124 resulting in a cascade involving proneuronal alternative splicing events. We developed a protocol for a 2-week direct conversion of dermal fibroblasts to functional, induced neurons (iNeurons). The iNeurons generated from c9ALS/FTD patients formed more intranuclear RNA foci than fibroblasts and expressed RANT products (not detected in the parental fibroblasts). Moreover, we tested antisense short oligonucleotides (ASOs) targeting the pathogenic GGGGCC expansion in these cells and observed significant reductions in RNA foci, RANT product accumulation and cell toxicity. Taken together, our studies suggest iNeurons provide a fast and efficient tool for screening therapies.

P.124 Developmental expression of frontotemporal dementia protein C9orf72 in vivo and in vitro

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Abstract: A hexanucleotide repeat expansion in a non-coding region of the C9ORF72 gene is the most common genetic cause of frontotemporal dementia. It is unclear how this mutation causes disease and the encoded protein, C9ORF72, is currently uncharacterised. To provide insight into possible roles, we examined the protein expression and cellular localization of C9ORF72 over a developmental time-course. In vitro, primary neuron and glia cultures were derived from embryonic (E) and postnatal (P) mice, grown over a time-course of 1, 3, 7 14 and 21 days. In vivo, brains were harvested from mice at ages E15, E18, P1, P7, P14, P28 and P56. Immunolabelling and Western blotting were then performed. C9ORF72 was present in neurons and glial cells (microglia and oligodendrocytes) and had punctate expression. C9ORF72 was predominantly cytoplasmic at younger time-points and became more nuclear in specific cell populations from 7 days in vitro and P7 in vivo. In vitro it localized to discrete vesicles, present throughout the cytoplasm, axons and dendrites, and extended beyond the microtubule cytoskeleton into actin-rich structures. C9ORF72 was not localized to golgi apparatus or mitochondria but shared some co-localization with components of the endosome/lysosome system. It rarely co-localised with synaptic markers. Western blotting analysis demonstrated that total protein levels did not differ significantly over either time-course. These data suggest that C9ORF72 is a vesicular and nuclear protein, expressed throughout development and into adulthood. Determining the normal role of C9ORF72 protein may help to determine the role it plays in disease.

P.125 *C9orf72* repeat expansions cause neurodegeneration through arginine-rich proteins

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Abstract: A non-coding repeat expansion in C9orf72 is the most common genetic cause of frontotemporal lobar degeneration and amyotrophic lateral sclerosis. The mutation may lead to neurodegeneration through loss of C9orf72 protein, or gain-of-function mechanisms. Novel species emanating from the expanded repeat include repeat RNA, which forms frequent neuronal RNA foci that may sequester important RNA-binding proteins, and dipeptide repeat (DPR) proteins generated by repeat-associated non-ATG (RAN) translation. The GGGGCC repeat can be translated in all six sense and antisense frames, producing five different DPR proteins. A fundamental question is whether the repeat RNA itself is toxic or whether toxicity is driven by dipeptide repeat (DPR) proteins. To address this question we developed in vitro and in vivo models that allowed dissection of repeat RNA and DPR protein toxicity. 'RNA-only' repeats were generated with interruptions containing stop codons in all sense and antisense frames within the repeat sequence, which prevented RAN translation. Expression of 36 and 103 pure repeats in Drosophila caused striking adult-onset neurodegeneration that was ameliorated by inhibition of protein synthesis with cycloheximide. In contrast, 36 and 108 'RNA-only' repeats did not cause neurodegeneration, indicating that pure repeats cause neurodegeneration through DPR proteins. To assess whether DPR protein expression alone is sufficient for toxicity 'protein-only' constructs were generated using alternative codons to those found within the GGGGCC repeat. Only poly-(glycine-arginine) and poly-(proline-arginine) DPR proteins resulted in neurodegeneration and decreased survival. These data provide evidence that C9orf72 expanded repeats cause neurodegeneration specifically through neurotoxic arginine-containing DPR proteins.

P.126 Alanine-rich repeat dipeptides arising from the *C9orf72* expansion form cytoplasmic inclusions in a cellular model of FTD/ALS

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Abstract: A hexanucleotide repeat expansion in a non-coding region of C9ORF72 has been identified as the most common cause of both frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). However, the pathogenesis of FTD/ALS remains unclear. There are three potential mechanisms through which the expansion may cause neurodegeneration: (i) C9ORF72 haploinsufficiency, (ii) production of toxic RNA and (iii) translation of toxic peptides from the expansion through repeat-associated non-ATG translation (RAN-translation). Immunohistochemical analysis of post-mortem FTD/ALS tissue shows that five dipeptide repeat proteins (DPRs) are translated from the expansion region in patients. One such peptide, glycine-alanine (GA) has been shown to form inclusions within the cytoplasm of neurons in cerebellar and hippocampal patient tissue. We have used alternative codon sequences to generate less repetitive constructs for each DPR, thus allowing us to express GA in cells without the production of repetitive toxic RNA. Therefore we can assess the individual role of GA peptide in disease pathogenesis. GA forms cytoplasmic inclusions when expressed in T98G cells, which closely resemble the inclusions observed in patient tissue. GA inclusions co-localise with p62, ubiquitin and ubiquilin-2, important components of protein degradation systems within the cell. Our findings demonstrate that our cellular model of DPR pathology is comparable to human disease, thus validating this system as a useful tool to study the role of DPRs in FTD/ALS pathogenesis. Furthermore, our results suggest a relationship between DPR generation and impaired protein degradation systems, which may play a role in the pathogenesis of C9ORF72-linked FTD/ALS.

P.127 Regulation of synapse growth in a fly model for frontotemporal dementia: *Rab8* mutants reveal roles for 'Plenty-of-SH3s' and TAK1

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Abstract: Formation and growth of synaptic connections are highly dynamic process. How signals driving synaptic elaboration are regulated during neurodegenerative processes remains unclear. We identified mutations in Rab8 in a genetic screen for enhancement of a frontotemporal dementia (FTD) phenotype associated with ESCRT-III (CHMP2B) dysfunction. Examination of Rab8 mutants or motorneurons expressing a mutant ESCRT-III subunit, CHMP2BIntron5, at the Drosophila neuromuscular synapse reveal synaptic overgrowth and endosomal dysfunction. Expression of Rab8 rescues an excessive TGF-ß signaling and synaptic overgrowth phenotype generated by CHMP2BIntron5. In CHMP2Bin5 expressing and Rab8 mutant synapses, JNK/AP-1 and TGF-ß signaling are excessively activated and act synergistically to potentiate synaptic growth. We identify novel roles for the endosomal JNK-scaffold Plenty-of-SH3s (POSH) and a JNKKK, TAK1, both normally involved in innate immune and pro-apoptotic responses, in regulating excessive growth activation. Our data uncover Rab8 and POSH as regulators of synaptic growth responses and reveal that POSH coordinates, at the endosome, JNK/AP-1 and TGF-ß signaling to achieve synapse elaboration. We suggest that these signaling events contribute to neuronal dysfunction in FTD caused by CHMP2Bin5 mutations.

P.128 MicroRNA-132/212 deletion in mice recapitulates neuropathological features of FTLD-Tau

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Abstract: Tau-positive inclusions are observed in approximately 40-45% of FTD cases (FTLD-Tau). Despite intensive research, the underlying mechanisms involved in tau metabolism dysregulation remain unclear. Recently, we and others have shown that the microRNA-132/212 cluster is strongly downregulated in FTLD-Tau brain. The small regulatory microRNAs function are key mediators of brain function and provide a novel basis for the understanding complex neurodegenerative disorders. In this study, we evaluated the effects of miR-132/212 deletion on tau expression, phosphorylation, and aggregation in vivo in mice. By Western blot analysis, we observed a significant increase in endogenous tau expression starting from P16 and until adulthood in miR-132/212 knockout (KO) mice. Using reporter assays and cell-based studies, we identified a functional miR-132 binding site within the tau 3' untranslated region, providing a mechanism for the abnormal regulation of tau expression. Starting at 6 months of age, tau becomes hyperphosphorylated at several pathological epitopes (e.g., S422). At the age of 12 months, hyperphosphorylated tau was found in (sarkosyl) insoluble aggregates. Notably, similar results were obtained in miR-132/212 KO mice expressing human Tau P301L. Both biochemical and electronic microscopy analyses showed that miR-132/212 deficiency induced age-dependent changes in autophagy, as seen in FTD patients, which could explain in part the observed effects on tau aggregation. Collectively, these results provide strong evidence that loss of miR-132/212 function in the brain could contribute significantly to FTD neuropathology in a subset of patients.

P.129 Tau splicing and phosphorylation in patient-derived cortical neurons from FTD patients with a 10+16 splice site mutation in *MAPT*

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Abstract: We generated an in vitro model to study tau splicing and phosphorylation, by differentiating induced pluripotent stem cells (iPSC) from control and FTD patients with the 10+16 splice site mutation in MAPT into cortical glutamatergic neurons. Analysis of tau expression and splicing showed control neurons express only the fetal 0N3R isoform of tau, even at extended time points (day 200) in culture. Neurons with the 10+16 mutation expressed 0N3R and 0N4R tau isoforms, suggesting this mutation overrides the developmental regulation of exon 10 splicing. Tau phosphorylation was observed at multiple epitopes during differentiation, reflecting the need for plasticity of the microtubule network during neuronal development. No differences in tau phosphorylation between control and 10+16 neurons were observed. Neural differentiation and tau expression could be accelerated by notch inhibition, however this was accompanied by a permanent increase in tau phosphorylation. Alternative methods to accelerate mature tau splicing are currently under investigation. Tau was detected in the conditioned media from cultured neurons and we are currently investigating the mechanisms of tau release. We have shown that iPSC-neurons are immature with respect to tau splicing, which has important implications for disease modeling, as many clinically aggressive tau mutations are located within exon 10 and therefore the mutant protein would not be present in this context. Our work suggests iPSC-neurons could be a useful model to study tau splicing in development and disease. Current work is investigating the consequences of aberrant splicing of tau and how this links to neurodegeneration.

P.130 Restoration of progranulin expression rescues corticogenesis in frontotemporal dementia-derived induced pluripotent stem cells

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Abstract: To understand how haploinsufficiency of progranulin (PGRN) causes frontotemporal dementia (FTD), we created induced pluripotent stem cell (iPSC) lines from three patients with a GRNIVS1+5G>C mutation (FTD-iPSCs). FTD-iPSCs were fated to neuroprogenitors and subsequently to cortical neurons, the cells most affected in FTD and known to express PGRN. As expected, in all cell stages a ~50% reduction in PGRN expression levels was noted. Although generation of forebrain neuroprogenitors was unaffected, their further differentiation into neurons and especially the generation of CTIP2, FOXP2 and TBR1 Tuj1 double positive cells for cortical neurons was significantly decreased on day 40 in FTD-iPSC progeny. These results demonstrated that PGRN haploinsufficiency causes inefficient cortical neuron generation. Zinc finger nucleases-mediated integration of one copy of PGRN cDNA into the AAVS1 locus corrected defects in corticogenesis, confirming earlier results. Transcriptome analysis identified 2299 transcripts differentially expressed between control and FTD derived neuronal cultures, of which only 122 remained significantly differentially expressed in progeny of genetically corrected FTD-iPSC. Aside from identifying significantly lower levels of neural gene expression in FTD-iPSC progeny, the Wnt signaling pathway was among the top three canonical pathways differentially expressed in progeny of H9-hESC or genetically corrected FTD-iPSC as compared to FTD-iPSC, suggesting that PGRN haploinsufficiency may hamper cortical neurogenesis through enhanced Wnt signaling.

P.131 Genetic background modifies neuropathology in mice deficient for the FTD-associated protein progranulin

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Abstract: Loss-of-function mutations in the progranulin gene (GRN) are a common cause of familial frontotemporal dementia (FTD). Progranulin-knockout mice display subtle behavioral abnormalities and progressive neuropathological changes, as well as altered dendritic morphology and synaptic deficits in the hippocampus. In this study we evaluated multiple neuropathological endpoints in aged progranulin knockout mice and their wild-type littermates on both the C57BL/6 (B6) and 129/SvImJ (129) inbred background strains. We find that in the thalamus, the brain region of highest progranulin expression, both strains are susceptible to progranulin-mediated neuropathological changes, including astrogliosis, microgliosis, and highly accelerated deposition of the aging pigment lipofuscin. Neuroinflammation due to progranulin deficiency is exaggerated in the B6 strain and present but less pronounced in the 129 strain. Neuronal loss in the thalamus and hippocampus of progranulin knockout mice was observed on the B6 background but not on the 129 background. Conversely, alterations in neuronal morphology and decreased spine density in pyramidal neurons in the CA1 region of the hippocampus are penetrant in progranulin knockout mice on the 129 background, but not on the B6 background. Our results highlight the importance of examining genetic mutations on multiple genetic backgrounds to evaluate differential penetrance and expressivity. We conclude that progranulin-mediated neurodegenerative phenotypes are variably penetrant on different inbred mouse strains, indicating that underlying genetic variability contributes to phenotypic heterogeneity in progranulin-mediated diseases.

P.132 TDP-43-mediated regulation of Progranulin content and secretion: a comparative study in human and mouse disease cell models

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Abstract: Loss-of-function mutations in progranulin (PGRN) gene account for 5-25% FTLD cases. PGRN is involved in multiple biological processes, including neuronal development and neuroprotection. We previously described that TDP-43 post-transcriptionally regulates PGRN by binding to its 3'UTR and that in condition of TDP-43 knock-down PGRN mRNA stability increases with a consequent up-regulation of PGRN protein content in mouse motoneuronal NSC34 cells. Given the importance of TDP-43 effect on PGRN, we investigated whether TDP-43-mediated regulation of PGRN is also conserved in man. Human and mouse PGRN 3'UTR sequences show a 80% conservation, including miRNA and TDP-43 consensus binding motifs, indeed suggesting similar regulatory mechanisms in humans and mice. By mimicking the pathological condition of TDP-43 loss-of-function occurring in FTLD- and ALS-affected neurons, we analyzed changes in PGRN mRNA and protein levels in human neuroblastoma (SKNBE) cells. A significant increase in PGRN protein levels was observed in human SKNBE cells upon TDP-43 knock-down compared to controls, similarly to what observed in murine NSC34 cells. However, the secreted PGRN content increased only in mouse, but not human conditioned medium. To try to account for such differences we also analyzed expression and alternative splicing of the PGRN receptor Sortilin, known to be affected upon TDP-43 knock-down. A similar approach in another non-neuronal human cell line confirmed this species-specific difference in TDP-43-mediated regulation of PGRN content in human disease cell models. Our findings suggest that potential species-specific differences should be carefully taken into account when studying TDP-43 and its dysfunction in human versus mouse cell models.

P.133 CSF p-Tau181/Tau ratio as biomarker for TDP pathology in frontotemporal lobar degeneration

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Abstract: Disease-modifying clinical trials in frontotemporal lobar degeneration (FTLD) have been hindered by the inability to clinically distinguish patients with FTLD-TDP and Tau pathology. A recent study by Hu and colleagues has identified in the cerebrospinal fluid (CSF) phospho-Tau181 to total Tau (p/t-Tau) ratio a biomarker to identify FTLD with TDP-43 pathology as compared to FTLD-Tau. This study evaluated the CSF p/t-Tau ratio in a multicenter cohort of 79 FTLD patients with accurately predictable neuropathology, i.e. Tau (affected by Progressive Supranuclear Palsy or carriers of mutations within MAPT gene) or TDP-43 (carriers of mutations within Granulin, C9orf72, TARDBP genes or affected by FTD with motor neuron disease). FTLD patients were randomly assigned to a training cohort (n=39), to assess the best CSF p/t-Tau cut-off score according to ROC curve analysis, and a validation cohort (n=40) to evaluate accuracy values of the previously identified marker. In the training cohort, we found a significantly reduced CSF p/t-Tau ratio in FTLD-TDP relative to FTLD-Tau. ROC analysis for p/t-Tau ratio was 0.873 and the best cut-off score of 0.136 allowed to differentiate FTLD-TDP and FTLD-Tau with 81.8% sensitivity and 88.2% specificity. Analysis in the validation cohort showed CSF p/t-Tau ratio <0.136 to distinguish FTLD-TDP from FTLD-Tau with 83.3% specificity and 63.6% sensitivity. The positive predictive value of detecting TDP neuropathology was 82.4%. A reduced CSF p/t-Tau ratio represents a reproducible biomarker to correctly identify FTLD-TDP in FTLD, with important implications for defining distinctive therapeutic approaches, guiding genetic screening and for patients' selection in clinical trials.

P.134 MicroRNA modifications associated with *C9orf72* expanded repeat in frontotemporal lobar degeneration

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Abstract: Hexanucleotide repeat expansion within C9orf72 gene was found to be a relatively common genetic cause of frontotemporal lobar degeneration (FTLD), accounting up to 20% of the familial cases. C9orf72 function is currently unknown, even though recent studies indicated that the expanded repeat may enable the formation of DNA/RNA complex structures, may cause changes in RNA transcription and formation of toxic RNA foci. MicroRNAs (miRNAs) are small non-coding RNAs (20-22 nucleotides) playing a major role in post-transcriptional regulation of gene expression. Increasing evidence indicates that miRNAs may play a key role in the biological pathways that regulate brain functions. In order to evaluate a putative involvement of miRNA regulation in the pathogenetic mechanisms associated with C9orf72 expansion, we analyzed the miRNome profiles (>1800 miRNA levels) in a sample of 6 FTLD patients carrying C9orf72 expansion, and in 15 siblings (7 asymptomatic carriers and 8 non-carriers). Differences in miRNA levels between carriers and not-carriers evidenced a miRNA signature associated to C9orf72 expansion. Interestingly, a pattern of miRNAs was regulated in an opposite manner in FTLD patients and asymptomatic carriers. The miRNA target gene prediction and the pathway analysis indicated a potential effect of the differentially expressed miRNAs on a number of brain functions, i.e. PI3K-Akt signaling, long-term potentiation, neurotrophin and Wnt signalings, and axonal guidance. These findings support a role of miRNAs in the detrimental effects induced by the C9orf72 mutation and suggest that these small RNAs may have a role in changes from presymptomatic disease stages through clinical disease onset.

P.135 Eye movements in frontotemporal dementia

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Abstract: Behavioural changes in Frontotemporal dementia (FTD) are often insidious and difficult to quantify. Eye movements have a well identified pathway through the brain and poor performance on basic tasks can reflect damage in specific areas. Deficits in eye movements have the potential to be used as biomarkers. They can provide insight as to where a participant's attention is directed. We evaluated basic saccades and scanpaths towards emotional faces, in an attempt to characterise both basic and higher level eye movements in 16 controls and 17 FTD patients (12 Behavioural variant (bvFTD), 2 Semantic and 3 Progressive Non-fluent Aphasia). Participants performed reflexive saccades, antisaccades, memory-guided and self-paced saccades, then were presented pictures of emotional faces with the task of identifying the emotion. Performance was compared to age matched controls. A significant difference was found for horizontal (FTD=222.15ms, control=166.73ms $p<0.001$) and vertical saccade (FTD=224.10ms, controls 166.87ms $p<0.001$) latency. FTD participants had significantly higher error rates for antisaccades and memory guided saccades than controls but correct antisaccade latencies were not significantly different to controls. In the self-paced task bvFTD participants produced significantly fewer saccades in 30s than controls (36.41 vs.65.25 $p<0.001$). FTD participants displayed significantly more errors in identifying emotions in faces ($p<0.001$) however unlike other similar neurodegenerative groups with an emotional deficit, they produced the classical triangle scanpath and did not spend a proportionately longer time in any facial region than controls. FTD appears to impair both initiation of correct saccades and inhibition of incorrect ones.

P.136 Electrophysiological characterization of patients with frontotemporal dementia using statistical pattern recognition

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Abstract: Early symptoms of frontotemporal dementia (FTD) are often changes in behavior and/or speech, and there are difficulties in distinguishing the clinical features of FTD from other types of dementia or diseases. A definite diagnosis can only be obtained by a neuropathological post mortem analysis of the brain. The analysis of digital electroencephalogram (EEG) sequences is a simple, noninvasive and inexpensive method to diagnose different types of dementia. Seventy-nine EEG recordings from patients with a clinical frontotemporal dementia (FTD) diagnosis were retrieved from the memory clinic at Karolinska University Hospital at Huddinge and analyzed by Mentis Cura ehf using statistical pattern recognition to a large set of EEG features. Three distinct classifiers, each expressed as a numerical index, were developed. In an EEG database a pair-wise comparison of different groups based on classifiers were applied that demonstrated discrimination between FTD patients and individuals representing 1) normal controls 2) Alzheimer disease (AD) and 3) Parkinson and Lewy body (LP).The accuracy, sensitivity, and specificity of each classifier were estimated using 10–fold cross validation. Discrimination as measured by area under the receiving operator curve (ROC) was 0.95, 0.88, and 0.92, respectively. In conclusion, preliminary results indicate that the classifiers were able to distinguish FTD patients into a distinct phenotype separated from controls, AD, and LP. The technique can potentially be an important tool in the future differential diagnosis of dementias and to identify subgroups and disease phases of FTD.

P.137 Longitudinal diffusion tensor imaging in the primary progressive aphasias

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Abstract: Primary Progressive Aphasia (PPA) is characterised by progressive erosion of the language network, and is most commonly associated with Frontotemporal Lobar Degeneration. Few biomarkers exist for diagnosis and tracking of disease progression in PPA. Novel techniques such as diffusion tensor imaging (DTI) may allow early disease detection and monitoring, as well as improving our understanding of the trajectory of PPA. 28 patients with PPA (11 with semantic variant, 11 with non-fluent variant, 6 with logopenic variant), and 20 age-matched healthy participants were assessed using serial DTI at baseline and ~1.2 years later. Baseline and follow-up DTI scans were registered using a group-wise approach and a region-of-interest analysis performed for individual white matter tracts. Annualised rates of change for DTI metrics were calculated and compared between healthy controls and each syndromic group. In the semantic group, rates of change in fractional anisotropy (FA) and mean diffusivity (MD) were most significant within right uncinate fasciculus (FA, -15.1%/year, pThis study demonstrates the feasibility of longitudinal DTI, identifying rates of disease progression across the spectrum of PPA. Syndrome specific trajectories of disease progression emerged. This highlights the potential use of serial DTI as a disease biomarker in PPA.

P.138 Increased cerebrospinal fluid total-tau levels in hereditary behavioral-variant frontotemporal dementia

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Abstract: Cerebrospinal fluid (CSF) measurement of the microtubule-binding protein, tau, is an emerging biomarker for behavioral-variant frontotemporal dementia (bvFTD). The total level of CSF tau (t-tau) is considered a non-specific marker for neuronal injury/neurodegeneration, while CSF levels of tau phosphorylated at threonine 181 (p-tau181) are reduced in TDP-43 proteinopathies. A significant subset of bvFTD is associated with a pathogenic mutation, and previous studies find atypical clinical features and increased neurodegeneration in hereditary bvFTD. Here, we examine CSF t-tau and p-tau181 levels in 109 clinical bvFTD (ALS-bvFTD=9). All cases were tested for major pathogenic mutations associated with FTD and 29 cases were found to have a pathogenic mutation (C9orf72=17, GRN=8, MAPT=2, TARDP=2) while 79 were mutation-negative. Non-autopsied mutation-negative cases with a CSF t-tau/Aβ1-42 ratio (>0.34) predictive of a neuropathological diagnosis of Alzheimer's disease were excluded. Mutation-positive bvFTD had significantly higher levels of t-tau (56.1+29.1pg/ml) compared with mutation-negative bvFTD (39.3+24.0pg/ml) (MWU=2.9;p=0.004), while both groups had similar levels of p-tau (11.5+7.9 vs. 11.3+10.7pg/ml) (MWU=0.8;p=0.4). Groups did not differ in age (MWU=0.03,p=0.9) or disease duration (MWU=0.4,p=0.7) at CSF collection. A linear regression model (R2=0.15, p=0.001) to predict CSF t-tau finds a significant association with mutation status (β=16.8,p=0.002) and age (β=0.7,p=0.02) but not disease duration (β=-1.9,p=0.09). Subset analysis of mutation-positive TDP-43 (n=27) with mutation-negative autopsied FTLD-TDP cases (n=8) also finds a higher t-tau level in mutation-positive cases (MWU=2.2;p=0.03). Mutation-positive bvFTD may have more severe neurodegeneration that is detectable in CSF and it may be important to stratify bvFTD CSF biomarker analyses based on underlying molecular diagnoses.

P.139 Longitudinal changes in brain MRI and neuropsychological measures in asymptomatic and symptomatic familial frontotemporal lobar degeneration with mutations in *MAPT*

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Abstract: As disease modifying therapies for familial frontotemporal lobar degenerations (f-FTLD) move forward, it will be necessary to develop robust biomarkers that are sensitive to disease progression in both symptomatic and asymptomatic populations. We investigated the longitudinal change in brain MRI and neuropsychological measures in asymptomatic and symptomatic carriers of microtubule associated protein tau (MAPT) mutations. All available neuroimaging and neuropsychological data on MAPT mutation carriers (symptomatic n=21 and asymptomatic n=9) evaluated at Mayo Clinic were analyzed; non-mutation carrier family members (n=11) were used as controls. Longitudinal brain MRI scans were processed using the Symmetric Diffeomorphic Image Normalization method for normalization of serial scans to obtain tensor based morphometry maps (TBM-SyN). We also compared longitudinal data on the Controlled Oral Word Association Test, Trailmaking Test B, Boston Naming Test and Category Fluency. Symptomatic subjects were declining significantly in frontal and temporal regions (~3%/y, $p<0.01$) with marked ventricular expansion (~10%/y, $p<0.01$). These rates were significantly different from both asymptomatics and controls ($p<0.01$). Asymptomatic subjects were clearly declining in the temporal ROI ($p<0.05$) with some evidence of frontal atrophy and ventricular expansion. Control family members were stable. A similar pattern was also observed for all neuropsychological measures without any evidence for non-zero rates of change in asymptomatics. Sample size estimates demonstrated a significant advantage for longitudinal changes in ventricular volume over any other measure analyzed. Of the metrics investigated, change in ventricular volume has the most potential to be used as a biomarker in trials aimed at symptomatic f-FTLD subjects with MAPT mutations.

P.140 Promoter methylation is an epigenetic disease modifier of mutant *C9orf72*

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Abstract: C9orf72 promoter hypermethylation inhibits the accumulation of RNA foci and dipeptide repeat aggregates which have been postulated to be neurotoxic. We tested here whether C9orf72 methylation may be an epigenetic disease modifier of mutant C9orf72. C9orf72 methylation was quantified from brain, blood or saliva using methylation-sensitive restriction enzyme digest-qPCR in a cross-sectional cohort of 133 C9orf72 repeat expansion carriers and 37 non-carrier family members. Multivariate regression models were used to determine whether C9orf72 methylation was associated with age at onset, disease duration, or age at death. While there were differences in C9orf72 methylation between blood and saliva-derived DNA measurements, there was a high correlation between C9orf72 methylation in brain versus blood. C9orf72 methylation was not significantly different between ALS and FTD, and did not predict age at onset. However, brain and blood C9orf72 methylation was associated with later age at death in FTD. Furthermore, blood C9orf72 methylation was associated with longer disease duration in FTD. Finally, permutation analysis of pedigrees with multiple mutation carriers demonstrated a significant association between C9orf72 methylation and family relatedness. The attenuated clinical phenotype associated with C9orf72 hypermethylation suggests that slower clinical progression in FTD is associated with reduced expression of mutant C9orf72. These results support the hypothesis that expression of the hexanucleotide repeat expansion is associated with a toxic gain of function.

P.141 Free TDP-43 CSF, serum and brain fractions analysed by two-dimensional immunoblotting

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Abstract: TDP-43 can be found pathologically aggregated in neurons and glial cells in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). By performing two-dimensional immunoblots (2D-WB) we wanted to differentiate TDP-43 isoforms of human brains with and without TDP-43 pathology to strengthen our hypothesis that most of the TDP-43 measured in the CSF is serum derived. We have performed 2D-WB from brain urea-fractions, CSF and serum. In the TDP-43 positive brain we observed an additional three spot pattern at about 50kDa shifted to a more acidic pI than the six spots at 45kDa. In the control brain without TDP-43 pathology only six spots at 45kDa were detected. In the CSF and serum of ALS and FTD we observed a six spot pattern at 45kDa, in the control CSF and serum we only observed a weaker four spot pattern. Regarding pI-range of all samples, the brain urea-fractions are shifted to a more acidic pI, most obvious in TDP-43 positive brain, while pIs in CSF and serum are between 5.5-7. We found a similar spot pattern in the CSF and serum of the ALS and FTD patients (6 spots), but also in controls (4 spots). Post-translational modifications of TDP-43 are similar in CSF and serum. In the brain urea fraction with TDP-43 pathology there is an additional higher spot pattern at about 50kDa shifted to a more acidic pI. This may represent phosphorylated TDP-43.

P.142 The contribution of multimodal MRI to the diagnosis of primary progressive aphasia

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Abstract: Challenges emerged in making an accurate clinical diagnosis of primary progressive aphasia (PPA). This study aimed at testing the ability of a multimodal MRI-based approach, comprising cortical thickness and white matter (WM) tract damage metrics, to discriminate the nonfluent (nfvPPA) and semantic (svPPA) variants of PPA. T1-weighted and diffusion tensor (DT) MRI scans were obtained from 13 patients with nfvPPA, 13 patients with svPPA, and 23 healthy controls. Cortical thickness and DT MRI indices from the long-associative and interhemispheric WM tracts were obtained. A random forest (RF) analysis was used to identify the image features associated with each clinical syndrome. Individual patient classification was performed using ROC curve analysis with cortical thickness, DT MRI, and a combination of the two modalities. RF showed that the best diagnostic markers to differentiate the two PPA variants at an individual patient level were diffusivity abnormalities of the left inferior longitudinal and uncinate fasciculi and cortical thickness measures of the left temporal pole and inferior frontal gyrus. A combination of cortical thickness and DT MRI measures ("GM&WM" model) provided the best classification pattern (accuracy 0.89). Leave-one-out analysis validated these findings demonstrating that the "GM&WM" model had an higher accuracy (0.86) compared with both "GM-only" (0.73) and "WM-only" (0.69) models. A combination of structural and DT MRI metrics provides a quantitative procedure to distinguish nfvPPA and svPPA at an individual patient level. The discrimination accuracies obtained are high enough to suggest that the "GM&WM" model is potentially relevant to clinical practice.
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P.143 Screening for possibly curable FTD: 4 cases of progranulin deficiency and the novel mutation Y294X

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Abstract: As the high proportion of familial cases in frontotemporal dementia (FTD) of about 40% suggests, causal associations to a number of genetic mutations were discovered during recent years. Mutations in the Granulin-Gene (GRN) coding for progranulin (PGRN), which is involved in growth, tumor genesis and the immune system, are of particular clinical interest: treatment seems to be within reach, as the progranulin level, which is diminished by haploinsufficiency, can be increased by drugs. The autosomal dominant pattern of inheritance allows early diagnosis in affected relatives and therefore treatment on time. Identifying GRN mutation carriers by clinical phenotype is demanding: Distinguishing FTLD from psychiatric disorders is challenging in early stages of the disease and family history can be misleading due to variable penetrance and incomplete or unreliable information. Fortunately mutation carriers can be screened at reasonable cost via a lowered progranulin level in peripheral blood. In German speaking countries, GRN-mutations have as yet been diagnosed rarely and epidemiolgic data is sparse. We report a series of 4 genetically confirmed GRN-mutation carriers from Germany detected by a progranulin level screening in 170 suspected cases of FTD hitting on the previously unpublished mutation Y294X. The blood progranulin-level is a reliable and cost effective screening parameter for progranulin mutations. As altered progranulin levels were more frequent than expected, have implications for many other diseases and are a promising target of treatment, broader epidemiological studies should be conducted.

P.144 Serum TDP-43 measurements in *C9orf72* vs *GRN* mutation carriers

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Abstract: TDP-43 is the major component of protein inclusions found in frontotemporal dementia due to progranulin (GRN) and C9ORF72 (C9) mutations. We hypothesize that TDP-43 and its metabolic products measured in serum can be used to distinguish mutation carriers from non-carriers and controls. Antibodies against the N-terminal and the phosphorylated C-terminal of TDP-43 were developed. We used two detection platforms to measure TDP-43 levels: 1) BIAcore, a label-free state-of-the-art biosensor that utilizes the principles of surface plasmon resonance technology to detect biomolecular interactions in real time, and 2) a sandwich ELISA assay. In both assays, we found that C9 carriers (n=5) but not GRN carriers (n=5) have significantly higher level of phosphorylated C-terminal TDP-43 compared to non-carriers (n=9) and other healthy controls (n=14). The levels of N-terminal TDP-43 were not significantly different in C9 nor GRN mutation carriers compared to controls. However, using the ratio of phosphorylated C-terminal of TDP-43/N-terminal TDP-43 increased the sensitivity in detecting difference between C9 mutation carriers and controls. Our preliminary findings suggest that TDP-43 measurements may have clinical utility to detect C9 mutation carriers, which may extend to other FTD/ALS patients. These findings will need to be replicated in a larger sample.

P.145 Assessment of variability of progranulin concentrations in human cerebrospinal fluid (CSF)

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Abstract: The variability in CSF progranulin concentrations was evaluated in serial samples (catheter sampling over 36-hour epochs) that were collected from 19 healthy subjects (HS) and 12 patients with mild cognitive impairment/early Alzheimer's disease (MCI) on 2 occasions (Days 1 and 14). Progranulin concentrations were determined using a qualified enzyme-linked immunosorbent assay. During qualification, precision (%CV) and accuracy (%bias) were <5.71% and <0.103%, respectively, for quality control samples (21.3 to 2396 pg/mL) and <11.0% and <10.4%, respectively, for calibration standards (18.8 to 2500 pg/mL). Moderate linear increases in progranulin concentrations with time were observed during intensive serial CSF sampling as has been reported for other proteins/peptides. To account for such increases, progranulin concentrations were modeled as a dynamic response controlled by a zero-order input and a first-order out. The model parameters were zero-time concentration (BSLN), output rate (Kout) and scaling factor (Sf). The typical value and inter-individual variability (as the coefficient of variation) were 867 pg/ml and 18.8%, respectively, for BSLN; and 0.00234 pg/mL/h and 114%, respectively, for Kout. Sf as a fixed effect was -0.043. Residual variability as a proportional error was 8.6%, indicating a minimal impact of other potential sources of variability. There were no significant differences in BSLN and Kout between MCI and HS (p-value > 0.05). These data indicate CSF progranulin concentrations are stable over time, with some increase during intensive sampling. CSF progranulin concentrations may be a useful biomarker in patients with FTD due to progranulin mutation to assess therapies that could increase progranulin expression.

P.146 bvFTD and PSP can be accurately classified from their impact on effective connectivity within and between resting-state networks

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Abstract: FTD syndromes target specific large scale neural networks, which can be assessed from fMRI in the absence of specified tasks ('resting state'). Until recently, resting-state fMRI was limited to functional connectivity but stochastic dynamic causal modeling (sDCM) now allows the use of resting-state fMRI to interrogate causal relationships among brain regions i.e. effective connectivity. We used sDCM to compare network dynamics in behavioral variant frontotemporal dementia (bvFTD, n=13), progressive supranuclear palsy (PSP, n=33) and controls (n=26). Cortical nodes of the Salience (SN), Default mode (DMN) and Executive Control Network (ECN) were used to construct biologically plausible generative network models (54 SN models, and 62 ECN, DMN models), which were optimised to the observed data for each subject, and compared by model evidences. Then, connectivity measures in each subject were used as inputs to a SVM binary classifiers with radial basis function kernels. Based on SN connectivity, SVM classification differentiated bvFTD from PSP with 100% accuracy ($p<0.001$), and bvFTD from controls with 92.3% accuracy ($p<0.001$). From ECN, SVM classification differentiated PSP from bvFTD with 95.7% accuracy ($p<0.001$), and bvFTD from controls with 94.9% accuracy ($p<0.001$). The DMN showed no between group differences, nor DMN based SVM classification above chance. Conclusion: we provide further evidence that neurodegenerative diseases target specific neural networks, including differential effects of bvFTD and PSP on the salience and executive control networks respectively. We also demonstrate that machine learning methods applied to within-network measures of effective connectivity using sDCM enables accurate classification of clinical syndromes.

P.147 Cerebrospinal fluid biomarkers and [11C]Pittsburgh compound-B PET concordance in AD vs. FTD syndromes

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Abstract: [11C]Pittsburgh compound-B PET and CSF (Aβ-42 and total tau) both measure AD pathology in vivo, but their concordance in a memory clinic setting is not well established. We compared PIB and CSF biomarker results in 78 patients (24 clinical AD syndromes, mean age:61.9±8.2, MMSE:23±7.2; 54 clinical FTD syndromes, age:63.8±8.7, MMSE:23±8.0) who underwent both tests within two years (mean 175±189 days). PIB images were rated visually (+/-) blinded to diagnosis, and CSF biomarkers were rated as AD-like based on published values (Shaw 2009). Eleven patients also underwent neuropathological examination (PIB-autopsy interval: 2.1±1.2 years). PIB was positive in 75% of patients with AD and in 13% of patients with FTD, while CSF tau:Aβ42 ratio was positive in 75% of AD and 17% of FTD patients. Of the CSF biomarkers, tau:Aβ42 ratio had the highest concordance with PIB (88% overall agreement [kappa=0.74]; 91% AD [κ=0.74]; 87% FTD [κ=0.51]), followed by Aβ-42 (86% overall agreement [κ=0.68]; 79% AD [κ=0.52]; 89% FTD [κ=0.60]). Both PIB-PET and CSF tau:Aβ42 were concordant with autopsy results in 8 of 11 cases. One patient with a pathologic diagnosis of FTLD-TDP-U/MND was misclassified by both PIB and CSF tau:Aβ42. Two patients with pathologically-confirmed FTLD (CBD and FTLD-TDP-B/MND) and CERAD frequent neuritic plaques (ADNC A2B1C3 and A1B1C3) were PIB-negative but had a CSF tau:Aβ42 in the AD range. Overall, PIB-PET and CSF Aβ42 biomarkers showed high concordance in classifying patients, though PIB showed slightly better correlation with both clinical and pathological diagnoses.

P.148 Neurochemical approaches in frontotemporal lobar degeneration – data from the multicentric FTLD consortium's study within Germany

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Abstract: Laboratory diagnosis of patients with Frontotemporal lobar degeneration (FTLD) is a challenge. Conflicting results even for established biomarkers have been reported, possibly mainly caused by low numbers of investigated patients and/or less rigid standard operation for cases and control populations. Within our nationwide multicenter FTLD study we have now analysed cerebrospinal fluid samples of 280 patients (behavioural variant frontotemporal dementia (bvFTD, n=82), corticobasal syndrom (CBS, n=16), progressive supranuclear palsy (PSP, n=20), non-fluent variant of primary progressive aphasia (nfvPPA, n=26), semantic variant (sv) PPA (n=16), logopenic (lv) PPA (n=10), amyotrophic lateral sclerosis (ALS)+FTD (n=20), ALS (n=11), Alzheimer disease patients (AD, n=33)) and 46 other neurological diseases) for tau protein, phospho-tau protein (ptau), Abeta1-42, neurofilament light chain (NfL), phosphorylated neurofilament heavy chain (pNfH) and progranulin. Patients were also investigated for c9orf72, progranulin and MAPT mutations. Highest and significantly elevated levels of tau protein and ptau protein were seen in AD and lvPPA. However 20 % of bvFTD patients also had elevated level of tau protein. Whereas Abeta1-42 was mainly unaffected in these patients. Elevated levels of NfL and pNfH were restriced to ALS and ALS+FTD. Progranulin levels were only decreased in Progranulin mutation carriers. Biomarker levels of other mutation carriers were all within normal range. Current biomarkers may help in subtyping FTLD patients. In bvFTD patients biomarker levels are mainly within normal range. Elevated levels of NfL and pNfH might indicate a motoneuron involvement.

P.149 Association between cerebrospinal fluid and *MAPT* haplotype in frontotemporal degeneration

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Abstract: There is increasing evidence for the utility of multimodal biomarkers in frontotemporal lobar degeneration (FTLD). In this study we investigate genetic and cerebrospinal fluid (CSF) associations. Prior evidence suggests that CSF levels of total-tau (t-tau) and phosphorylated-tau (p-tau) may improve diagnostics in FTLD. The single-nucleotide polymorphism (SNP) rs8070723 is located in the microtubule-associated protein tau (MAPT) gene and the minor allele (G) marks the H2 haplotype, which is associated with decreased risk of tauopathies. To evaluate whether MAPT haplotype contribute to CSF levels of p-tau and t-tau, we collected CSF and isolated DNA from 161 patients with clinical FTD spectrum diagnoses. We excluded potential non-FTLD pathology using a previous autopsy-validated t-tau to amyloid-beta ratio (<0.34) predictive of AD. We evaluated CSF t-tau and p-tau using previously reported standard operating procedures and genotyped all patients for rs8070723. Non-parametric Kruskall-Wallis and post-hoc Mann Whitney tests were used to assess the association between MAPT haplotype, p-tau and t-tau. We observed a significant association with rs8070723 and p-tau ($X2=6.59$; $p=0.037$): H2/H2 haplotype had significantly decreased p-tau relative to H1/H1 haplotype ($Z=2.50$, $p=0.012$). There was no significant association between MAPT haplotype and t-tau ($X2=1.611$; $p=0.447$). This suggests that the MAPT H2 haplotype may influence the CSF level of abnormally hyperphosphorylated tau in FTLD. Lack of association with t-tau suggests that the observed finding in p-tau is not related to a non-specific measure of neurodegeneration. Together, these findings contribute additional evidence for multimodal biomarkers and emphasize the importance of considering genetic background in CSF biomarker studies.

P.150 Elevated CSF Tau in neuropathological confirmed FTD cases

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Abstract: CSF biomarker studies in fronto-temporal dementia (FTD) have not shown uniform results. This is partly due to the use of clinically diagnosed cases and the lack of pathological verification. Here we compare CSF biomarkers in FTD and AD (Alzheimer's disease) patients with known pathology. Neuropathological or genetically confirmed FTD (FTLD-TDP43 N=22 and FTLD-Tau N=3) and neuropathological confirmed AD cases (N =13) were included from the Amsterdam Dementia Cohort. All patients provided antemortem lumbar CSF samples, and post-mortem neuropathologic data were collected at the VU University Medical Center. Levels of CSF Tau, and P-tau were measured using immunoassays (INNOGENETICS©). These measurements were compared (non-parametrical median; min-max pg/mL) with CSF data of non demented subjects (N=31, clinical follow-up median of 6.3 years ; min 5.0 and max 9.6 years). Significance was set at 0.01. Group differences for all two biomarkers were significant. Post-hoc analysis revealed significant intermediate Tau levels for FTLD (353; 844-120) compared with SMC (274; 1134-79) and AD (536; 955-257). No difference was found in P-Tau levels between FTLD (38, 70-17) and SMC (41, 121-19). As expected, in AD higher levels for P-Tau (67; 121-39) were found when compared with FTLD and SMC. The CSF biomarker profile of definite FTD consists of an isolated intermediate level of tau. To set biomarker accuracy, research has to be performed in larger patient cohorts with neuropathological/ genetic confirmation.

P.151 Decreased levels of amyloid beta 38, 40, and 42 in definite FTD patients

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Abstract: Recently, lower amyloid-beta (Aβ) 38 and Aβ40 were measured in clinically diagnosed fronto-temporal dementia patients (FTD) compared to Alzheimer's disease patients (AD) and controls, indicating that this may be a useful biomarker for FTD. However, these results have not yet been confirmed in a cohort with definite FTD cases. We measured CSF Aβ38, Aβ40 and Aβ42 in FTD (N=27), AD (N=25) and patients (N=24) with subjective memory complaints (SMC). We used genetically or pathologically confirmed FTD cases or clinical FTD with EMG confirmed motor neuron disease. AD cases were either PIB positive or pathologically confirmed. All cases were included from the Amsterdam Dementia Cohort and provided antemortem lumbar CSF. Post-mortem neuropathologic evaluation was performed at the VU University Medical center. Levels of CSF Aβ38, Aβ40 and Aβ42 were measured using electrochemiluminescence detection (Meso Scale Discovery©). One-way ANOVA with Bonferroni post-hoc was used as statistical analysis. Group differences for all three biomarkers were significant. Post-hoc analysis revealed lower Aβ38 and Aβ40 for FTD compared with controls (pdefinite FTD cohort. This resembles earlier studies in which the diagnosis FTD was clinically set. As a result, a combination of these biomarkers may be used as a tool to discriminate FTD from AD patients and controls.

P.152 Pupillometric biomarkers of fronto-temporal lobar degeneration

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Abstract: There is currently considerable interest in altered reward and valuation of salient sensory stimuli as a potential early signal of frontotemporal lobar degenerations (FTLD), however there are currently few candidate biomarkers to index such processes. Here we addressed this issue using a novel physiological biomarker of salience processing: pupillometry. In a well-characterised cohort of patients with FTLD, we assessed recognition (semantic processing) and physiological (pupillometric) correlates of processing natural (behaviourally salient, 'meaningful', M+) versus synthetic (behaviourally 'meaningless', M-) nonverbal sounds. All major FTLD syndromes were represented (svPPA, n=10; behavioural variant frontotemporal dementia (bvFTD), n=10; progressive nonfluent aphasia (PNFA), n=6), and assessed in relation both to healthy older controls (n=20) and patients with Alzheimer's disease (AD, n=10). Neuroanatomical associations were assessed using voxel-based morphometry of patients' brain MR images. The SD, bvFTD and AD groups had sound recognition deficits relative both to the healthy older control and PNFA groups but all patient groups showed significantly greater pupillometric responses to M+ than M- sounds and the magnitude of the M+/M- response difference was inversely correlated with sound recognition performance in groups with focal temporal lobe damage (SD, bvFTD, AD). Overall pupil reactivity correlated with grey matter in optic tectum while the M+/M- pupil response discrepancy correlated with grey matter atrophy in left anterior temporal lobe. These findings suggest that pupillometry can generate novel, behaviourally and neuroanatomically relevant physiological biomarkers of FTLD with the potential to stratify syndromes.

P.153 Clinical correlates and baseline predictors of progressive brain atrophy in progressive supranuclear palsy: results from the AL-108-231 davunetide trial

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Abstract: The AL-108-231 study was a phase 2/3 double-blind, placebo-controlled trial for progressive supranuclear palsy (PSP). It was conducted at 48 centers on three continents and randomized 313 patients to davunetide (a neurotrophic peptide) or placebo for one year with serial MRI scans and clinical data. This study evaluated the clinical correlates of volumetric MRI changes in PSP. Patients with baseline and week 52 MRI scans, Progressive Supranuclear Palsy Rating Scale (PSPRS) (n=167), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (n=153) and color trails 1, 2 (n = 170, 167) test scores were included for analysis. Brain volumes derived by label propagation in SPM5. Linear regression was used to investigate the relationship between baseline, changes in PSPRS, RBANS, color trails scores and whole brain, ventricular, midbrain and superior cerebellar peduncle (SCP) volume changes. Age, sex, disease duration, H1 haplotype, CoQ10 status, treatment group and total intracranial volume were used as covariates. Change in PSPRS, RBANS and color trails were correlated with brain volume changes ($p<0.01$). Baseline RBANS attention, memory scores and color trails scores significantly predicted whole brain, midbrain volume changes respectively ($p<0.01$). Baseline PSPRS did not predict brain volume changes. MRI brain changes reflect functional and cognitive abilities of PSP patients overtime and may be a viable outcome to support therapeutic efficacy in future trials. Neuropsychological testing in executive and memory domains may be a marker for disease progression rate in PSP. This will be useful for determining suitable size, length and candidates for future trials.

P.154 Contribution of neuro-imaging and CSF in differentiating bvFTD within a 'frontal' neuropsychiatric cohort

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Abstract: The behavioural variant of Frontotemporal dementia (bvFTD) clinically presents with a 'Late Onset Frontal lobe syndrome' (LOF) and neuro-imaging shows abnormalities in 50-70 % (MRI) up to 90% (18F-FDG-PET). CSF-biomarkers (amyloid-beta, total-tau and phosphorylated-tau) especially have high clinical value in differentiating bvFTD from Alzheimer's disease, although total-tau may be elevated in bvFTD compared to controls. Nevertheless, these previous studies have been conducted in a general memory clinic population. We investigated the diagnostic value of these biomarkers for bvFTD within a neuropsychiatric cohort. In this naturalistic prospective multicentre study 137 patients (aged 45-75, 72% males) with a LOF were included based on their scores on the Frontal Behavioral Inventory (FBI) and the Stereotypy Rating Inventory (SRI). All subjects underwent a standardized clinical and neuropsychiatric diagnostic process, MRI, 18F-FDG-PET and CSF examination, after which a multidisciplinary diagnosis was made. 33% received a probable bvFTD diagnosis, 7% possible bvFTD, 36% a psychiatric diagnosis, and 23% another neurological (including neurodegenerative) diagnosis. In 71 patients (52% of total of 137) the MRI results played a decisive role (change in (probability of) diagnosis). In 59 patients (63% of a total of 94 that underwent a FDG-PET-scan) the FDG-PET decisively contributed to the final diagnosis. In 44 patients (43% of a total of 103 who underwent lumbar punction) the CSF results played a decisive role. In 31 patients (23%) one or more of the biomarkers changed the initially suspected diagnosis. Both neuroimaging and the CSF biomarkers played an important role in differentiating bvFTD from other neuropsychiatric disorders.

P.155 Is it possible to measure dementia-related diagnostic proteins for frontotemporal dementia in blood and saliva?

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Abstract: Peripheral diagnostic biomarkers for Alzheimer's disease using the core proteins underlying the disease process are already in clinical practice. Similar concepts for α-synucleinopathies are being pursued. However whether the core biomarkers identified in frontotemporal lobar degeneration (FTLD) occur in peripheral fluids has not been systematically studied. This study investigates core FTLD proteins in plasma, serum and saliva samples, initially looking at ways of increasing the levels of commonly measured proteins (Aβ1-40 and Aβ1-42), and then assessing the levels of tau, TDP43 and FUS. Samples from 24 subjects (12 FTLD cases, 6 controls without neurological or psychiatric symptoms and 6 cases with an alternate dementia, Alzheimer's disease) were collected with consent. Albumin and IgG depletion of blood samples was applied before western blotting with the enrichment of protein targets. FTLD core protein levels and different forms were assessed using commercial enzyme-linked immunosorbent assays (ELISA) kits and western blotting respectively. Consistent with previous publications, Aβ1-40 and Aβ1-42 could be measured in saliva and plasma. TDP43 was confirmed as being most abundant in plasma, while tau could only be detected in enriched serum samples, but FUS could not be consistently detected. We have identified methods for the consistent measurement of two of the three core FTLD proteins in peripheral fluid samples. Further assessment of their utility as potential biomarkers for diagnosis and monitoring of dementia cohorts, in association with peripheral biomarkers for Alzheimer's disease, is now warranted.

P.156 Neuropsychiatric symptoms in patients with frontotemporal lobar degeneration compared with Alzheimer's disease. Are important the night time-behaviors?

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Abstract: Neuropsychiatric symptoms (NPS) are common in dementia and helpful to differentiate types of dementia; the instrument most widely used to explore them is the Neuropsychiatric Inventory. The goal of this study is identify the NPS in subjects with Alzheimer´s Disease (AD) and Frontotemporal lobar degeneration (FTLD) and compare the risk for presenting them for both groups. Two samples of patients were studied: one included 30 AD patients and the other, 64 FTLD patients [20 language variant (FTLD-l) and 44 behavioral variant (FTLD-b)]. For the whole group, the mean age was 61.1 years (SD ±12.21), 51.1% were women. None sociodemographic variable showed statistical significant difference among the samples studied. Related to the risk of developing NPS, taking as category of reference AD we found for FTLD-b, Odds Ratio (OR) from 3.3 to 5.5 in increasing order (CI 95%), for: appetite-eating, delusions, disinhibition, elation-euphoria and night time-behaviors. For FTLD-l we found a high night time-behaviors risk too. When we use as category of reference FTLD-b the risk of developing depression/dysphoria for AD was OR=3.2 (CI 95% 1.2-8.4) and for FTLD-l OR=6.4 (CI 95% 1.9-21.2). Our results coincide with the international literature. However what attract our attention was the risk of depression/dysphoria in patients with FTLD-l since it was higher for this group than for AD and FTLD-b subjects. Also, it is remarkable the risk of night time-behaviors in patients with FTLD-b and FTLD-l, this particular association has not been fully studied therefore further studies are needed to clarify the importance of it.

P.157 Utilization behaviour and imitation behaviour are seen across the frontotemporal spectrum of disorders but not in early onset Alzheimer's disease

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Abstract: Persistent imitation behaviour (IB) and persistent and coherent utilization behaviour (UB) are considered pathognomonic of a frontal lesion with largely preserved post-rolandic function. Recent studies have demonstrated their usefulness in distinguishing behavioural variant frontotemporal dementia (bvFTD) from Alzheimer's disease (AD). Although UB and IB have also been reported in progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), the variability in the way these behaviours have been tested may have diluted their diagnostic significance. Moreover, these behaviors have not been studied in the other canonical FTD syndromes. We therefore studied the occurrence of UB or IB in 184 consecutive patients, comprising 144 FTLD patients (60 bvFTD, 13 PNFA, 15 SD, 32 CBD, 24 PSP) and 40 early onset AD (EOAD) patients who attended the Cognitive Neurology Clinic at our hospital and compared them with 60 healthy controls. UB and IB were tested by previously described methods. To avoid ambiguity and to ensure robustness of the study, only persistent and coherent UB or persistent IB had to be present for a positive result. UB, IB or both was seen in 72% bvFTD, 33% PSP, 27% SD, 25% CBD and 23% PNFA patients. None among the EOAD patients or healthy subjects exhibited these behaviours. We conclude that UB and IB can be seen across the spectrum of FTLD disorders. Whether these nearly pathognomonic behaviours of frontal dysfunction have the potential of predicting FTLD pathology in life in patients with corticobasal syndrome or primary progressive aphasia may be an issue for future research.

P.158 Mild cognitive impairment-FTD (MCI-FTD): a nosological entity missed by current criteria

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Abstract: Mild cognitive impairment (MCI) has been introduced to identify subjects with preserved activities of daily living (ADLs), but at higher risk to develop Alzheimer disease. In frontotemporal dementia (FTD) field, the earliest disease stages have not been still completely explored. In a consecutive series of patients with behavioural variant FTD (bvFTD), enrolled from 2001 to 2013, we defined MCI-FTD those patients with cognitive and/or behavioural impairment but with no deficits in the ADLs. Aim of the present study was to i) define the prevalence of MCI-FTD in our cohort, ii) evaluate whether MCI-FTD fulfilled current clinical criteria for bvFTD, iii) establish disease progression of MCI-FTD. At enrolment, 84 patients out of 220 (38.2%) were classified as MCI-FTD. Considering current clinical criteria (Raskovsky et al., 2011), 35 (41.6%) MCI-FTD were classified as possible bvFTD, whilst 49 (58.4%) did not (less than 3 criteria). The annual conversion rate from MCI-FTD not fulfilling clinical criteria to possible bvFTD was 30% (range 27.6-50%), at fourth year follow-up almost all MCI-FTD responding to clinical criteria. MCI-FTD group showed frontotemporal grey matter atrophy, even though with less extend than bvFTD (FWE 0.05 whole-brain). MCI-FTD not fulfilling clinical criteria showed predominant bilateral temporal atrophy, while MCI-FTD that met criteria had greater frontal atrophy. In conclusion, MCI-FTD represents the earliest stage of FTD, but in most of the cases this entity is missed by Raskovsky criteria. Considering clinical criteria able to identify MCI-FTD is key to diagnostic purposes and to future therapeutic interventions.

P.159 The neurolinguistic profile of behavioural variant frontotemporal dementia

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Abstract: Behavioural variant frontotemporal dementia (bvFTD) is clinically and pathologically heterogeneous. In contrast to the syndromes of primary progressive aphasia (PPA), language dysfunction is not a defining feature of bvFTD and is generally not emphasised clinically. However, very little information is available concerning neurolinguistic processing in bvFTD. Here we present a systematic analysis of key language functions in a large, comprehensively characterised cohort of patients with bvFTD (n=25) in relation both to healthy older controls (n=24) and a cohort of patients representing core PPA syndromes (progressive nonfluent aphasia and semantic dementia; n=34). Relative to healthy controls, patients with bvFTD showed a profile of neurolinguistic deficits that were less severe than PPA but still extensive, affecting naming, semantic and literacy skills. Voxel-based morphometry in the bvFTD cohort revealed a correlated profile of widespread grey matter loss affecting dominant prefrontal, peri-Sylvian and anterior temporal cortices comprising the canonical language network. Our findings suggest that language decline may be a significant if under-recognised issue in bvFTD, with implications both for clinical diagnosis and management of these patients and emerging models of language network disintegration in neurodegenerative disease.

P.160 Kluver-Bucy syndrome occurs early in bv-FTD with predominant right-side temporal lobar atrophy

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Abstract: The Kluver-Bucy syndrome (KBS) has been well described in patients with behavioral-variant frontotemporal lobar degeneration (bv-FTLD). As the disease course progresses, bv-FTLD would cause significant, symmetric lobar atrophy of bilateral temporal lobes and thus lead to the presentation of KBS. Majority of these patients develop KBS in the later severe stage of the disease. Moreover, clinical observation showed asymmetric lesion, primarily involving one temporal lobe, could also cause KBS. Here, I presented a case of bv-FTLD with predominantly right-side temporal lobar atrophy exhibiting characteristic features of KBS in the early stage of the disease course. In this presentation, I will review the clinical and radiographic features of patients with bilateral temporal-lobe-predominant bv-FTLD compared to patients with bilateral frontal-lobe-predominant bv-FTLD. Furthermore, I will discuss the conclusion that among patients with bilateral temporal-lobe-predominant FTLD, patients with asymmetric "right"-side temporal-lobe predominant FTLD seems to show KBS in the early stage, whereas patients with asymmetric "left"-side temporal-lobe predominant FTLD commonly would present language dysfunction in the beginning.

P.161 A case of apraxia of speech with de novo emergence of artistic abilities

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Abstract: A 61 year-old right-handed taxi driver presented with a one-year history of progressive speech problems. Her previous neurological history was non-contributory. Basic neurological examination was normal. However, speech rate was slow, dysprosodic, with lengthened intersegment duration and sound distortions. Formal speech examination revealed intact written expression and comprehension, but there was marked bucco-facial apraxia as well as articulatory and phonation deficits. Neuropsychological testing showed intact language, memory, executive, and visuospatial skills. There were no behavioural changes. These findings suggested strictly isolated progressive deficits in speech production, therefore not compatible with primary progressive aphasia criteria. MRI showed focal atrophy of the left frontal lobe while FDG-PET corroborated focal hypometabolism of the left posterior portion of the frontal lobe. After five years of evolution, speech deficits progressed markedly. Indeed, the only intelligible words she could produce were 'yes' or 'no'. She nonetheless communicated by writing on a notepad, showing otherwise preserved cognitive functioning. To this date, she continues to live independently. Interestingly, four years into her disease, she showed a newly developed interest for painting, taking weekly courses. Over the following two years, and despite any previous interest for arts, she generated multiple truly impressive paintings. Altogether, she was diagnosed with apraxia of speech (AOS), a condition recently revisited by Josephs et al. (2012). Although AOS criteria do not include emergence of artistic abilities, we postulated that atrophy of her language network was associated with overexpression of her right artistic brain. Whether this represents a feature of AOS remains to be studied.

P.162 US Alzheimer centers' NACC FTLD module: initial experience

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Abstract: Because of the low prevalence of frontotemporal degenerations, multicenter collaboration is critical for scientific investigations in FTLDs. In February 2010, the NIA, NINDS and the Association for Frontotemporal Degeneration initiated an effort to enhance characterization of persons with bvFTD and PPA being enrolled in US Alzheimer Centers. Work groups were convened to develop efficient and informative case report forms for clinical diagnosis, neurological examination, genetics, imaging and neuropsychological and behavioral assessments. Enrollment using the “FTLD Module” began in February 2012. Persons who are enrolled also receive the “standard” Uniform Data Set evaluation that was intended for patients in the Alzheimer spectrum. As of June 1, 2014, 17 Centers had contributed FTLD cases or controls: 141 diagnosed with probable bvFTD, 45 possible bvFTD, 50 with semantic PPA 39 with nonfluent agrammatic PPA, 28 logopenic PPA, 35 probable AD dementia and 143 controls. The bvFTD and PPA cases are generally under age 70, highly educated, and men are a majority. Over half of bvFTD and a third of PPA cases had a family history of dementia. Although there was a wide range of scores, the bvFTD patients had MMSE around 22-23, while the PPA patients MMSE scores were 2-4 points lower. The FTLD module data collection also includes additional neuropsychological testing and extensive assessments of behavior completed by family and research team observers. The availability of a large number of well characterized FTLD patients should facilitate new research opportunities because of the large number of available subjects. Supported by UO1 AG016976.

P.163 Establishing dimensionality of sexual behaviors in subjects with acquired neurological injury

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Abstract: Changes in sexual behavior following onset of dementia and traumatic brain injury (TBI) has been minimally studied. This is surprising given that disorders in sexual behaviors commonly occur in these disorders, can be very challenging to manage, and commonly impact the lives of both patient and caregiver. The objective of this study was to develop the first validated measurement scale to assess the range and type of sexual behaviors in a sample of 86 patients with penetrating TBI, and 65 patients with dementia from FTD and CBS. Beginning with a 40-item questionnaire, nonparametric item response theory (IRT) methodology was used to construct a scale with appropriate dimensionality, monotonicity, item discrimination power, and scalability within a sample of patients with dementia and TBI. A sexuality questionnaire with three primary domains or subscales was established. The scales presented with sufficient reliability (rho .70 to .80), while meeting the Mokken IRT criteria of medium scalability. The first scale was labeled “Prosocial sexual behavior” and obtained an H coefficient of .42. The second and third scales were defined as “Sexual interest” and “Sexual aggression”, with respective H coefficient of .50 and .41. A fourth dimension emerged but with very few items, “Detachment” (H= .47). Construct validity was established for groups of items pertaining to four unique aspects of sexuality. This is the first known caregiver-based measurement scale that has been validated to specifically assess sexual behaviors in patients with dementia and brain injury.

P.164 Sensitivity of the FTDC revised criteria for bvFTD among the *C9orf72* expansion carriers

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Abstract: Abnormal expansion of a hexanucleotide repeat in a noncoding region of the chromosome 9 open reading frame 72 gene (C9ORF72) is the most common genetic cause of familial FTD in Finland. The phenotype of the patients with the C9ORF72 expansion varies, while the behavioral variant of FTD (bvFTD) is the most common presentation. We analyzed 36 patients with the C9ORF72 expansion, suffering from bvFTD, by using the International Behavioural Variant FTD Criteria Consortium (FTDC) criteria for bvFTD. Seventy-five percent of the cases met the possible bvFTD criteria and 64% met the probable bvFTD criteria. The mean age of the onset of the symptoms was 59.3 years (SD±6.6) and mean age at the moment of diagnose was 61.2 years (SD±6.5). The mean age at the death was 67.1 years (SD±6.5, n=18). Sixty-one percent of the cases suffered from psychiatric symptoms, and more detailed, 50% from psychotic and 31% from mood symptoms. These findings suggest that FTDC criteria for bvFTD seem to identify significant amount of bvFTD patients with the C9ORF72 expansion. However, one quarter of the patients didn't fulfill the criteria and may be misdiagnosed on account of heterogeneity of the phenotype. Because of the vast amount of psychiatric symptoms, middle-age psychosis should be considered as a possibility for bvFTD.

P.165 Corticobasal syndrome in familial frontotemporal lobar degeneration and serial imaging associated with a mutation in progranulin

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Abstract: Corticobasal syndrome (CBS) can be a unique presenting feature in frontotemporal lobar degeneration (FTLD). We describe a patient who presented at age 47 with behavioral features of frontotemporal dementia (FTD), which evolved to corticobasal syndrome. Fluorodeoxyglucose positron emission tomography (FDG PET) two years after presentation showed marked hypometabolism in the right greater than left frontal, anterior temporal, and parietal regions. Serial magnetic resonance (MR) imaging showed marked progression of atrophy. The patient was subsequently found to have a mutation in exon eight of the progranulin gene (c.813_816delCACT). This case illustrates the evolution of CBS, parietal involvement on imaging, and striking asymmetry and profound progression of atrophy that are often associated with mutations in progranulin.

P.166 Dementia progression in FTLD differs markedly from AD: applicability of the CDR-FTLD in detecting change

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Abstract: We aimed to verify CDR-FTLD psychometric properties and to investigate its sensitivity to measure progression in comparison to AD patients. The dataset from US Alzheimer Centers collected by the National Alzheimer Coordinating Center (NACC) was interrogated in Nov/2012 (Sept/2005-Aug/2012) to identify FTLD and AD patients. 615 consecutive patients were included (FTLD=372; AD=243; patients were excluded if there was concurrent diagnoses of PSP, CBD, HD, depression). Of these, 120 were included in the Rasch analysis to verify psychometric properties (Sample 1); 495 (Sample 2:FTLD=252; AD=243) were included in the analysis of dementia progression pattern, and 195/495 were followed-up (Sample 3: FTLD=82; AD=113). Instruments included: CDR-FTLD, MMSE; demographics and disease duration were examined. The CDR-FTLD fulfilled expected psychometric standards, and correlated well with the MMSE and disease duration (p's<.05). At baseline, FTLD patients were more severe than AD (p<.001; 70% FTLD patients were severe-extremely severe; 25% AD), even when matched for MMSE and disease duration. A second Rasch analyses demonstrated different patterns of progression for FTLD and AD: FTLD had early impairment in behavioural and comportment; memory was preserved until later; AD showed the opposite pattern. At follow-up (M=26 months), both CDR-FTLD and MMSE had significant changes (p's<0.05), but these were more marked on the CDR-FTLD. Importantly, AD patients needed additional 4 years to match the CDR-FTLD rate of change in comparison to FTLD. The CDR-FTLD satisfies required parameters to measure dementia severity in FTLD, is sensitive to change and reveals a different pattern of disease progression in comparison to AD.

P.167 Long term follow up of the phenocopy of behavioural variant FTD

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Abstract: The bvFTD phenocopy syndrome was recognized a decade ago, mimicking symptoms and carer reports of bvFTD, but with a very slow or static time course and without significant neuroimaging abnormalities. Although some cases have emerged as carriers of the C9orf72 hexanucleatide expansion, its nosological status and long term outlook are poorly understood. We reassessed a cohort of phenocopy patients from the Cambridge Early Onset Dementia Clinic (1992-2004). We characterised functional status in terms of independent living, employment, and rates of reported behavioral abnormality (Cambridge Behavioural inventory, CBI-R) over time: initial diagnostic clinic visit (V1, mean length symptoms=5.6 years, n=18), last clinic visit (V2, mean length symptoms=12.6 years, n=14), and recent remote correspondence (V3, mean length symptoms=18.3 years, n=8). CBI-R scores at V1 showed low rates of ADL dysfunction (15.5/100), moderate disinhibition (36/100) and stereotypical behavioural (38.6/100) but severe apathy (62.3/100). There was no significant change in CBI-R domains over time (linear models, p=ns). The 8 patients at V3 were living in the community. We confirm the long term prognosis in phenocopy-bvFTD patients. In contrast to typical bvFTD, long term functional decline is minimal, up to 18 years. Patients remain living at home long term, but do show persistent behavioural symptoms. There is heterogeneity across the cohort, but we suggest that a pathological neurodegenerative process for the symptoms is unlikely in the majority of phenocopy cases.

P.168 Clinical and survival data in cases of pathologically proven Pick's disease

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Abstract: Pick's disease pathology refers to a specific, rare, pathologic subtype of frontotemporal lobar degeneration. Our objective was to describe the clinical features and survival data among patients with Pick's disease pathology. This was a retrospective case series evaluating demographic and clinical characteristics among cases of autopsy confirmed Pick's disease seen at Mayo Clinic Rochester or Jacksonville. Cases of Pick's disease were identified through a pathology database. Clinical data were abstracted from the medical chart including age at disease onset, clinical features, speech/language evaluations, disease duration, and age of death. Patients were categorized based on clinical diagnosis by subspecialty trained behavioral neurologists. Two cases had pathologic data with insufficient clinical data. 11 patients had behavioral variant FTD (bvFTD). 8 patients had primary progressive aphasia. 2 patients presented with corticobasal syndrome, and 1 patient presented with an Alzheimer's phenotype. Mean age at disease onset was 56 (SD 10.6), with no significant difference between bvFTD (μ=57, SD 7.4) and PPA (μ=57 SD 11.6), (p=0.12). Mean disease duration overall was approximately 10.2 years (SD 2.8) and did not differ significantly between the bvFTD (μ=10.7, SD 2.8) and PPA (μ=10.4, SD 2.9, p=0.79). Our findings suggest age of onset and disease duration in Pick's disease do not differ between PPA and bvFTD. Apraxia of speech which predicts tau pathology in neurodegenerative disease was present in half of the patients categorized as PPA. Finally, the clinical phenotypes of pathologically confirmed Pick's may be more heterogenous than initially suggested.

P.169 Clinical and neuropsychological comparisons of early-onset versus late-onset frontotemporal dementia: a CREDOS FTD Study

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Abstract: We compared cognitive and behavioral symptoms in patients with early-onset (EO) and late-onset (LO) frontotemporal dementia (FTD) to investigate whether they were clinically heterogeneous with respect to age of onset, like patients with Alzheimer's disease. A total of 200 FTD patients were enrolled consecutively from multi-center memory clinics using a nationwide FTD register. To control for the effects of normal aging on neuropsychological scores, subjects with normal cognition were also enrolled during the study period and regression models were set up. Neuropsychological scores that were detrended with the regression models and the behavioral symptoms of the EO-FTD and LO-FTD groups were compared. Subgroup analyses were performed for three main subtypes of FTD, behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SD) and progressive non-fluent aphasia (PNFA). Among 200 FTD patients, there were 78 bvFTD, 70 SD and 32 PNFA patients. EO patients were more common in the bvFTD group (62.8%) than in the PNFA group (36.4%). EO-FTD patients had lower memory and frontal/executive scores and more prominent frontal/behavioral symptoms than LO-FTD patients. Our study suggested that FTD may be heterogeneous with respect the age of symptom onset. After controlling for the effects of normal aging, EO-FTD patients exhibited more profound memory and frontal/executive dysfunction and more behavioral symptoms than LO-FTD patients.

P.170 Psychopathological profile of a sample of behavioral variant frontotemporal dementia patients

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Abstract: Behavioral changes use to be the most frequent onset traits of early Behavioral Variant of Frontotemporal Dementia (bvFTD) and outpost cognitive impairment. New Diagnostic criteria include the following early manifestations: behavioral disinhibition; apathy or inertia; loss of sympathy; perseverative, stereotyped or compulsive-ritualistic behavior; hyperorality. Most of them could resemble a true psychiatric condition yielding a diagnosis delay. Research on these behavioral manifestations has attempted to identify these changes as psychiatric categories like depression and mania, psychosis, obsessive-compulsive symptoms and late onset personality changes. Most of research on bvFTD was performed using blunted psychopathological tools like NPI, which lacks precise definition of psychopathological traits and can miss more subtle manifestations. In the present study we will present our findings based on a sample of 12 bvFTD evaluated with a more comprehensive psychopathological structured interview, the AMDP system (Assessment and Documentation Psychopathology system). This system includes definitions for more than 100 symptoms extracted from classic psychopathology. A comparison was made with a sample of bipolar patients, Major Depressive Patients and controls, in order to assess true clinical similarities between bvFTD and psychiatric conditions. The aim of our study is to point towards what in modern psychiatry is viewed as a dimensional approach versus the classical categorical one. On the other hand a comprehensive psychopathological assessment seems to be a good way to understand true behavioral manifestations of bvFTD in order to clarify to which extent they resemble classic psychiatric syndromes.

P.171 Extrapyramidal signs across variants of primary progressive aphasia

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Abstract: Primary Progressive Aphasia (PPA) has been recently physiopathological related to motor tauopathies like corticobasal degeneration or progressive supranuclear palsy. The objective of this work is to determine the prevalence of extrapyramidal signs in the variants of PPA: Semantic Dementia (SD), Progressive Nonfluent Aphasia/Agramatic (PNFA) and Progressive Logopenic Aphasia (PLA). We included subjects in an observational prospective study between 2009-2012. The participants were assessed by a movement disorders specialist using the motor part of the Unified Parkinson´s Disease Rating Scale (UPDRS). We compared the 3 groups using the Kruskal-Wallis test and the proportion of affected subjects in each group using chi-square test. A total of 14 patients with PPA were compared (SD=7, PNFA=5, PLA=2), 9 men, mean age was 65 years, SD 9.05. Bradykinesia was present in 100% of subjects with PNFA and SD but it was absent in PLA. 100% of PNFA presented rigidity unlike a 43% of SD group. 60% of PNFA and 50% of PLA presented tremor, sign that was absent in the SD variant. The 3 groups differed significantly for rigidity in all items of the UPDRS X2 (df=2)=7.00, p=0.030 and bradykinesia in all items of UPDRS X2 (df=2)=14.00, p=0.001. PNFA patients presented more frequently extrapyramidal signs probably reflecting the underlying tau pathology. The more typical motor sign in PNFA and SD was bradykinesia. Extrapyramidal signs may represent a diagnostic feature that complements the linguistic profile and imaging studies in PPA variants. This might contribute to a correct diagnosis and became useful for future treatments.

P.172 A progranulin mutation carrier with clinically sporadic FTD: is it incomplete penetrance or a de novo mutation?

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Abstract: Mutations in the granulin gene (GRN) coding for progranulin (PGRN), recently gained interest among clinicians as cause of frontotemporal dementia (FTD): since drugs can increase the progranulin level, which is diminished by haploinsufficiency, causal treatment might be within reach. Usually GRN-mutations show an autosomal dominant pattern of inheritance. But several epidemiological investigations identified apparent sporadic FTD cases that proved to result from GRN-mutations during genetic screening. Incomplete penetrance and de novo mutations are discussed as explanation. The mechanisms of incomplete penetrance are poorly understood and to our knowledge not a single case of a genetically validated GRN-mutation was described in the literature. We consider a case with the unpublished mutation Y294X who developed symptoms in his early fifties. The father of the patient died in his mid-sixties from asthma without any signs of neurodegeneration. The fathers ancestors were reported as unaffected from neurologic and psychiatric disorders. On the mothers side of the pedigree chart an aunt suffered from schizophrenia and another aunt as well as the grand father had parkinson's syndrome. In contrast to this slightly suspicious family history a GRN-mutation was ruled out by genetic testing in the healthy 79 year old mother of the patient. We argue that a significant number of GRN-mutation-carriers might be missed due to an unremarkable family history. Therefore the blood progranulin level as screening test should be applied broadly.

P.173 Divergent neural regions underpin emotion processing deficits in right-lateralised semantic dementia and behavioural-variant frontotemporal dementia

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Abstract: The typical clinical presentation of semantic dementia (SD) with left > right temporal atrophy is that of profound loss of semantic knowledge. In contrast, SD with right > left atrophy, referred to here as right SD, is accompanied by changes in behaviour and interpersonal functioning. These symptoms resemble behavioural-variant frontotemporal dementia (bvFTD), and differential diagnosis between these subtypes is therefore challenging. The extent that emotion processing ability can improve differentiation between right SD and bvFTD, however, has been underexplored. Here, we systematically examined emotion recognition in 12 right SD, 19 bvFTD and 20 healthy controls. Right SD showed significantly greater language dysfunction and prosopagnosia, but less apathy, than bvFTD. Both patient groups were impaired on emotion selection tasks (Ekman 60, Emotion-Selection). Importantly, however, only bvFTD were impaired on the Emotion-Matching task (bvFTD: p=.003; right SD: p=.512). Neuroimaging analyses revealed distinct, lateralised neural correlates according to diagnosis. In right SD, emotion recognition ability was associated with integrity of the right medial and lateral temporal lobe, and the right orbitofrontal cortex. In contrast, performance in bvFTD was associated with the left inferior frontal cortex, orbitofrontal cortex and temporal lobe. These results are the first to contrast emotion processing ability in right SD with bvFTD, and demonstrate that although both frontotemporal dementia phenotypes demonstrate abnormal emotional decoding ability, the neural regions underpinning these deficits differ. Our findings suggest that development of tasks specifically targeting the right temporal lobe such as face processing, may assist in the differentiation of right SD from bvFTD.

P.174 DSM IV psychiatric diagnosis in behavioral variant frontotemporal dementia

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Abstract: Psychiatric misdiagnosis in bvFTD is well-known, but a systematic definition of DSM- IV psychiatric diagnosis in bvFTD is still missing, with risks of psychiatric overestimation or under-exposure as a consequence. We defined frequency and characterisation of DSM- IV diagnosis among possible and probable bvFTD patients compared to patients with other neurodegenerative diseases, using the MINI-International Neuropsychiatric Interview, and in this context also compared prodromes of bvFTD to prodromes of other neurodegenerative diseases. For this cross-sectional cohort study we made use of the ongoing late onset frontal lobe (LOF)study, a longitudinal multicentre follow-up study aiming to identify prodromal bvFTD among a neuropsychiatric cohort. Out of 137 patients, 45 probable bvFTD, 10 possible bvFTD and 23 patients with a non bvFTD neurodegenerative disease were included. Patients were interviewed conform the (MINI(-Plus)), a diagnostic interview according to DSM-IV and ICD-10criteria. Probable bvFTD patients met DSM-IV criteria significantly more often (22%) than possible bvFTD patients (10%) and patients with other neurodegenerative diseases (9%) ($p<0.05$). Depression and obsessive compulsive disorders were most common in probable bvFTD patients (20%). Prodromes of probable bvFTD were mainly characterized by depression or dysthymic disorder (22%) which differed from prodromes of other neurodegenerative diseases ($p<0.05$) wherein unipolar, anxiety and psychotic disorders were predominantly (17%). The current study reveals higher frequencies of DSM-IV diagnoses in probable bvFTD than in possible bvFTD due to symptom overlap and comorbidity, and sheds lights on mood disorders in prodromal bvFTD in contrast to prodromes of other neurodegenerative diseases which is of diagnostic and therapeutic importance.

P.175 Variability in clinical measures in pre-dementia mutation carriers in familial frontotemporal dementia

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Abstract: Symptoms of frontotemporal dementia (FTD) often follow an insidious course. Understanding the earliest clinical characteristics may help identify patients at risk for FTD and initiate earlier management plans. We hypothesize that there are subtle clinical symptoms that may differentiate mutation carriers from non-carriers in family members at risk for autosomal dominant FTD prior to onset of clinical dementia. Longitudinal clinical scales including MMSE, modified mini mental status (3MS), Frontal Assessment Battery (FAB), Frontal Behavioural Inventory, Clock Drawing Test, Disability Assessment in Dementia, Functional Rating Scale (FRS), Neuropsychiatric Inventory, Beck Depression Inventory (BDI), and an ALS rating scale were applied annually for up to 8 years to a cohort at risk for FTD due to GRN (n=26) or C9ORF72 (C9) (n=35) mutation. Variance for each scale within each pre-dementia subject was calculated when at least 2 longitudinal assessments were available. The average years prior to mean age of onset of dementia in their family was -9.2 in GRN family members and -3.1 in C9 family members. While there were no significant differences between carriers and non-carriers in the overall performance in each of the scale, there is significant increased variability in the FRS (p=0.01) in both carriers of C9 or GRN mutations compared to non-carriers. Moreover, significant fluctuations in the FAB and MMSE were observed in C9 carriers, and fluctuations in the BDI was also seen in GRN carriers. Our findings suggest that unstable performance in certain clinical scales may herald the onset of dementia in C9 and GRN mutation carriers.

P.176 Presymptomatic neuropsychological and neuroimaging abnormalities in a family with a mutation in the VCP gene

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Abstract: Inclusion body myopathy (IBM) with Paget's disease of the bone (PDB) and frontotemporal dementia (FTD) (IBMPFD) is a rare autosomal dominant disease caused by mutations in the valosin containing protein (VCP) gene. Five members of a family with IBMPFD were assessed and genetic analysis performed to look for a mutation in the VCP gene. The subjects underwent a standardized interview, neurological examination, neuropsychometry and (apart from subject 5) an MRI brain, at baseline and then at a follow-up visit. Baseline volumetric T1 MRI scans from the subjects were compared with scans from 26 age-matched cognitively normal subjects in a voxel-based morphometry (VBM) analysis. Genetic analysis confirmed the presence of the R155H mutation in the VCP gene in all subjects. Clinically, all had a progressive myopathy that affected the shoulder and pelvic girdles predominantly although PDB was only found in two subjects (4 and 5). All subjects were cognitively and behaviourally asymptomatic when first seen. Only subject 1 later developed behavioural changes typical of FTD (loss of empathy, preference for sweet food and delusions). At the initial assessment only subject 2 showed any abnormalities in neuropsychological testing with evidence of executive dysfunction. Subject 1 developed executive dysfunction on follow-up assessment. Visual assessment of brain MRI was normal for all subjects. However, the VBM analysis showed evidence of grey matter atrophy in frontal (premotor, prefrontal and orbitofrontal) and temporal (particularly medial) lobes. These findings suggest that executive dysfunction and brain atrophy can occur presymptomatically in VCP mutation carriers.

P.177 The prevalence of frontotemporal dementia and progressive supranuclear palsy the UK: preliminary data from the PiPPIN Study

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University of Cambridge

Abstract: The spectrum of disorders caused by frontotemporal lobar degeneration encompasses cognitive syndromes such as language and behavioural variants of Frontotemporal Dementia (FTD) and conditions where motor features are also present and may dominate the clinical picture e.g. Progressive Supranuclear Palsy (PSP) or Corticobasal Syndrome (CBS). Two factors have presented special difficulty in estimating the prevalence of these disorders. First, many patients exhibit intermediate syndromes which may fall outside consensus diagnostic criteria for the classical syndromes. Second, the diagnostic criteria for FTD subtypes were extensively revised in 2011. Furthermore, many patients change their dominant phenotype over time. We present results from the first 17 months of the 2-year PiPPIN study estimating the prevalence of FTD, PSP, CBD and intermediate syndromes, across two counties in East Anglia (Norfolk and Cambridgeshire, population ~1.6 million). We used multisource case reporting from clinical services and third sector agencies, together with the revised diagnostic criteria including neuropsychological and neuroimaging data. We recruited 122 cases of FTLD spectrum disorders, mean age 69.8 (range 40.8-91.9) giving a crude prevalence of 7.22/100,000 and 27.7/100,000 in those aged over 65. The commonest syndromes were PSP (n=31), CBS (n=30) and behavioural variant FTD (n=27). The peak prevalence was between 70-74.9 years of age (40.3/100,000). The prevalence in those aged 75 and over (23.6/100,000) was more than twice that of those aged 40-74.9 (11.9/100,000). Our data demonstrates that FTLD remains common among the older population, and the introduction of new validated diagnostic criteria has not substantially reduced the prevalence of these disorders.

P.178 Progressive behavioural changes and frontal lobe atrophy: a case from 1846 with implications for 2014

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Abstract: We represent a case published in the Medical Times and Gazette in 1846 of progressive behavioural change with frontal lobe atrophy at post mortem. This remarkable case was the basis of one of the earliest modern associations between focal brain atrophy and a frontal behavioural syndrome. The case, reported by Scipion Pinel (but erroneously attributed to his father Phillipe) was diagnosed as having General Paresis of the Insane (GPI), a diagnosis that in modern times is reserved for cases of neurosyphilis. However, in the early 19th century, the term GPI was also used to describe a range of different syndromes and pathologies including, we suggest, Frontotemporal Dementia (FTD). It was only after the discovery of spirochaetes in the brains of paretics in 1913 that the term became used exclusively in cases of neurosyphilis. The gradual expansion over time of the breadth of the phenotype of GPI during the 19th century was followed by refinements in the diagnosis and then a marked contraction of the diagnostic boundaries, when further scientific discoveries were made. We suggest that this process of expansion, refinement and contraction of nosology, has much in common with the evolving field of FTD, including the discoveries of autosomal dominant forms of the disease and distinct neuropathological profiles.

P.179 Cognitive and behavioural characteristics in frontotemporal dementia with and without amyotrophic lateral sclerosis

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Abstract: Approximately 15% of patients with Frontotemporal dementia (FTD) develop amyotrophic lateral sclerosis. A prevailing assumption is that the behavioural and cognitive syndrome in frontotemporal dementia with amyotrophic lateral sclerosis (ALS/FTD) is indistinguishable from that of 'pure' FTD. We examined a retrospective cohort of 121 patients with clinical diagnoses of FTD (N=73) or ALS/FTD (N=48) with respect to changes in behaviour, affect and cognition, dietary changes, and psychotic symptoms. ALS/FTD was associated with a significantly later age of onset and shorter duration of symptoms at presentation than FTD. Apathy and inertia, and loss of social manners or decorum were all significantly more common in FTD. With regard to affect, loss of sympathy and empathy were common to both groups; however, patients with ALS/FTD were significantly more likely to retain a warm affect. Cognitively, a dysexecutive syndrome, characterised by impaired performance on executive tasks with relative sparing of episodic memory and visuospatial skills, was present in over 90% of both FTD and ALS/FTD patients. ALS/FTD patients, however, showed greater impairment of language: they were significantly more likely to exhibit agrammatism and impaired sentence comprehension than patients with 'pure' FTD. Dietary changes, though common in both FTD and ALS/FTD, did not distinguish the groups. Psychotic features, including hallucinations and delusions, were relatively rare and prevalence did not differ significantly between groups. Our findings suggest specific differences between FTD and ALS/FTD, particularly with respect to behaviour and language, which should be further explored prospectively to improve our understanding of the relationship between these conditions.

P.180 Co-occurrence of language and behavioural features in frontotemporal lobar degeneration

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Abstract: Three principal clinical syndromes are associated with frontotemporal lobar degeneration (FTLD) pathology: behavioural, semantic and nonfluent. Currently, language and behavioural features are evaluated by separate primary progressive aphasia (PPA) and behavioural variant frontotemporal dementia (bvFTD) criteria. We aimed to explore the relationship between language and behaviour and to evaluate whether co-occurrence of features improves prediction of underlying pathology. Two hundred and three consecutive patients with either Alzheimer's disease (AD; n = 103) or FTLD (n = 99) pathology were identified from a pathological cohort. The presence of behavioural and linguistic features was recorded by raters blinded to clinical and pathological diagnosis. Behavioural features were more common than language features and there were significant associations between certain language and behavioural features. In the full cohort 'aspontaneity and economy of speech' and 'impaired object knowledge' were able to predict underlying FTLD pathology with reasonable accuracy. Notably, there were significant associations between semantic features and the behavioural features 'early perseverative, stereotyped or compulsive/ritualistic behavior' and 'early behavioural disinhibition'. Indeed, in patients with evidence of a semantic disorder these behavioural features were highly predictive of underlying FTLD pathology. The co-occurrence of behavioural and semantic deficits aids prediction of underlying pathology. This finding suggests that progressive disorders of semantic knowledge extend beyond the realm of language and therefore should not be construed as an 'aphasia' but rather a discrete FTLD dementia syndrome. The separation of criteria for PPA and bvFTD hinders prediction of underlying pathology.

P.181 Abstract withdrawn

P.182 Distinct social behavioral changes in frontotemporal dementia and early onset Alzheimer's disease

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Abstract: Frontotemporal dementia and Alzheimer's disease are the most common neurodegenerative dementias of early-onset (<65 years of age). Social behavioral changes characterize behavioral variant frontotemporal dementia (bvFTD); however, these changes also occur in early-onset Alzheimer's (EOAD) disease. This study evaluated differences in pathologic social behavior in bvFTD and EOAD using a family-caregiver rating scale. Sixteen patients with bvFTD and 20 with EOAD were rated on a 40-item scale of behaviors, the Socioemotional Dysfunction Scale (SEDS) and the Neuropsychiatric Inventory (NPI). As expected, the bvFTD group exhibited greater overall social symptoms compared to the EOAD group ($p < .001$) which included: failure to anticipate others' reactions (100% of sample), decreased self-consciousness or embarrassability (94%), social disengagement (94%), and inability to understand others' responses (88%). In the bvFTD group, these changes correlated with increased neuropsychiatric symptoms on the NPI of disinhibition, elation/euphoria, and motor behaviors. The EOAD group also exhibited disturbances in social behavior which included: failure to share feelings or experiences with others (40%), waiting for others to take the initiative (40%), failure to understand the viewpoints or motivations of others (30%), and difficulty recognizing sarcasm (30%). In the EOAD group, the changes were correlated with greater irritability, agitation and apathy on the NPI. Thus, social behavioral changes occurred in both bvFTD and in EOAD. However, they were more prevalent in bvFTD than in EOAD. Moreover, social behaviors were associated with distinct neuropsychiatric symptoms in each dementia.

P.183 Distinct clinical phenotypes associated with *MAPT*, *GRN* and *C9orf72* mutations

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Abstract: Frontotemporal dementia (FTD) is associated with three principal causal genes, MAPT, GRN and C9orf72. Although the clinical manifestations of mutations in these genes have been well documented, direct comparisons between patients with MAPT, GRN and C9orf72 mutations are sparse. The study compared demographic, neurological, cognitive, and behavioural characteristics in a consecutive cohort of 73 FTD patients in whom a genetic mutation was identified. Expansions in C9orf72 accounted for more cases than other mutations (37 cases compared 19 MAPT and 17 GRN). MAPT was more strongly familial than GRN and C9orf72, as determined by the presence of dementia in a first degree relative. MAPT was associated with a significantly earlier onset age (mean 52 years, SD 6.0, compared to 59, SD 5.6 and 58, SD 7.8 respectively) and longer duration of symptoms at referral. No differences in gender distribution were identified. ALS was recorded exclusively in association with C9orf72. Parkinsonism was non-discriminatory. Behavioural changes were present in all groups. However, psychotic features were significantly more common in C9orf72 than other cases and dietary changes and motor stereotypies less common. Aphasia associated with loss of fluency in language production was a prominent presenting characteristic of 41% of GRN, 11% of C9orf72 and 0% of MAPT cases. The presence of semantic disorder, by contrast, measured by impaired word comprehension, was significantly more common in MAPT (71%) than GRN (21%) and C9orf72 (20%) cases. The findings highlight the clinical heterogeneity of FTD and reinforce the view that genetic variation influences clinical characteristics.

P.184 Comparison of phenotypes in FTD-TDP43 with and without comorbid Alzheimer disease

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Abstract: Neuronal inclusion bodies consisting of TAR-DNA binding protein 43 (TDP43) define a large subclass of frontotemporal degeneration (FTD), but are also identified in 30% of Alzheimer disease (AD) cases. The relative contributions of AD and TDP43 pathology to the features of the dementia is often unclear, as the phenotypic differences between subjects with TDP43 pathology and those with mixed AD and TDP43 have not been described. This study compared the clinical characteristics of FTD-TDP43 cases (n=26), to those of their counterparts with mixed AD and TDP43 pathology (n=12), in cases from the Johns Hopkins and University of Pennsylvania brain banks. Subjects were classified using immunohistochemical analysis of brain sections and neuropathologic diagnostic criteria. Retrospective demographic and clinical data were collected with a structured instrument. FTD-TDP43 cases had negligible co-morbid amyloid and tau pathology. Of the “mixed” AD and TDP43 pathology cases, half had a primary neuropathological diagnosis of AD, and the other half a primary diagnosis of FTD-TDP43. The FTD-TDP43 cases were younger at illness onset than the mixed cases (54.8 vs. 65.9 years); the groups did not differ in illness duration. FTD-TDP43 cases had higher frequency, in the first year, of abnormal eating behaviors. A few FTD-TDP43 cases, and no mixed cases, had irritability/agitation and psychosis in the first year. Mixed cases had more prevalent amnesia and parkinsonism. These findings indicate that AD and TDP43 pathologies make separable contributions to the clinical phenotype, with implications for AD and FTD diagnosis, prognosis and treatment.

P.185 A systematic analysis of illness duration in the frontotemporal degenerations

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Abstract: Illness duration is incompletely characterized in the frontotemporal degeneration (FTD), which encompasses clinically and histopathologically heterogeneous dementias usually arising in midlife. This study is a meta-analysis of illness durations extracted from 30 studies identified in a systematic search of the medical literature. Studies were grouped by sampling strategy (clinical, n=17, and post-mortem, n=13). Summary estimates of illness duration were computed using a random effects model implemented with the R package 'metafor'. The studies collectively had 2039 subjects and 13603 years of illness. The mean illness duration in studies that did not specify FTD type was 8.3 years (95% confidence interval, CI: 6.0-11.5). In the FTD subtypes, illness duration was shortest for FTD with motor neuron disease (FTD-MND, 2.4 years, CI: 2.2-2.6), longest in progressive non-fluent aphasia (PNFA, 9.7 years, CI: 7.4-12.6), and intermediate in behavioral FTD (7.8 years, CI: 7.1-8.6), corticobasal degeneration (6.7 years, CI: 5.5-8.2), semantic dementia (5.9 years, CI: 3.6-9.9) and progressive supranuclear palsy (5.9 years, CI: 5.1-6.8). There were no differences between clinical and autopsy studies in the estimates of illness duration. FTD-MND had the shortest illness duration, PNFA the longest, and estimates for other FTD types were comparable. These illness durations (other that for FTD-MND) appear comparable to that of AD. There is still much to learn about the factors that shape illness duration in individuals, which will require prospective studies.

P.186 Clinical characteristics of behavioral-variant frontotemporal dementia across stages of disease severity

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Abstract: Behavioral-variant frontotemporal dementia (bvFTD) is a complex clinico-pathological entity, characterized by changes in cognition, behavior and personality in association with anterior cortical degeneration. Because of small available sample sizes, the prevalence of both common and secondary symptoms remains unclear. Also, accurate clinical characterization of how the disease manifests at different stages not only facilitates correct diagnosis but enables proper counseling of patients and families across the disease course. The objective of the current study was to characterize a large set of clinically diagnosed bvFTD patients, at different stages of disease severity. 169 patients meeting FTDC criteria for possible bvFTD seen at the UCSF Memory and Aging Center between 1998 and 2013 participated in the study. Patients underwent multidisciplinary clinical evaluation, neuropsychological and socio-emotional testing and structural magnetic resonance imaging. Sporadic bvFTD patients were significantly more likely to have the MAPT/H2 allele or the GRN/T allele. In addition to behavior, more than 25% of patients showed motor, language, and memory symptoms early (CDR 0.5). Personality changes, apathy, and disinhibition were the most common behavior symptoms throughout the disease, and greater than 70% had impaired emotion reading and social cognition on direct testing, but no behavioral symptom was universal across all bvFTD patients. Detailed characterization suggests distinct clinical variations within bvFTD that vary according to laterality and temporal lobe involvement. Our results demonstrate the heterogeneity of the bvFTD clinical syndrome, and suggest that socio-emotional impairments predominate over other behavioral symptoms and are quantifiable at the initial visit by standardized testing.

P.187 Criminal behavior in prevalent dementia types

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Abstract: Neurodegenerative brain disease can cause dysfunction of structures essential for judgment, executive function, emotional processing, sexual behavior and violence. Such dysfunctions can lead to antisocial and criminal behavior that may appear for the first time in the adult or middle-aged individual. We investigated the frequency and type of criminal behavior among patients with either behavioral variant of frontotemporal dementia (bvFTD), semantic variant of primary progressive aphasia (svPPA) or Alzheimer's disease (AD). In a screening of the UCSF Memory and Aging Center's clinic and research database between 1999 and 2012 (2,397 patients), we found 171 bvFTD cases, 89 svPPA and 545 AD cases. Notes containing specific keywords denoting criminal behavior were reviewed. Data was stratified by criminal behavior type and by diagnostic groups. Of all 805 patients with either bvFTD, svPPA or AD in the database, 130 individuals had a history of criminal behavior that emerged in the course of their illness, distributed as 64 bvFTD, 24 svPPA and 42 AD, 37%, 27% and 8% respectively. The types of behavior had different profiles for the diagnostic groups. The difference in occurrence of criminal behavior was statistically significant between bvFTD and AD (p Criminal behavior is more common in bvFTD than in other dementing disorders. The appearance of new onset criminal behavior in an adult person should elicit a search for frontal and anterior temporal brain disease and for dementing disorders.

P.188 Frontotemporal Dementia – a diagnostic challenge: first diagnosis and medical delays in patients with neuropathologically verified FTD

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Abstract: Early diagnosis in FTD is a challenge. Previous studies have showed misdiagnoses and diagnostic delays. In this study we evaluated time between symptom onset and first diagnosis as well as time to FTD diagnosis. We explored demographic variables and neuropsychiatric symptoms that may lead to clinical misdiagnosis. Finally, we compared the clinical diagnostic accuracy between histopathological subtypes. We retrospectively analysed the clinical records of 97 neuropathologically verified FTD cases, either referred to or self-referred to the Department of Psychogeriatrics. The neuropathological examinations were carried out at the Department of Pathology between 1969 and 2013, later re-evaluated with modern diagnostic methods. FTD was diagnosed during life in 78% (n=76), median time from symptom onset to FTD diagnosis being 4 (1-15) years. Median total disease duration was 7,5 (2-27) years. Only 14 patients received FTD as the first clinical diagnosis. Other first clinical diagnoses were psychiatric disorders (n=43: psychosis n=13, depression n=21, other psychiatric diagnosis n=9), other dementia (n=33) and MCI or speech disturbances (n=5). Subsequently, all but four patients received a dementia diagnosis. The patients that were initially diagnosed with a psychiatric disorder were significantly younger than the patients with other first clinical diagnoses (p=0.001). The majority of patients with an initial psychiatric diagnosis were tau-negative, most often TDP-43 type B. Earlier findings of diagnostic delays and misdiagnosis could be reconfirmed. This may be due to clinical heterogeneity, limited experience among non-dementia specialists and to FTD mimicking other psychiatric conditions. Our findings demonstrate the importance of longitudinal follow-up including neuropathology feedback.

P.189 The association between frontotemporal degeneration and traumatic brain injury

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Abstract: Prior work in smaller cohorts suggests that traumatic brain injury (TBI) may be a risk factor for frontotemporal degeneration (FTD). We sought to confirm and extend these results using the larger population of FTD-spectrum subjects included in the National Alzheimer's Coordinating Center Uniform Dataset. FTD-spectrum subjects were matched to cognitively normal controls 2:1 for age, sex, and years of education, yielding 963 FTD subjects (677 behavioral variant [bvFTD], 144 progressive non-fluent aphasia [PNFA], and 142 semantic dementia [SD]) and 1,939 controls. Relative to controls, FTD-spectrum subjects were more likely to have a history of significant TBI (loss of consciousness >5 minutes without persistent neurologic deficits; 4.3% vs. 2.9%, p=0.040). The prevalence of TBI was similar across clinical FTD subtypes. bvFTD subjects with a history of TBI had significantly less global impairment (Clinical Dementia Rating Sum-of-Boxes), functional impairment (Functional Assessment Questionnaire scores), and impairments on attentional tasks than those without a history of TBI. In contrast, SD subjects with a history of TBI had significantly greater behavioral disturbances (Neuropsychiatric Inventory total severity scores) than those without a history of TBI. FTD-spectrum subjects with and without a history of TBI had similar rates of underlying frontotemporal lobar degeneration pathology (75% vs. 73%) and intervals between symptom onset and formal evaluation (4.99 vs. 4.12 years). TBI may be a risk factor for FTD that differentially affects the severity and symptomatology seen in different clinical FTD subtypes.

P.190 Aims and baseline epidemiological data from the German multicentric FTLD consortium's study

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Abstract: Background: Until 2010 there was no clinical network for frontotemporal lobar degeneration (FTLD) established in Germany. Therefore we aimed to develop, prospectively validate and standardize clinical methodology and tools suitable for screening/differential diagnosis, comprehensive clinical phenotyping over a broad range of etiological entities and clinical stages of FTLD, appropriate for serial assessments and for defining endpoints for clinical trials. Patients and Methods: We set-up standardized protocols for neuropsychological assessment, to prospectively acquire and store high quality biological specimen and imaging data. To aquire patients also at very early disease stages and possible transitions between clinical syndromes our inclusion criteria were formulated as such. Results: The actual mean recruitment rate is 20 participants per month. 636 participants were enrolled between 05.04.2011–30.04.2014. Online monitoring was conducted for 579 participants. From these on-site monitoring was conducted for 509 participants and for the first analysis verified (visit 1) data is available for 503 participants. The current cohort consists of 123 bvFTD (behavioural variant of frontotemporal dementia), 26 CBS (corticobasal syndrome), 35 PSP (progressive supranuclear palsy), 35 nfvPPA (non-fluent variant of primary progressive aphasia), 26 svPPA (semantic variant of PPA), 17 lvPPA (logopenic variant of PPA), 23 PPA nc (not classified yet), 28 ALS+FTD, 1 ALS+PPA, 12 FTLD nc, 16 ALS (Amyotrophic Lateralsclerosis), 44 AD (Alzheimer), 69 OND (other neurological diseases) and 48 healthy controls. Summary: We established a register and trace study within Germany. Especially as for 200 particapants a follow-up visits is obtained. Baseline epidemiological data will be presented.

P.191 Primary progressive aphasia unclassified

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Abstract: The classification system for Primary Progressive Aphasia (PPA) requires fulfillment of basic PPA criteria before assignment to one of three clinical variants: Semantic variant (sv), non-fluent/agrammatic variant (nfv) and logopenic variant (lv) PPA. This case series examines some of the reasons why patients may not meet criteria for a PPA variant (PPA-unclassified). We reviewed case notes of patients presenting to our clinic meeting basic PPA criteria in whom a subtype diagnosis could not be reached. All patients had standardized clinical assessment with a semi-structured history, neurological examination and neuropsychological testing. All patients had 3T MRI and FDG PET scans. We found six patients who despite meeting basic PPA criteria could not be assigned a subtype. Two patients had early speech production features of nfvPPA, another had word finding and phonologic errors but good repetition, whilst another made semantic errors yet also had dysprosodic speech with poor repetition. Two patients met criteria for two subtypes simultaneously (lvPPA and nfvPPA) yet had differing phenotypes. In all cases structural and functional imaging revealed predominantly left hemisphere change but in most instances in a non-specific pattern reflecting the difficult clinical picture. This series suggests there are a number of reasons for PPA-unclassified cases: some patients are at an early stage in their illness, some patients have mixed features defying any classification and some have so many features they meet multiple classifications. PPA criteria need to recognize early presentations and mixed phenotypes need to be acknowledged and better described.

P.192 FTD predominant phenotypes in French families with *TARDBP* mutations

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Abstract: TARDBP mutations are responsible for autosomal dominant amyotrophic lateral sclerosis (ALS) and, rarely, for ALS associated with frontotemporal dementia (FTD). We report 7 patients from 5 apparently unrelated families presenting isolated FTD of FTD-ALS carrying TARDBP mutations; two of them carried homozygous p.Ile383Val mutation. Two patients presented isolated FTD, three had FTD-ALS, one semantic dementia-ALS and one had cortico-basal syndrome. Five patients had initial behavioural symptoms consistent with bvFTD criteria, three of them secondarily developed ALS. A remarkable apparent anticipation was present in one family where the disease begun in the proband at 71 years after his child died of ALS. Ages at onset and disease duration were similar in homozygous and heterozygous mutation carriers, suggesting that the predominant pathological mechanism is a gain of function. This study enlarges the phenotypic spectrum of TARDBP mutations and indicates that they should be searched for also in patients with isolated FTD phenotypes. The variability of phenotype and age at onset in patients carrying the TARDBP mutations emphasizes a major role of genetic modifiers in this disease.

P.193 Clinical update on frontotemporal dementia linked to chromosome 3 (FTD-3)

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Abstract: Amongst families with autosomal dominant frontotemporal dementia (FTD), a large Danish family has been identified and mapped through 6 generations, today including more than 500 individuals [Gydesen et al. Neurology. 2002]. Identification of a truncating mutation in CHMP2B on chromosome 3 has coined the illness FTD-3 [Skibinski et al. Nature Genetics. 2005]. The course of disease is highly variable with age of onset (AOO) ranging from 46 to 68 years (mean AOO: 56 years), and a duration ranging from 3 to 21 years (mean: 8 years) from diagnosis until death. FTD-3 patients develop behavioral changes as seen in other behavioral variant FTD phenotypes . Some patients have a general apathetic phenotype while other exhibit aggressive behavior. In recently diagnosed patients the clinical features include extrapyramidal symptoms in 8 of 9 patients and motor neuron signs in 5 of 9 patients. Neuropsychological testing show a wider spectrum of cognitive deficits compared to other FTDs [Stokholm et al. JNNP. 2013], indicating an overall impairment of cognition in FTD-3 patients. The variability of symptoms indicates that other genetic or non-genetic factors may contribute to the course of phenotype. A clinical update of previous and current cases of FTD-3 in Denmark is presented, including findings in recently diagnosed patients in early disease stages. A comprehensive review of known cases will help identify early markers for disease. Focusing on clinical outliers improves the possibility of identifying factors contributing to onset and course of disease.

P.194 Prolonged visual fixation suggesting a visual grasp reflex during social interactions in frontotemporal dementia

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Abstract: Impaired social interaction is one of the major manifestations of behavioral variant Frontotemporal dementia (bvFTD). The precise length of eye contact is crucial for modulating social interactions. Patients with bvFTD, may exhibit prolonged eye fixation on others suggesting a "frontal visual grasp reflex" which can make others uncomfortable during social interactions. We studied visual fixation on others, in the context of facial expressions, among 10 patients with bvFTD, 18 patients with early-onset Alzheimer's disease (eAD), and 15 healthy controls (HC). We presented 50 pictures to each participant, and, using the Facial Action Coding System, coded their facial expressions per six basic emotions (Fear, Anger, Disgust, Happiness, Sadness, Surprise) as well as Neutral and Interest facial expressions. Visual Fixation Time (VFT), or length of eye fixation the pictures, was measured during the "Interest" facial expression. Based on 2078 stimuli, the bvFTD group expressed fewer basic emotions but greater Neutral and Interest facial expressions than the eAD and HC groups (all $p<0.01$). Additionally, during the 235 "Interest" facial expressions, the bvFTD group had a significant higher mean VFT at 4.0±1.2s (seconds) when compared to the eAD (3.1±1.2s) and HC (3.2±1.1s) groups (all $p<0.01$). In summary, patients with bvFTD may appear to show greater "Interest" in visual stimuli because of a prolonged VFT suggestive of a visual grasp reflex. This prolonged visual gaze may be a factor in the disturbed social interactions of patients with bvFTD and may also help distinguish them from eAD and normal individuals.

P.195 Exploring eating and metabolism in frontotemporal dementia: potential effects on prognosis and disease progression

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Abstract: Eating abnormalities are a core criteria for the diagnosis of behavioral variant frontotemporal dementia (bvFTD), yet their occurrence in other subtypes of FTD and effect on metabolic health (body mass index: BMI, blood insulin and lipid levels) is not known. Metabolic health is known to effect prognosis in motor neuron disease, which shares a common pathology with FTD. We aimed to define the patterns of eating behavior and metabolic health in bvFTD (n=30), semantic dementia (SD; n=30) compared to Alzheimer's disease (AD; n=28) and healthy controls (n=18), by validated questionnaires of eating habits, and measurement of fasting lipid and insulin levels. BvFTD patients exhibited significant abnormalities in all domains of eating behavior. Compared to controls, bvFTD patients had significantly higher carbohydrate intake, while SD patients showed significantly higher sugar intake. Hunger and satiety scores did not differ between FTD groups and controls. The abnormal eating behavior was found in the two FTD groups with the highest BMI. BvFTD patients had significantly increased triglyceride levels and lower HDL cholesterol levels suggesting hyperlipidemia. Both FTD groups had significantly increased insulin levels and were insulin resistant. Abnormal eating behaviors are prominent in both bvFTD and SD. These changes are not limited to increased appetite and not related to changes in satiety and hunger. Similar changes have been found in obese patients and related to orbitofrontal and hypothalamic pathology, suggesting these structures may be involved in FTD. The two FTD groups have significant metabolic changes including peripheral insulin resistance, which may affect prognosis.

P.196 Frontal variant Alzheimer's disease: clinical and neuroimaging features of 55 autopsy/biomarker-confirmed patients

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Abstract: Frontal variant Alzheimer's disease (fvAD) is characterized by behavioral and/or dysexecutive deficits in the face of AD pathology. fvAD is a relatively rare syndrome and therefore still poorly understood. We assembled the largest sample of fvAD patients (n=55) to date, all diagnosed with fvAD or bvFTD with a neuropathological diagnosis of intermediate/high-likelihood AD (n=17) and/or biomarker evidence of AD pathology on PET (n=27) or CSF (n=19). We performed structured chart reviews to ascertain clinical features. First symptoms in fvAD were more often cognitive (52.7%) than behavioral (25.2%, apathy as most common feature). 51.9% met diagnostic criteria for possible bvFTD. We also compared neuropsychological test performance and brain atrophy (applying voxel-based morphometry) in fvAD with carefully matched autopsy/biomarker-confirmed typical AD (tAD, n=58), autopsy-confirmed/AD biomarker-negative bvFTD (n=59) and controls (n=61). fvAD showed worse memory scores than bvFTD and controls and similar performance as tAD. Executive, visuo-spatial and language function in fvAD was worse than controls and comparable with bvFTD and tAD patients. Voxelwise contrasts between fvAD and controls revealed marked atrophy in bilateral temporoparietal regions plus more limited atrophy in the frontal pole, superior and middle frontal gyrus and orbitofrontal cortex. Compared with fvAD, bvFTD patients showed more frontal atrophy and less posterior involvement, whereas tAD patients were slightly more affected posteriorly and showed less frontal atrophy. Memory function and posterior atrophy thus distinguish fvAD from bvFTD. Atrophy explains only part of the frontal symptomatology, suggesting that vascular pathology, subcortical lesions or disruptions in frontal networks may contribute to an fvAD phenotype.

P.197 Abstract withdrawn

P.198 Familiar frontotemporal dementia with mutation Glu318Gly in presenilin 1 gene

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Abstract: Background: The significance of the presenilin1 Glu318Gly mutation has been described as either a causal mutation with reduced penetrance or a benign polymorphism. The clinical phenotype of affected persons varies in wide range. There were described cases that show late and early onset Alzheimer's disease (AD), atypical AD and also frontotemporal dementia phenotype. Patient and Methods: A 46 years-old woman with 10 years history of personality and behavioral changes, bizarre affect, and general disengagement, has undergone a clinical and genetic examination. Results: The clinical examination has shown signs of the severe dementia of frontal type, severe mixed aphasia and a spastic quadriparesis. MRI showed severe brain atrophy with frontotemporal predilection. Genetic testing revealed mutation in presenilin1 gene Glu318Gly. The patient was ApoE4 carrier. Patient's mother and grandmother, as well as two siblings suffered from the same disease. Her brother's first symptoms of the disease occurred at age 41 and he has been also identified as an ApoE4 carrier. The first symptoms of the patient´s sister started at age 60 and she has not been an ApoE4 carrier. Conclusion: In the family the mutation of Glu318Gly was connected with pathological phenotype. Interesting indicator was age of the onset of the first clinical symptoms whereas ApoE4 carriers have had significant earlier (36 and 41) onset of the disease compared with non carrier (59). Mutation Glu318Gly is still assessed as potentially pathogenic and extent of the pathogenicity depends also from other genetic promoting factor such as ApoE isoform.

P.199 Is FTD underestimated among older patients? Results from the LUnd PROspective Frontotemporal dementia Study (LUPROFS)

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Abstract: Frontotemporal dementia (FTD) has been considered as mainly an early onset disorder. However, recent community- and registry-based studies challenge this notion. We report here the demography of patients with frontotemporal dementia disorders included in the prospective study LUPROFS. Between 2009 and 2013 patients referred to the Memory Clinic in Lund with suspicion of a FTD complex disorder were screened for inclusion in the study. All included patients were discussed at consensus meetings and specific diagnoses made according to existing clinical criteria. Out of 234 screened patients, 104 patients were included in the study. The cohort consisted of 41 (39.6%) patients with behavioural variant FTD (bvFTD), 10 (9.6%) with semantic dementia (SD), 12 (11.5%) with progressive non-fluent aphasia (PNFA), 20 (19.2%) with progressive supranuclear palsy (PSP), 7 (6.7%) with corticobasal degeneration (CBD) and 14 (13.5%) with unclassified FTD (FTD-nc). The median age at onset was 66.0 years for bvFTD, 65.0 years for SD, 65.0 years for PNFA, 64.0 years for PSP, 67.0 years for CBD and 67.0 years for FTD-nc. A majority of the patients in this cohort has a late onset, in contrast to the present paradigm of FTD being mainly a presenile disorder. The age at onset was very similar in the different diagnostic groups. The most common diagnosis was bvFTD followed by PSP. Although the clinical criteria for the whole spectrum of FTD complex disorders were used, a substantial part of the patients could not be classified.

P.200 From TARDBP and FUS/TLS to *C9orf72* in ALS/FTD: further changing paradigms in the genotype-phenotype correlation

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Abstract: ALS and FTD appear more than ever today as merging disorders with lots of common neuropathologic and genetic bases: this what we are learning from TDP-43, FUS/TLS and C9orf72. The definition of genotype/phenotype correlations is attracting both clinicians and basic scientists. However, the specific clinical features able to address the search for selective mutations in TARDBP and/or FUS/TLS genes are still quite difficult to designate. This complex scenario was not made simpler after C9orf72 identification. Heterogeneous clinical features have been observed in our ALS/FTD patients and families carrying C9orf72 repeat expansions (RE): corticobasal syndrome, progressive supranuclear palsy, multiple system atrophy, Alzheimer's disease, even if ALS-FTD and ALS-plus cases seem to be the best candidates for the presence of pathological REs in our series. To further estimate the cognitive/behavioral features of ALS/FTD, the recent ECAS test for both cognitive and behavioral changes has been applied in our ALS/FTD series with/without C9orf72 RE. The validity of the existing methods of clinical staging, outcome measures suitable for use in clinical trials, and potential CSF biomarkers are being tested in our C9orf72 RE patients. The most recent identification of mutations in MATR3 gene, which also cause defects in RNA metabolism, is further increasing our need to define genotype-phenotype correlations in ALS/FTD.

P.201 Identifying bvFTD in a 'frontal' neuropsychiatric cohort

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Abstract: The behavioural variant of Frontotemporal dementia (bvFTD) commonly presents with a 'Late Onset Frontal lobe syndrome' (LOF), but this behavioural syndrome has a substantial neuropsychiatric differential diagnosis. In this naturalistic prospective multicentre study 137 patients (aged 45-75, 72% males) with a LOF were included based on their scores on the Frontal Behavioral Inventory (FBI) and the Stereotypy Rating Inventory (SRI). All subjects underwent separate neurological and psychiatric assessment, MMSE and the Frontal Assessment Battery (FAB), after which a diagnosis was made. 45 patients (33%) received a probable bvFTD diagnosis, 10 patients (7%) possible bvFTD, 50 patients (36%) a psychiatric diagnosis, 31 patients (23%) another neurological (including neurodegenerative) diagnosis. MMSE, FAB and FBI did not differentiate between bvFTD and other LOF causes. A higher SRI-score significantly (AUC=.73) increased the chance of receiving a bvFTD diagnosis. In 41 patients (30%) the neurological and psychiatric diagnosis did not match. In these cases a consensus diagnosis was made, leading to a consensus co-morbidity of a neurological ánd psychiatric diagnosis in 17 of these 41 cases. This is the first large scale prospective study aiming to identify (prodromal) bvFTD among a neuropsychiatric cohort. Cross-sectional examination resulted in a heterogeneous group of diagnoses, with about a third probable bvFTD, another third a psychiatric diagnosis and 10% a possible bvFTD diagnosis. Especially the presence of stereotyped behaviour played an important role in the diagnostic process. The neurological and psychiatric mismatch in diagnosis illustrates the advantage of a multidisciplinary approach in the early diagnosis of bvFTD.

P.202 Clinical and neuroimaging characterization of frontotemporal dementia in a Colombian sample: preliminary findings

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Abstract: Here we describe preliminary findings on the clinical presentation and functional connectivity patterns of the behavioral variant FTD (bvFTD) and semantic dementia (SD) in a Colombian sample. Eighteen patients underwent neurological and cognitive examinations. Resting-state BOLD data were collected on a Philips 3.0 T MRI scanner. Eleven patients received a diagnosis of bvFTD, and five received a diagnosis of SD. A clinical diagnosis of bvFTD was made according to the criteria of Rascovsky et al. (2011), while a diagnosis of SD was made according to Gorno-Tempini et al. (2011). All bvFTD patients showed a neuropsychological profile characterized by deficits in executive function with relative sparing of memory and visuospatial functions. Seven bvFTD exhibited early symptoms of behavioral inhibition and apathy. Four patients displayed early loss of empathy, and two displayed early altered food preferences, and stereotyped and ritualistic behaviors. Eight of these patients met criteria for probable bvFTD and had atrophy in frontal or anterior temporal regions. Six patients had a family history suggestive of FTD, including one who exhibited a clear autosomal inherent pattern. All five SD patients showed impaired confrontation naming and comprehension in the context of spared speech repetition. The estimated average age of clinical onset was 58 years for the bvFTD group, and 60 years for the SD group. SD and bvFTD patients did not differ in educational level (10.9 ±2 years), MMSE (21.5±4.1) or disease severity (GDS=4.5±0.8). We are in the process of analyzing structural and resting-state fMRI data from these subjects.

P.203 bvFTD-like syndrome in late-life bipolar disorder

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Abstract: Although bipolar disorder has been understood classically as a cyclic disease with full recovery between mood episodes, in the last decade evidence has accumulated supporting progressive features of bipolar disorder. The pathophysiological changes observed in bipolar disorder (brain structural alterations, cognitive deficits, immunological deregulation) converge to a model of accelerated aging. Here we describe a case series of 4 male patients with bipolar disorder, aged 62-78 years who developed a bvFTD-like syndrome in the absence of a mood episode. All subjects had been diagnosed with bipolar disorder at least 15 years prior to presentation and were stable on adequate treatment. Whereas the patients reported some memory complaints, their informants emphasized a gradual change in behavior and personality, consisting of a combination of apathy, disinhibition (i.e., public urination and masturbation), compulsiveness (i.e., repetitive clock watching and time setting), and agitation. Their MMSE varied between 23 and 30 and Frontal Assessment Battery between 12 and 18. On neuropsychological examination mild executive disturbances were found. In one out of 4 subjects episodic memory disorders were found. In all cases, at least 2 years of follow-up yielded no progression. Repeated neuroimaging was within normal limits. CSF biomarker studies were not suggestive of underlying Alzheimer's disease pathology. C9orf status was negative in all cases. In conclusion, combinations of apathy, disinhibition and compulsiveness, fitting with a diagnosis of possible bvFTD, may be present in later stages of bipolar disorder. Pathophysiologically, functional involvement of the frontal-subcortical networks in bipolar disorder might play a role.

P.204 Completing the picture: autoimmune disease in FTD/MND and *C9orf72* mutation carriers

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Abstract: The majority of motor neuron disease (MND) and almost half all behavioral variant frontotemporal dementia (bvFTD) share underlying FTLD-TDP pathology. Previously, we observed an increased amount of select non-thyroid autoimmune conditions in PGRN and semantic variant primary progressive aphasia (svPPA). PGRN and svPPA typically display underlying FTLD-TDP pathology, types A and C, respectively. Here we investigated whether there are also elevated rates of non-thyroid autoimmune disease in symptomatic C9ORF72 (C9) carriers and bvFTD with MND features (FTD/MND), conditions that generally display FTLD-TDP type B pathology. In a combined C9 and FTD/MND sample of 98 patients, 11% (n=11) had a history of non-thyroid autoimmune disease, similar to the amount previously observed in PGRN and svPPA. Further, they clustered into the same three general categories: GI disorders, cutaneous conditions, and inflammatory arthritides. Together, this suggests that select patterns of autoimmune disorders may be a common feature of TDP-43 neurologic disease. Dividing this cohort by C9 status (positive and negative) and by clinical status (FTD/MND vs. bvFTD), non-thyroid autoimmune disease distributed equally among FTD/MND clinical presentations with 16% (7/43) in the C9 negative FTD/MND and 17% (4/24) in the C9 positive FTD/MND. Interestingly, non-thyroid autoimmune diseases were absent in the C9 bvFTD cohort (n=31) raising the possibility that in C9 carriers the presence of non-thyroid autoimmune disease might predict disease phenotype. Thus, select autoimmune disorders might not only play a privileged role in the development of TDP-43 disease, but might also affect the trajectory of this disease, as well.

P.205 *SQSTM1* mutations in frontotemporal dementia spectrum of disease

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Abstract: Mutations in the SQSTM1 gene, coding for the p62 protein, were initially identified as a cause of Paget disease of bone (PDB) and amyotrophic lateral sclerosis (ALS) and more recently in familial frontotemporal dementia (FTD). To further investigate the genetic contribution of SQSTM1 in the FTD spectrum, we have studied a cohort of 187 French probands with FTD or FTD-ALS. We have identified four heterozygous missense mutations in 4 unrelated families with FTD. Only one family had clinical symptoms of Paget disease, and only one family had clinical symptoms of FTD-ALS, possibly owing to the low penetrance of some of the clinical manifestations. p62 binds to TDP43 and could be involved in degradation of TDP-4. The mutations identified in this study are located in the ubiquitin-associated domain that binds to ubiquitinated proteins; therefore, it is possible that these mutations might eventually abrogate the binding of p62 to ubiquitinated proteins. Although the frequency of the mutations is low in our series (2%), our results, similar to those already reported, support a direct pathogenic role of p62 in different types of FTD.

P.206 Hexanucleotide repeat expansion in the *C9orf72* gene in jewish patients of various ethnic origins with familial amyotrophic lateral sclerosis

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Abstract: Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease of motor neurons in the brain and spinal cord with rapid progression and fatal outcome. 10% of ALS cases are familial. Up to 50% of ALS patients have subtle impairment of temporal and frontal function and 5-10% fulfill criteria for fronto-temporal dementia (FTD). Almost of FTD patients develop clinical symptoms of motor neuron dysfunction. A hexanucleotide repeat expansion in the C9ORF72 gene was recently identified as the most common genetic cause of familial and apparently sporadic ALS, FTD and ALS-FTD syndromes in patients of Northern European ancestry, but was only very rarely described in non-European populations. We analyzed 42 DNA samples from Jewish ALS patients with a family history of ALS, for the presence of the hexanucleotide repeat expansion in the C9ORF72 gene. Forty samples were from unrelated patients (40 families). Hexanucleotide repeat expansions were found in ten patients from eight (20%) families. Only half of them were of European (Ashkenazi) origin, while two originated from North Africa, one from the Caucasus area and one is a very mixed Sephardic family with mainly Yemenite and Middle Asian traits. In some families there were both ALS and FTD cases. 36% of the patients carrying the mutation had dementia versus 14% dementia in familial patients without the mutation and 6% in sporadic patients. The C9ORF72 gene mutation is the most frequent ALS mutation in Israel and occurs in Jewish patients with familial ALS of different ethnic origins, with or without FTD.

P.207 Strategies for filtering whole-exome sequencing data of frontotemporal dementia patients

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Abstract: MAPT, GRN and C9ORF72 mutations account for 30-50% of familial FTD cases. For the remainder the disease mutation is still unknown, indicating that additional FTD genes remain to be identified. We performed whole-exome sequencing of 16 FTD probands with a family history of early-onset dementia or motor neuron disease (MND) and no mutations in known dementia or MND genes. We examined possible strategies for prioritising disease variants, in the absence of additional family members. We filtered variants based on: predicted function (nonsense, coding sequence insertion/deletion, splice-site variants and missense variants predicted to be damaging by all four programs (PolyPhen2, SIFT, MutationTaster, LRT)); allele frequency in databases of normal human variation (dbSNP, 1000Genomes, Exome Variant Server); and coexpression with known FTD/MND genes (Brain Architecture Project, http://addiction.brainarchitecture.org/). In our first strategy, we prioritised genes harbouring likely pathogenic variants in multiple probands. Four genes showed significant coexpression with at least one known FTD/MND gene, including PPA1, a phosphate metabolism gene that regulates neurite outgrowth and coexpresses with C9orf72, OPTN and ATXN2. In a parallel strategy we performed pathway analysis of all genes with likely pathogenic variants to determine functions that were enriched in this dataset. We detected a significant enrichment of genes involved in nucleotide-excision repair (5.4 fold enrichment, $p = 0.03$). One of these, a highly conserved RNA polymerase subunit with a missense variant in an FTD-MND patient, coexpresses with VAPB, PFN1, DCTN1, UBQLN2 and CHMP2B. In summary, our complementary strategies have identified several highly plausible candidate FTD genes for downstream analysis.

P.208 Mutation analysis of *C9orf72* in patients with corticobasal syndrome

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Abstract: Corticobasal syndrome (CBS) is a neurodegenerative disease characterized by progressive asymmetrical rigidity and apraxia, cortical sensory loss, myoclonus, dystonia, and cognitive impairment. CBS is usually associated with tau pathology and genetics of CBS is mainly unknown. We investigated if some of the CBS cases could be explained by G4C2–repeat expansion in a noncoding region of C9ORF72 gene, which is a common cause of two other neurodegenerative disorders - Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis. Screening of 20 CBS patients revealed a single patient with a large (>60 repeats) expansion in C9ORF72. Our case features a 63-year-old right-handed woman who developed mild apathy 9 years prior to presentation which progressed followed by behavioral changes including disinhibition, and significant language impairment with both decreased fluency and semantic loss. Five years ago she developed bradykinesia and apraxia for some common daily activities. On presentation two years ago, she was Parkinsonian with bilateral rigidity and bradykinesia, and a shuffling, wide based gait. She was apraxic and had difficulty performing the neurological exam. No sensory exam was possible because of severe cognitive impairment noted on neuropsychological testing. An MRI 3 years ago revealed significant asymmetric left > right frontotemporal atrophy, including orbitofrontal and parietal areas. She has progressed to complete dependence for all ADLs and being mute and wheelchair-bound because of gait apraxia. Her father had developed a behavioral syndrome and died at an early age. This case highlights the importance of genetic screening for C9ORF72 in patients with CBS.

P.209 Characterization of the *C9orf72* repeat expansion in Italian ALS/FTD cases

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Abstract: A hexanucleotide repeat expansion within C9orf72 gene represents the most common genetic cause of Frontotemporal Dementia (FTD) and Amyotrophic Lateral Sclerosis (ALS). Concomitant ALS/FTD and positive family history of dementia or motor neuron disease increase the risk of carrying C9orf72 repeat expansions. By performing fragment length analysis and repeat-primed PCR, we investigated the frequency of pathogenic expanded repeats in a large Italian cohort of 749 ALS patients (66 familial, 683 sporadic), including 18 patients with concomitant FTD and 31 ALS patients reporting a positive family history for FTD/dementia. C9orf72 expansions were identified in ~20% (13/66) of familial ALS cases and in 4% (26/683) of sporadic ALS cases: C9orf72 carriers included 3 (17%) of 18 ALS/FTD cases and 5 (16%) of 31 ALS patients reporting a positive family history for FTD/dementia. To evaluate potential correlations of repeat length with clinical phenotype, we determined the size of the repeat expansion in positive carriers by a non-radioactive Southern blot protocol. Moreover, we analyzed the clinical intra-variability of an ALS/FTD family by comparing the size of the repeat expansion between one member affected by ALS and the other by FTD, and examined the expansion size in two different tissues (peripheral blood and fibroblasts). In conclusion, our results confirm a higher frequency of C9orf72 carriers in individuals with a FTD/ALS phenotype and with a positive family history for ALS and/or dementia. An accurate estimation of repeat size is important to better evaluate clinical phenotypic differences and to recognize other related phenotypes in family members.

P.210 *SQSTM1* mutation in a family with progressive non-fluent aphasia

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Abstract: SQSTM1 mutations, coding for the p62 protein, were identified as a monogenic cause of Paget disease of bone and of amyotrophic lateral sclerosis. SQSTM1 mutations were also identified more recently in few families with frontotemporal dementia (FTD). We describe a new family carrying a heterozygous p.Lys238del mutation in SQSTM1 gene segregating with a clinical phenotype of progressive non fluent aphasia with apraxia of speech. This family illustrates the variability of bone and motor phenotype that can be moderate or absent in SQSTM1 families. This report supports the implication of SQSTM1 in FTD, and widens the phenotypic spectrum associated with SQSTM1 mutations. We propose that SQSTM1 gene should be integrated in the 'multisystem proteinopathies'.

P.211 Identification of novel FTLD-TDP genes using whole-genome sequencing

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Abstract: FTLD with TDP-43 aggregates (FTLD-TDP) is the most common pathological subtype of FTLD accounting for more than 50% of FTLD patients. So far, 2 major genetic causes have been shown to be responsible for FTLD-TDP: mutations in progranulin (GRN) and repeat expansions in C9ORF72. However, to date, 60% of FTLD-TDP remains unexplained by known genes. To identify novel genetic causes of FTLD-TDP our laboratory uses next-generation sequencing in FTLD families followed by prioritization of the variants/genes using whole-genome sequencing data from a unique collection of 100 FTLD-TDP cases. In this study, whole-genome sequencing was performed in 3 family members comprising two siblings and the mother, all affected with FTLD and/or ALS, in which mutations in GRN and C9ORF72 were excluded. After validation using Sanger sequencing, we identified 21 potentially pathogenic variants segregating with disease which were absent from public databases (ESP, 1000 Genomes). Comparison of these variants with our larger cohort of FTLD-TDP patients showed that one of these variant was present in another case. However, since this variant is located in the GPR33 pseudogene, it is unlikely to cause FTLD. Subsequent study of the complete sequence of the 21 genes with novel variants identified in our FTLD/ALS family in the FTLD-TDP cohort did identify 28 new variants in 11 genes. Interestingly, 3 new variants are present in a member of KIF protein family involved in vesicle and mRNA transport. These findings are likely to bring new insights into our understanding of the pathophysiology of FTLD.

P.212 The novel *GRN* g.1159_1160delTG mutation is associated with behavioural variant frontotemporal dementia

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Abstract: Mutations in progranulin gene (GRN) represent a common cause of autosomal dominant Frontotemporal dementia (FTD). The clinical presentation is extremely heterogeneous, either in terms of symptoms and age at disease onset. The majority of such genetic defects cause haploinsufficiency, and are associated with extremely low plasma progranulin levels. Here, we describe two probands with behavioral variant Frontotemporal dementia with a novel mutation in exon 5: g.1159_1160delTG, that leads to a frameshift, which in turn creates a stop codon (c.445_446delTG, p.Cys149fsX10). Both had a positive family history for dementia and showed atypical features at imaging. Their progranulin plasma levels were undetectable, and the mutation was not present in cDNA, suggesting haploinsufficiency. Results described enlarge current knowledge on genetic causes of the disease and clinical characteristics of carriers.

P.213 *C9orf72* expansion mutation in patients with different neurodegenerative disorders in Russian population

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Abstract: The hexanucleotide repeat expansion in C9ORF72 gene is causative for a proportion of cases of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS), but its role has not yet been studied in other clinically and pathologically related neurodegenerative disorders, such as atypical parkinsonism (AP) and Parkinson's disease (PD). We screened for this mutation a large cohort of Russian patients, including 235 patients with ALS, 54 with AP (progressive supranuclear palsy, corticobasal syndrome and multiple system atrophy), 87 with PD and 131 healthy controls, using a fluorescence fragment length analysis of PCR fragments and a repeat primed PCR method. In ALS group, 6 patients (2.6%) with a pathogenic expansion of 42-61 repeats were identified, including 1 case with FTD in family history. In PD group, 4 patients (4.6%) with an intermediate expansion of 19-20 repeats were found, including 1 familial case. In all groups we found persons carrying 9-16 repeats (15.7% in ALS, 13.0% in AP, 10.3% in PD, and 9.9% in controls). Our results demonstrate that in Russian population the pathogenic C9ORF72 expansion is relatively frequent among ALS cases and the intermediate expansion - among patients with PD, but there were no cases with significant expansion among AP patients. This study was supported by the Russian Foundation for Basic Research (grant # 13-04-01718a).

P.214 Epigenetic study of *C9orf72* in FTD and ALS patients including the family with identical twins

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Abstract: C9orf72 transcription is reduced in expansion carriers, suggesting haploinsufficiency as one of the disease mechanisms. We investigated DNA methylation of the CpG-island (5'of the repeat) in ALS, FTD and control samples. Methylation level was variable between the samples (any of the 26 investigated CpGs could be methylated). Hypermethylation (>4 CpGs) was expansion-specific (it occurred only in carriers of >50 repeats), but not syndrome-specific (ALS vs. FTD). Intriguingly, we detected a high methylation level in only 36% of carriers; however down-regulation of C9orf72 expression was demonstrated in all previously published carriers. Therefore, additional DNA region(s) could be subject to methylation (e.g. the repeat itself). The diversity of C9orf72-phenotypes implies the existence of modifying factors, which could be investigated in monozygotic twins. Despite the identical genetic background, twins from a Canadian family have been ALS-discordant for ~5 years, while the first signs of FTD were recently observed only in the twin unaffected by ALS. Based on the analysis of blood DNA, the twins have no methylation at the CpG-island and a similar range of repeat size (800-1350 repeats); however, expansion size in brain DNA could be different from blood. Cumulatively, the identical genetic background of the twins, similarities in both methylation level and repeat size, rather argue in favor of an environmental vs. genetic phenotype modifier in this family. Of note, both twins have had similar environmental exposures; except the twin with ALS was a smoker and had a head-trauma. The results of another unique C9orf72 family will also be presented.

P.215 An integrative approach to identify onset age modifier genes in a large founder *GRN* FTLD family

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Abstract: In frontotemporal lobar degeneration (FTLD) a wide distribution of onset age, ranging from 20 to 91 years, suggests a significant contribution of factors modifying the disease onset. In a Flanders-Belgian FTLD founder pedigree segregating a granulin (GRN) null mutation and exhibiting a wide onset age range between 45 and 84 years, we excluded an effect on onset age of functional candidate modifiers such as the unaffected copy of GRN and variations in TMEM106B. In the family we identified a quantitative trait locus (QTL) for onset age with strong evidence of linkage (Bayes' factor>10). This locus of 7Mb contains 119 genes and explains up to 91% of the genetic variance in onset age. From whole genome sequencing data of 23 mutation carriers, a set of 122 candidate modifier variations was selected. All variations associated with onset age with a p-value in silico clues are being sought, as well as biological evidence in brain transcriptome and serum proteome data of the family and in targeted expression analyses of candidate modifier genes, by comparing expression levels between patients with early and late onset of disease. Candidate modifier variations and genes will be studied in extended patient cohorts. The identification of genetic modifiers may shed further light on the disease mechanisms of FTLD and may provide stepping stones for the development of therapies that can halt or delay, or even prevent the disease.

P.216 Co-occurrence of *MAPT* and *SQSTM1* gene mutations in an Italian patient with frontotemporal lobar degeneration

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Abstract: Frontotemporal lobar degeneration (FTLD) is a genetically heterogeneous syndrome that has been associated with mutations in different genes. Recent studies reported that some FTLD patients with pathogenic C9ORF72 gene expansions may also carry mutations in GRN, MAPT or SQSTM1 genes. We report the case of a 54-year-old Italian female affected by FTD associated with the co-occurrence of double gene mutations. She had a positive family history for dementia. The onset of symptoms was at 44 year-old when the first behavioural changes were noticed. As her disease progressed, she also developed memory loss and initial language deficits. MRI brain showed asymmetrical frontal and temporal lobe atrophy. SPECT showed asymmetrical pattern, with hypoperfusion in left frontal lobe and less marked in left tempo-parietal lobe. CSF examination showed normal values of T-tau, P-tau and Ab-42. In 2009 a clinical diagnosis of bv-FTD was made. The clinical picture progressively deteriorated and in 2012 she resulted in global dementia and mutism. Neurological examination showed extrapyramidal and frontal release signs. Diffusion-tensor tractography showed abnormal diffusion in the arcuate and inferior longitudinal fasciculi. Genetic analysis detected the P301L variant in MAPT gene and the E319K variant in SQSTM1 gene. No DNA of relatives was available to test for co-segregation. Our case report confirms previous studies suggesting that the interaction of several genetic factors needs to be taken into account when investigating patients with FTLD. Furthermore, we provide additional data supporting a role for SQSTM1 gene in the etiopathogenesis of the disease.

P.217 Screening for mutations in frontotemporal dementia with a targeted next generation sequencing panel

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Abstract: Frontotemporal dementia (FTD) is characterized by progressive changes in language and/or behavior. Up to 50% of individuals with FTD have a family history of a similar disorder. Mutations in GRN, MAPT, C9orf72 and a few others are associated with FTD; however some of these mutations are rare. In addition, there is clinical and pathologic overlap between FTD and amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), and Parkinson disease (PD); therefore, genes associated with these conditions are candidates to cause or modify FTD. We developed a targeted next generation sequencing panel to screen for mutations in 45 genes associated with FTD, ALS, PD, and AD thereby enabling cost-effective identification of pathogenic mutations, as well as discovery of novel and rare variants. Identification of mutations enables counseling for the patient and family, stratification for pathological protein-based clinical trials, and phenotype-genotype correlations. A negative result can be used to select patients for subsequent genome sequencing for discovery. Variants of unknown significance (VUS), when properly evaluated using available tools, may lead to new genotype-phenotype associations. Here we report the frequency of pathogenic mutations and VUS in behavioral variant FTD (n=156) and pathologically-defined frontotemporal lobar degeneration with TDP-43 inclusions (n=67). In addition to known pathogenic mutations 84 novel or rare variants, absent in a 276 neurologically normal controls, were identified. A significant number of variants in genes typically associated with PD and ALS were identified suggesting pathway overlap. We demonstrate that a targeted sequencing panel provides a cost-effective approach to screening for mutations in FTD.

P.218 Using family history as a tool to detect causal mutations in patients with FTLD/FTLD-ALS

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Abstract: Frontotemporal lobar degeneration (FTLD) is a neurodegenerative disease leading to dysfunction in behavior and language, and sometimes to the development of amyotrophic lateral sclerosis (ALS). Up to 50% of the FTLD patients have a family history of dementia. Mutations have primarily been detected in chromosome 9 open reading frame 72 (C9orf72), progranulin (GRN) and microtubule-associated protein tau (MAPT). We have examined 111 FTLD pedigrees with a family history classification tool, consisting of seven categories, in order to investigate the mutation frequency of C9orf72, GRN and MAPT in each category. The seven categories were based on age at onset and the number of family members diagnosed with dementia, FTLD-ALS and ALS. Independently of the patient classification, all index patients (n=111) were screened for mutations in C9orf72, GRN and MAPT. The mutation frequency was highest in families with early onset and at least three affected in two generations (80%, n=4/5), and in families with FTLD-ALS or ALS (71%, n=10/14). No mutations were detected in the sporadic group (n=0/2). In the category with patients with unknown family history the mutation frequency was 20% (n=10/49). In conclusion, the mutation frequency increases with the number of affected family members with early onset dementia. However, in the clinic, genetic counseling of patients with FTLD should be considered even if the family history is unclear.

P.219 *C9orf72* G4C2 repeat size associates with genetic anticipation, hyper-methylation and transcriptional down-regulation in FTLD and ALS

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Abstract: Pathological expansions of a G4C2 repeat in the 5' non-coding region of C9orf72 are the most common causes of FTLD and ALS. Different disease mechanisms were proposed but their role in the disease process is unclear. Here, we investigated the involvement of a toxic gain-of-function mechanism by studying the effect of repeat expansion length on onset age using Southern Blot in (un)related C9orf72 expansion carriers and the role of a loss-of-function mechanism by reporter gene expression and methylation studies of the C9orf72 promoter. Repeat expansion sizes in blood ranged from 45 to over 2100 units. We detected short expansions (45-78 units) in 6.5% of carriers and demonstrated segregation of a 50 units repeat in an FTLD family, indicating that expansions as short as 50 units may cause FTLD. Also, we showed for the first time negative correlation between repeat expansion size and onset age ($p=0.0006$). Further, an increment of 1500 units was observed from parent to offspring in one family, pointing to genetic anticipation. We established a gradual decrease of C9orf72 promoter activity with an increasing number of intermediate G4C2 repeats and a decrease of transcriptional activity of small deletions in the 3' flanking low complexity sequence in human kidney and neuroblastoma cells ($p<0.0001$). Further, we observed increased DNA methylation of G4C2 intermediate repeats and of the 5' flanking CpG island in carriers of intermediate and expanded repeats ($p<0.0001$). We provided evidence for both gain and loss-of-function disease mechanisms possibly acting on different transcripts, mutually involved in the disease process.

P.220 Using next generation sequencing to understand the genetics of frontotemporal dementia

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Abstract: Frontotemporal dementia (FTD) is a genetically heterogeneous disorder. In 2009, we reported the heritability and genetics in a cohort of 225 patients finding that over 40% of patients described some family history of dementia but only 20% carried a genetic mutation, in either GRN or MAPT. Since that time expansions in the C9orf72 gene have been shown to be a cause of genetic FTD. Also over that period next generation sequencing technologies (NGS) have become available as a quick and effective method of determining the presence of mutations. We have developed and validated gene panel based technologies to assess 16 genes known to harbour mutations causal of dementia and combined these with PCR based assessments of the C9orf72 hexanucleotide repeat expansion and the octapeptide repeat region of PRNP. We applied this panel to a cohort of 360 patients with FTD spectrum disorders: 167 behavioural variant FTD, 16 FTD-ALS, 2 IBMPFD, 63 semantic dementia, 68 progressive nonfluent aphasia, 30 corticobasal syndrome and 14 progressive supranuclear palsy. As in the earlier cohort, over 40% had a modified Goldman score of 1 (14%), 2 (11%), 3 (7%) or 3.5 (9%). Certain clinical features were predictive of finding a mutation. Mutations were found in several genes thought to be very rare causes of FTD, and we observed two causal mutations in individual patients. The proportion of FTD diagnosed using NGS is high and justifies the routine use of similar technologies in the work-up of FTD patients.

P.221 Rare mutations in *SQSTM1* modify susceptibility to frontotemporal lobar degeneration

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Abstract: Sequestosome 1 (SQSTM1) coding for the p62 protein is a strong functional candidate gene for FTLD. Mutations in SQSTM1 have been genetically associated with closely related disorders as ALS and Paget Disease of Bone. We analyzed the SQSTM1 coding sequence for mutations in an extended cohort of 1808 FTLD patients, ascertained within the European Early-Onset Dementia consortium. As control dataset, we sequenced 1625 European control individuals and analyzed whole exome sequence data of 2274 German individuals (total n = 3899). Association of rare SQSTM1 mutations was calculated in a meta-analysis of 4332 FTLD and 10240 control alleles. The complete patient and control dataset (n = 3433) was sequenced twice, once by classical Sanger sequencing and once by NGS after MASTR-assay target enrichment (Multiplex Amplification of Specific Targets for Resequencing, www.multiplicom.com). For validation of the novel high-throughput NGS multiamplicon panel, identified variants were compared between the 2 sequencing datasets and showed 100% concordance. We identified 25 coding variants in FTLD patients of which 10 had not been described. Fifteen mutations were absent from controls (carrier frequency Finally, detailed histopathology on 2 mutation carriers demonstrated that mutations in SQSTM1 associate with widespread neuronal and glial phospho-TDP-43 pathology.

P.222 Deep genetic profiling of frontotemporal lobar degeneration

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Abstract: Due to the growing number of genes in FTLD and related neurodegenerative brain diseases (NBD), further complicated by the overlap in symptoms between different clinical dementia subtypes, there is a need for high-throughput genetic profiling assays. We designed an amplicon-based gene panel for cost-effective screening of known genes in the NBD spectrum (NBD MASTR assay, n=30). Targeted exons are amplified in multiplex PCR panels developed with the MASTR technology (Multiplex Amplification of Specific Targets for Resequencing, www.multiplicom.com) as front-end for massive parallel sequencing. We currently screened 289 FTLD patients which identified 74 patients with 1 or more rare variants potentially affecting the protein. Amongst others, these included 21 variants that were definitely or probably pathogenic (15 GRN LOF,1 MAPT nonsense, 1 PS1, 1 SOD1, 2 VCP, 1 TARDBP missense) and 2 possibly pathogenic (2 CHMP2B missense mutations). An interesting finding was a double mutation of a GRN LOF with a C9orf72 repeat expansion. We are in the process of expanding this study to our complete cohort of 2000 FTLD patients, as well as our ALS, AD, and PD cohorts. Deep genetic profiling using the NBD MASTR assay is significantly faster and more cost-effective than Sanger sequencing, allows less stringent patient selection for genetic testing, and offers more complete genetic screening. It can be used as a screening tool for selection of mutation-negative patients for WES or WGS studies, will pinpoint atypical mutations originally associated to related phenotypes, and allow systematic investigation of double or multiple mutations.

P.223 Mutations in *GRN* and *MAPT* in Brazilian patients with frontotemporal lobar degeneration from two dementia research centers

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Abstract: Mutations in the genes that encode progranulin (GRN) and microtubule-associated tau protein (MAPT) are among the most common genetic causes of Frontotemporal Lobar Degeneration (FTLD). The frequencies of those mutations in FTLD cohorts are variable across the world, and there is limited information available from regions such as South America. To investigate the frequencies of GRN and MAPT mutations in Brazil, we collected DNA samples from patients diagnosed with either behavioral variant of Frontotemporal Dementia (bvFTD), semantic variant of Primary Progressive Aphasia (svPPA), or nonfluent variant of PPA (nfvPPA) – with or without motor neuron disease (MND). Sixty-two probands from a dementia research center located in the state of Sao Paulo (41 with bvFTD, three with FTD-MND, eight with svPPA, one with svPPA-MND, and nine with nfvPPA) and 22 from a center located in the state of Minas Gerais (19 with bvFTD, one with FTD-MND, one with svPPA, and one with nfvPPA) were included. Twenty-one probands (25% of the entire sample) had at least one first-degree relative who was diagnosed with or had symptoms suggestive of FTLD. Mean age at onset was 56.9 years (range 35-78). As preliminary findings, two mutations in GRN (p. Q300X in a proband with nfvPPA and p.Q130X in two siblings with bvFTD) and one mutation in MAPT (p.N279K in a proband with bvFTD) were identified in the Sao Paulo cohort. No mutations have yet been identified in the Minas Gerais cohort.

P.224 Genome-wide screen in FTLD/ALS patient cohorts for pathological G4C2 repeat expansions other than *C9orf72*

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Abstract: With the identification of pathological G4C2 repeat expansions in the regulatory region of the C9orf72 gene, the FTLD-ALS spectrum of neurodegenerative CNS diseases has joined the group of repeat expansion diseases. Disease mechanisms associated with repeat expansions include haploinsufficiency due to loss of one functional allele, RNA toxicity due to sequestration of RNA-binding proteins into RNA foci, and production of oligopeptide repeat proteins translated from abnormally transcribed repeat sequences. Experimental evidence has been reported, supporting the role of these mechanisms in FTLD-ALS associated with a C9orf72 repeat expansion mutation. Taken that a substantial portion of familial FTLD, FTLD-ALS or ALS patients have not yet been genetically resolved, we analyzed genome-wide in 47 patients G4C2 repeats for pathological expansions. In total, 94 G4C2 repeat sequences with a minimal size of 3 repeat units were identified in the human genome reference sequence hg19. Sixty two repeat sequences were located intragenic. Repeat-primed PCR analysis was performed of 26 intragenic G4C2 repeats. The allelic variability was limited to one or two alleles for 25 repeats. One noncoding G4C2 repeat in intron 11 of the gene encoding regulator of G-protein signaling 14 (RGS14) revealed at least eight alleles up to 12 repeat units in size, which may be suggestive of genomic instability. The RGS14 G4C2 repeat is analyzed in extended FTLD/ALS patient and control cohorts to identify pathologically expanded alleles.

P.225 Disease modifiers in patients with *C9orf72* repeat expansions

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Abstract: A repeat expansion in chromosome 9 open reading frame 72 (C9ORF72) is currently the most common genetic cause of two devastating neurodegenerative diseases: frontotemporal dementia (FTD) and motor neuron disease (MND). Intriguingly, in patients with these expansions substantial clinical variability has been observed; for instance, age at onset (second to eight decade) and survival after onset (several months to more than twenty years) vary greatly between expansion carriers. To identify genetic disease modifiers that could account for this phenotypic heterogeneity we studied a large cohort of C9ORF72 expansion carriers (n≥330) and controls (n≥374), and investigated repeat sizes, copy numbers and single nucleotide polymorphisms (SNPs). We discovered that C9ORF72 repeat size, ataxin-2 (ATXN2) intermediate repeats, and transmembrane protein 106 B (TMEM106B) variants are able to act as disease modifiers. In our most recent study, we also examined 36 candidates previously implicated in FTD and/or MND. We employed logistic regression models (disease risk), linear regression models (age at onset), and Cox proportional hazards regression models (survival after onset) to assess genetic associations. After adjustment for multiple testing, we identified eight potential disease modifiers, three of which were significantly associated with survival after onset in our FTD subgroup (rs7403881 [MT-Ie], rs13268953 [ELP3] and the epsilon 4 allele [APOE]). Although these variants have already been implicated in FTD and/or MND, we are the first to describe their modifying effect in the presence of a clear pathogenic mutation (i.e. C9ORF72 repeat expansion), thus revealing promising targets for novel treatment strategies and prognostic tests.

P.226 Potential role for homeobox genes in *C9orf72*-related diseases

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Abstract: Hexanucleotide repeat expansions in chromosome 9 open reading frame 72 (C9ORF72) represent the most frequent genetic cause of frontotemporal dementia (FTD) and motor neuron disease (MND). Although reduced C9ORF72 expression levels, RNA foci and dipeptide-repeat proteins have been reported in patients with C9ORF72 repeat expansions, the mechanisms underlying C9ORF72-related diseases remain largely unknown. To increase our understanding, we investigated 32 C9ORF72 expansion carriers (12 FTD, 10 FTD/MND and 10 MND), 30 disease controls (10 FTD, 10 FTD/MND and 10 MND), and 20 controls without neurological diseases. The Whole-Genome DASL HT Assay (Illumina) was used to examine expression profiles in two brain regions: the cerebellum and frontal cortex. Differentially expressed genes were identified using the lumi R package, and those genes were analyzed with enrichment and network modules (MetaCore). In the cerebellum, we discovered 40 differentially expressed genes when comparing C9ORF72 expansion carriers to disease controls (e.g. homeobox genes), all of which were significant after false discovery rate (FDR) correction; importantly, we also noted enrichment for gene ontology (GO) processes involved in development (e.g. organ morphogenesis and skeletal system development [FDRC9ORF72. All findings were comparable when focusing on disease subgroups, and when comparing cases to controls without neurological diseases. Based on our results, we postulate that homeobox genes may play a crucial role in the degeneration of neurons observed in patients with C9ORF72 repeat expansions.

P.227 Screening of FTD-associated genes in a cohort of patients with sporadic ALS

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Abstract: Increasing evidence conclusively indicates that frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) share a considerable clinical, pathological and genetic overlap. Among the six genes associated to autosomal dominant FTD so far, two (c9orf72 and TARDBP) are responsible for a significant fraction of genetically determined ALS cases, both familial and sporadic. Conversely, the mutational frequencies of the four remaining genes (MAPT, GRN, CHMP2B, and VCP) in ALS are poorly understood, although mutations have been reported in isolated cases. To better evaluate this point, we sequenced the exomes of 277 patients with sporadic ALS, pre-screened for mutations in c9orf72 and TARDBP, and analyzed MAPT, GRN, CHMP2B, and VCP genes for rare non-synonymous variants. Within GRN, we identified four mutations (three missense, one frameshift) annotated as pathogenic for FTD in OMIM in 4/277 (1.4%) ALS cases. We also identified three novel missense variants in MAPT (2/277, 0.7%) and CHMP2B (1/277, 0.4%). Of these, a p.V305M MAPT mutation is consistently predicted to be damaging by in silico bioinformatic tools. Conversely, no mutations were observed in VCP. All mutated patients had classic ALS phenotype without associated cognitive impairment and/or parkinsonism, although two individuals carrying GRN mutations had a positive family history for dementia. Our results indicate that, beside FTD, mutations in GRN, and possibly also in MAPT, may be responsible for a small number of ALS cases as well. Screening of larger cohorts will be needed in order to better assess their mutational frequencies in ALS and to establish genotype-phenotype correlations.

P.228 A novel splice site mutation in *GRN* (p.a237fs [A>T]) in a large italian family with FTD from the Apulia-FTD registry

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Abstract: Fifty per cent of FTD are familial. GRN Loss of function mutations (LoF) cause FTD through haploinsufficiency. GRN (p.A237fs [c.709-2A>G]) has been reported as causal in FTD families with predominant language impairment/parkinsonism at onset. Within an FTD population-based registry we identified a large FTD family. All the affected family members were female, with an apparent autosomal dominant mode of inheritance. The diagnosis was made according to Neary. Behavioural and personality changes were the first symptoms at onset. We collected blood samples from: 6 living FTD subjects, 19 unaffected first relatives. We screened for: GRN, VCP, MAPT, and TDP43 mutations, C9orf72 expansions. We measured plasma progranulin with ELISA. We found a novel pathogenic splice site mutation in GRN (p.A237fs [c.709-2A>T]), cosegregating with FTD. The mutation was found also in 2 unaffected relatives. Mean plasma GRN levels were: 26.5 ng/ml in 4 affected GRN+ (2 were deceased meanwhile); 21.5 ng/ml in the 2 unaffected first-degree GRN+; 82.0 ng/ml in the 4 unaffected first-degree GRN-; 142.7 ng/ml in the 28 unrelated controls GRN-, (p=0.005, Kruskal Wallis). This family confirms that clinical phenotypes associated with spectrum of GRN mutations are heterogeneous. A gradient in the reduction of progranulin levels was identified with the highest levels in healthy unrelated controls and the lowest in the mutation carriers, while intermediate levels were found in the unaffected non-carriers relatives. Plasmatic progranulin levels may mirror LoF mutations in GRN, being a useful biomarker to identify GRN mutation carriers, to follow-up treatments response and to identify at risk relatives.

P.229 Cytokine and chemokine gene expression in peripheral cells from patients with frontotemporal lobar degeneration due to *GRN* and *C9orf72* mutations

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Abstract: Mutations in Progranulin (GRN) and Chromosome 9 Open Reading Frame 72 (C9ORF72) genes are common causes of familial Frontotemporal Lobar Degeneration (FTLD). This study aimed to evaluate the expression of inflammatory factors in peripheral cells from GRN and C9ORF72 carriers as compared with sporadic FTLD and controls. Sabiosciences PCR array containing cytokines or chemokines was used to investigate the expression profile of cytokines in 3 C9ORF72 symptomatic expansion carriers, 3 GRN symptomatic carriers, 3 sporadic FTLD patients and 3 age-matched controls. We observed a generalized down-regulation of cytokine and chemokine expression levels in GRN symptomatic carriers compared with controls; in particular Interleukin (IL)-8 and IL-4 expression levels showed a significant down-regulation (-6.94, -4.94 fold decrease over controls, respectively, PPC9ORF72 expansion carriers compared with controls, we showed a more heterogeneous situation; in particular, chemokine (C-C motif) ligand 2 (CCL2) and chemokine (C-X-C motif) ligand 10 (CXCL10) were significantly over-expressed (12.79, 12.30 fold regulation over controls, respectively, PGRN and C9ORF72 expansion carriers. Preliminary results showed opposite trend of inflammatory molecules expression levels between FTLD GRN or C9ORF72 carriers and sporadic patients compared with controls, suggesting different pathogenic pathways between mutation carriers and sporadic FTLD.

P.230 *PRKAR1B* mutation associated with a new neurodegenerative disorder with unique pathology

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Abstract: Pathological accumulation of intermediate filaments can be observed in neurodegenerative disorders, and is characteristic for neuronal intermediate filament inclusion disease. Intermediate filaments type IV include three neurofilament proteins (light, medium and heavy molecular weight neurofilament subunits) and α-internexin. Here we describe a family with a novel late-onset neurodegenerative disorder presenting with dementia and/or parkinsonism in 12 affected individuals. The disorder is characterized by a unique neuropathological phenotype displaying abundant neuronal inclusions by haematoxylin and eosin staining throughout the brain with immunoreactivity for intermediate filaments, but negative immunoreactivity for fused in sarcoma. Combining linkage analysis, exome sequencing and proteomics analysis, we identified a heterozygous c.149T>G (p.Leu50Arg) missense mutation in the gene encoding the protein kinase A type I-beta regulatory subunit (PRKAR1B). The pathogenicity of the mutation is supported by segregation in the family, absence in variant databases, and the specific accumulation of PRKAR1B in the inclusions in our cases associated with a specific biochemical pattern of PRKAR1B. Screening of PRKAR1B in 138 patients with Parkinson's disease and 56 patients with frontotemporal dementia did not identify additional novel pathogenic mutations. Our findings link a pathogenic PRKAR1B mutation to a novel hereditary neurodegenerative disorder and suggest an altered protein kinase A function through a reduced binding of the regulatory subunit to the A-kinase anchoring protein and the catalytic subunit of protein kinase A, which might result in subcellular dislocalization of the catalytic subunit and hyperphosphorylation of intermediate filaments.

P.231 Assessment of the *C9orf72*, *PGRN* and *MAPT* mutations in clinically early-onset Alzheimer's disease in the absence of known mutations

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Abstract: Patients with early-onset Alzheimer disease (EOAD; C9ORF72, PGRN and MAPT mutations in Korean EOAD patients who do not have APP, PSEN1, PSEN2 and PRNP mutations. C9ORF72, PGRN and MAPT were analyzed by direct sequencing for 146 young Korean patients with clinical EOAD, followed by web-based splice sites prediction and/or protein function prediction, and in silico prediction and protein modeling. We found one new deletion mutation, one new missense mutation and one novel intronic polymorphism in the PGRN gene, and two silent mutations in the MAPT gene. However, we could not find any pathological elongation of GGGGCC hexanucleotide repeat in C9ORF72. This study provided new insight into FTD study.

P.232 Uncoupling of mGluR5 availability and glucose metabolism in behavioral variant FTD: a multitracer PET study

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Abstract: Although the pathogenic mechanisms underlying behavioral variant FTD (bvFTD) have yet to be fully elucidated, aberrant glutamatergic neurotransmission has been hypothesized to play a important role owing to significant involvement of glutamatergic pyramidal cells. Using Positron emission tomography (PET), mGlur5 availability ([11C]ABP-688) and glucose metabolism ([18F]FDG) were measured in bvFTD (n=5) and cognitively normal (CN, n= 10)) subjects. [11C]ABP-688 binding potential maps (BPND) were calculated using the cerebellum as a reference region, with [18F]FDG standardized uptake ratio maps (SUVR) normalized to the pons. Voxel-based group differences were obtained using RMINC. Correlation analyses were conducted voxel wise and within volumes of interest (VOIs). Decrements in mGluR5 were widespread throughout cortical and subcortical areas, with maxima in the orbitofrontal cortex, superior frontal gyrus, anterior insula, and temporal lobe (p 11C]ABP-688 BPND and [18F]FDG SUVR was partial, with the magnitude of declines in mGluR5 greater than that observed for FDG. Interestingly, a negative correlation was found between [11C]ABP-688 BPND and [18F]FDG SUVR in bvFTD, while positive correlations were observed among CN subjects. In addition to providing the first in vivo descriptions of mGluR5 dysfunction in bvFTD, these findings suggest that glutamatergic dysfunction may precede degenerative changes in bvFTD and that [11C]ABP-688 may prove a sensitive marker of this process.

P.233 Specific social impairments predict degeneration in dissociable intrinsically connected networks in FTLD patients

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Abstract: It has been demonstrated that regional atrophy in neurodegenerative diseases targets intrinsic connectivity networks (ICN) resulting in network-based degeneration. While these atrophic patterns and their relationship to ICNs are well known, their relation to behavioral performance in patients is not well understood. For example, variable performance deficits on socioemotional tasks are observed not only in bvFTD, but in neurodegenerative patients across diagnostic groups. However, if distinct social impairments predict damage to specific, dissociable ICNs, this provides important diagnostic information. We investigated this in 197 subjects [bvFTD(n=33), rtFTD(n=10), svPPA(n=11), nfvPPA(n=11), CBS(n=17), PSP(n=21), AD(n=50) and healthy older controls(n=44)], contrasting performance in non-emotional social cognition (cognitive perspective-taking task) with emotion reading (TASIT Emotion Evaluation Task). Behavioral performances across diagnostic groups revealed heterogeneous patterns of impairment in both tasks compared to controls ($p<0.05$). VBM of structural MRI shows atrophy in default mode network (precuneus, posterior cingulate, medial prefrontal cortex) and frontoparietal network (lateral parietal and frontal cortex) contributing to impairment in perspective taking/cognitive theory of mind ($pFWE<0.05$). Conversely, we found bilateral salience network (anterior cingulate and insula) and limbic/semantic appraisal network (anterior temporal, ventromedial PFC) atrophy predicted degree of impairment in emotion evaluation ($pFWE<0.05$). These results provide direct evidence that deficits on dissociable (cognitive versus emotional) aspects of social tests predict degeneration corresponding to distinct ICNs. Direct patient testing to identify distinct patterns of performance on these two brief tasks can provide important differential diagnostic information to clinicians.

P.234 Relationship between atrophy and resting state functional connectivity

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Abstract: Primary progressive aphasia (PPA) is a syndrome of progressive language decline caused by neurodegenerative pathology. Alterations in hemodynamic physiology have been documented in PPA, as assessed by both event-related and task-free functional magnetic resonance imaging (MRI). However, currently, it is unclear how these changes are related to the magnitude of atrophy as detected by quantitative morphometric methods such as FreeSurfer. In order to address this question, we identified a group of 10 patients diagnosed with the nonfluent/agrammatic variant of PPA, all of whom showed no significant atrophy according to cortical thickness analysis with FreeSurfer, using an FDR cutoff of 0.05. Task-free functional MRI scans were obtained on these 10 patients and on 33 healthy age-matched controls. The resultant spontaneous hemodynamic fluctuations were subjected to resting state functional connectivity (RSFC) analysis, in order to measure the coherence between nodes of the left temporosylvian language network. Nodal regions in this analysis included the left inferior frontal gyrus, posterior middle temporal gyrus, and anterior temporal lobe. Compared to controls, the PPA patients showed significantly decreased connectivity between the left inferior frontal gyrus and middle temporal gyrus. Connectivity between nodes of the spatial attention network, the frontal eye fields and intraparietal sulci, remained intact in those same patients, demonstrating the specificity of this finding. This study shows that RSFC may serve as an early biomarker of network-level perturbations caused by neurodegenerative disease processes.

P.235 Joint assessment of white matter integrity, cortical and subcortical atrophy to distinguish AD from behavioral variant FTD: a multi-center study

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Abstract: The frequent overlap of the clinical symptoms associated with Alzheimer's disease (AD) and behavioral variant frontotemporal dementia (bvFTD) pose serious problems in the differential diagnosis. We investigated the ability of cortical and deep gray matter (GM) atrophy in combination with white matter (WM) integrity to distinguish bvFTD from AD and controls. 24 patients with bvFTD (63y±8, 25%F, MMSE 25±3), 32 patients with AD (67y±8, 38%F, MMSE 23±3), and 37 controls (60y±6, 43%F, MMSE 29±1) were scanned on a 3T MRI. Cortical GM atrophy was determined using voxel-based morphometry (VBM), and volumes of deep gray matter (DGM) structures were estimated using FIRST. Fractional anisotropy (FA) was interpreted as measures of WM integrity using tract-based spatial statistics (TBSS). To determine which combination of MR markers differentiated the three groups with the highest accuracy, we conducted a discriminant function analysis. Adjusted for age, sex and center, bvFTD patients had more GM atrophy in orbitofrontal and inferior frontal areas, anterior cingulate and insula than AD patients. In addition, DGM structures, particularly caudate nucleus and nucleus accumbens were smaller in bvFTD than in AD. FA values in frontal areas of the brain were lower in bvFTD than in AD. Combination of modalities led to 90% correct classification of patients. GM and hippocampal atrophy contributed most to distinguishing any type of dementia from controls, while WM integrity was helpful to discriminate bvFTD from AD. These findings suggest that, FA measures add complementary information to measures of GM atrophy, thereby improving the classification between AD and bvFTD.

P.236 More atrophy of deep gray matter structures in behavioral variant frontotemporal dementia compared to Alzheimer's disease

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Abstract: The involvement of frontostriatal circuits in behavioral variant Frontotemporal Dementia (bvFTD) suggests that deep gray matter structures (DGM) may be affected in this disease. We therefore investigated whether volumes of DGM structures differed between patients with bvFTD, Alzheimer's Disease (AD) and controls and explored relationships between DGM structures and cognition. 24 patients with bvFTD were matched based on age, gender and education at a ratio of 1:3 to 72 AD patients and 72 patients with subjective memory complaints as controls. Volumes of hippocampus, amygdala, thalamus, caudate nucleus, putamen, globus pallidus and nucleus accumbens were estimated by automated segmentation of 3D T1-weighted MRI. MANOVA with Bonferroni adjusted post-hoc tests was used to compare volumes between groups. Relationships between volumes, and cognition were examined using Spearman correlations. Nucleus accumbens discriminated all groups, with most severe atrophy in bvFTD. Caudate nucleus and globus pallidus discriminated bvFTD from AD and from controls. Hippocampus only discriminated dementia from control subjects and amygdala differed solely between bvFTD and controls. Relations between cognitive performance and DGM volumes were mainly found in AD patients and control subjects, while in bvFTD patients only globus pallidus was correlated to executive functioning. The observed difference in volume of the DGM structures, especially of nucleus accumbens, caudate nucleus and globus pallidus, supports the idea that next to frontal cortical atrophy, DGM structures, as parts of the frontal circuits, are damaged in bvFTD rather than in AD.

P.237 Brain glucose metabolic abnormalities in prodromal FTD/ALS with *C9orf72* mutation

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Abstract: Brain imaging of FTD/ALS with abnormal expansion in the C9ORF72 gene has shown widespread damage in bilateral anterior and posterior regions. Here we investigated FDG-PET abnormalities in clinically unaffected carriers of the expansion. Twenty-three members of families with FTD/ALS caused by C9ORF72 mutation underwent clinical and genetic testing, and FDG-PET and MR imaging. Bilateral 8-mm anterior (frontal, anterior temporal), posterior (temporal, parietal), and subcortical (caudate, thalamus) regions-of-interest (ROIs) were applied to coregistered individual MRI/PET. FDG uptake was calculated as the ratio between each ROI's radioactivity concentration and that of the pons. ANCOVA adjusting for age was used to compare unaffected mutation carriers and non-carriers. Z scores normalized to non-carriers were computed to evaluate ROIs with impaired uptake in carriers. The study included 9 unaffected carriers, M age=46+11.3, 24-57, not meeting FTD or ALS diagnostic criteria, with normal cognitive, functional and motor assessment, 3 carriers with bvFTD (2 with ALS), M age=54+2.0, 52-56, and 11 non-carriers, M age=60+10.0, 47-83. Unaffected carriers had reduced averaged anterior and posterior uptake bilaterally, similar to affected carriers and significantly lower than non-carriers: M=1.57+0.39, 1.55+0.37, 1.79+0.22, p=.026, and M=1.50+0.13, 1.48+0.30, 1.66+0.24, p=.004, respectively. Their average count of ROIs with impaired uptake (z>-1) was between that of affected carriers and non-carriers (3, 5, 9, p=.033), and involved most often dorsolateral prefrontal, orbitofrontal, superior temporal and parietal ROIs. These findings on young/middle-aged clinically unaffected mutation carriers suggest that a diffuse neurodegenerative process associated with the C9ORF72 expansion begins well before onset of FTD and/or ALS symptoms.

P.238 Neuroanatomical changes in behavioral variant frontotemporal dementia correlate with risk-related behavior

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Abstract: The Balloon Analogue Risk Task (BART) assesses decision-making in a risk/reward context. Little work has investigated the relationships between BART performance and gray matter (GM) and white matter (WM) disease in behavioral variant frontotemporal dementia (bvFTD) although bvFTD is associated with decision-making deficits. We collected a modified version of BART on 22 patients with bvFTD and 24 demographically comparable healthy seniors. For each trial in this computer-based task, the participant pumps up a virtual balloon to accrue points until either they decide to add the points to their total bank or the balloon pops and they receive no points. However, the number of pumps required to pop a balloon varies and is unknown to the participant. Thus, higher bank totals correspond with more successful decision-making, and final bank totals were lower in bvFTD relative to controls. T1-weighted and diffusion-weighted images were acquired for these bvFTD patients and 36 demographically comparable healthy seniors. GM density and fractional anisotropy (FA) were assessed in bvFTD relative to healthy seniors, and BART bank total was related to GM density and FA in bvFTD using regression analyses. GM density and FA reductions were widespread in bvFTD throughout frontal and temporal GM and WM, respectively. BART bank total was associated with GM density in right orbitofrontal cortex, anterior insula, and dorsomedial prefrontal cortex and FA in related regions of WM. We conclude that patients with bvFTD demonstrate impairments in risk-related decision-making, which are associated with damage in frontotemporal networks involved in stimulus evaluation and decision-making.

P.239 Cortical thinning and white matter tract damage in relation to cognition in motor neuron diseases

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Abstract: The patterns of cortical thinning and white matter (WM) tract abnormalities in relation to cognition and behavioural symptoms were assessed in 100 patients with motor neuron disease (MND) compared with 59 healthy subjects. Patients were classified into MND with a pure motor syndrome (MND-motor) and those with cognitive/behavioural symptoms (MND-plus). A surface-based morphometry analysis was used to assess cortical thickness. Corticospinal tract (CST), corpus callosum (CC), and major association tracts diffusion tensor (DT) metrics were obtained. A Random Forest (RF) approach was used to identify the set of image features correlated with cognitive/behavioural deficits. There were 35 MND-motor and 65 MND-plus patients. Relative to controls, both patient groups showed cortical thinning of the bilateral precentral and postcentral gyri, cingulate cortex, inferior temporal and parietal regions. In all regions, there was a trend towards a more severe and extensive involvement in MND-plus vs MND-motor. Relative to controls, both patient groups showed a damage of the CST bilaterally and motor CC fibers, but such a damage was greater in MND-plus cases. MND-plus patients showed a severe involvement of the extra-motor WM tracts bilaterally. RF analysis showed that the best predictors of executive dysfunction, memory deficits and behavioural symptoms in MND patients were the DT MRI metrics of the frontotemporal, frontoparietal and CC fibers. Cortical thinning and WM degeneration are highly dependent upon neuropsychological and behavioural symptoms deficits in patients with MND. WM tract damage contributes to the severity of selective cognitive and behavioural manifestations more than cortical thinning. Funding: #RF-2010-2313220.

P.240 Connected speech production in the nonfluent variant of primary progressive aphasia and its relationship with white matter damage

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Abstract: Aim of this study is to investigate the association between the different components of the connected speech and white matter (WM) damage in nonfluent variant of primary progressive aphasia (nfvPPA). To assess the connected speech, we recorded speech samples from 11 nfvPPA patients while they described the image of the picnic picture subtest of the Western Aphasia Battery and analyzed them considering: lexical production rate and phonological/articulatory errors; pauses and repetitions; lexical typology; and syntactic structure. Diffusion tensor (DT) MRI metrics were obtained from the interhemispheric and major long association WM tracts. Speech samples in nfvPPA patients were characterized by slow rate, distortions, syntactic errors and reduced complexity of sentence production. The lexical production rate was positively related with the integrity of the left superior longitudinal (SLF) and inferior longitudinal (ILF) fasciculi and cingulum bilaterally; the Italian phoneme distortions were related with damage of the corticospinal tracts; the false starts were related with damage of the corpus callosum (CC); the lexical selection (such as the use of nouns, verbs, or prepositions) was related with DT MRI metrics of left SLF and CC genu; the syntactic complexity (i.e., mean length of utterance, ratio between number of words per sentence and number of sentences) and presence of morpho-syntactic errors were related with damage of the left SLF and ILF, and CC body. We reported associations between particular aspects of connected speech and specific WM tract integrity in nfvPPA. This study underlines the relevant role of WM in nfvPPA. Funding: GR#2010-2303035.

P.241 Longitudinal patterns of cortical thinning in behavioural variant frontotemporal dementia

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Abstract: Characteristic magnetic resonance imaging (MRI) abnormalities have been shown in cross-sectional studies of behavioural variant frontotemporal dementia (bvFTD) but little is known about patterns of change over time. In order to investigate this further we applied the technique of cortical thickness measurement to a cohort of 30 bvFTD patients (mean (standard deviation) disease duration at baseline = 4.6 (3.2) years) who had undergone three serial volumetric T1-weighted MRI scans over an interval of 2.8 (2.1) years and 86 healthy age-matched controls. At baseline, peak areas of cortical thinning included the entorhinal cortices (23% thinner than controls bilaterally), temporal poles (17% right, 19% left) and parahippocampal cortices (12% right, 15% left). Significant cortical thinning was also detected in the precentral gyrus (8% right, 10% left), anterior cingulate (4% right, 9% left), orbitofrontal lobe (6% bilaterally) and insula (6% right, 8% left). At follow-up, these areas showed further reduction, with thinning spreading more posteriorly in the cingulate and temporal lobes and through prefrontal areas (pars triangularis (4% right, 7% left) and pars opercularis (7% right, 6% left), inferior parietal lobe (6% bilaterally) and precuneus (7% right, 6% left). At the third visit, thinning was evident in all cortical areas except for the occipital and superior parietal lobes which remained spared. Disease progression is associated with spreading of cortical thinning from initial anterior areas in the insula, cingulate, frontal and temporal lobes to more posterior areas but with sparing of superior parietal and occipital lobes even late in the disease course.

P.242 Longitudinal rates of regional cortical thinning in behavioural variant frontotemporal dementia

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Abstract: Longitudinal measures of cortical thickness may provide a sensitive measure of disease progression in behavioural variant FTD (bvFTD) but have yet to be extensively studied. We applied an automated method of measuring cortical thickness in a cohort of 61 bvFTD patients (including 7 C9ORF72 expansion and 15 MAPT mutation cases) and 76 healthy controls who had undergone two serial volumetric T1-weighted MRI scans (mean (standard deviation) interval 1.5 (1.1) years). Annualised rates of cortical thinning in frontal, temporal, insular, cingulate, parietal and occipital cortices were analysed using linear regression adjusted for age, gender and scanner. Compared with controls, bvFTD demonstrated significantly reduced baseline cortical thickness and significantly higher rates of thinning in all 6 regions (all $p<0.001$), with rates highest in the insular (1.5%), cingulate (1.3%), temporal (1.2%) and frontal (1.1%) cortices (compared with 0.0% in all areas in controls). Comparing the genetic groups, areas that were significantly thinner at baseline in the MAPT compared with the C9ORF72 group were the temporal (2.1 vs 2.4mm, $p<0.001$) and insular (2.4 vs 2.7mm $p=0.023$) cortices but in contrast the rate of thinning was significantly higher in the same areas in the C9ORF72 group compared with MAPT (insular: 1.7 vs 1.2%, $p=0.015$; temporal: 1.4 vs 0.9%, $p=0.002$). Sample sizes required to detect a 20% reduction in rate of thinning with 90% power in a one year trial were smallest for the insular and cingulate cortices (~140). Cortical thickness measurements provide information about disease evolution in bvFTD and are promising surrogate biomarkers for trials.

P.243 Laterality of amyloid deposition in dementia phenotypes

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Abstract: Primary progressive aphasia (PPA) is a clinical dementia syndrome often characterized by asymmetric atrophy in the language-dominant (usually left) hemisphere. Common neuropathologies reported for PPA include Alzheimer's disease (AD), or a form of frontotemporal lobar degeneration. Previous studies have found that PPA patients with postmortem AD show a left lateralized distribution of neurofibrillary tangles, but not beta-amyloid (Aβ) plaques, in contrast to the symmetric pathology of patients with amnestic dementia of the Alzheimer's type (DAT). The present study investigated the laterality of in vivo amyloid burden in Aβ positive PPA patients and patients with amnestic mild cognitive impairment (aMCI) and DAT. Thirty-four patients were screened for amyloid positivity with the PET ligand 18F-labelled florbetapir. Thirteen PPA and five amnestic patients (two aMCI, and three DAT) showed elevated amyloid (cerebral-to-cerebellar standard uptake value ratio ≥ 1.10). Laterality was examined for each of six a priori volumes of interest (VOI; frontal, temporal, parietal, anterior cingulate, posterior cingulate, and precuneus) to determine the hemispheric asymmetry among amyloid positive subjects. The florbetapir burden showed a strong leftward asymmetry for the PPA group in the parietal VOI, while the amnestic group showed a symmetric pattern. The asymmetric distribution of amyloid in the parietal VOI of the PPA group is consistent with early cortical atrophy patterns. Moving forward, it will be important to determine how atrophy, disease stage, and imaging agent influence the estimations of amyloid in vivo.

P.244 Psychotic symptoms are related to cerebellar-thalamic-cortico networks in the motor neurone disease-frontotemporal dementia continuum

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Abstract: Delusions and hallucinations are prevalent in a subset of patients with FTD and MND, particularly those with TDP-43 pathology. Similarly, the C9orf72 genetic mutation causes TDP-43 protein accumulation and many FTD carriers present with psychosis. Imaging studies of the C9orf72 mutation have demonstrated thalamic and cerebellar atrophy in addition to frontal and temporal atrophy. The thalamus is responsible for sensory integration and together these findings suggest that cerebellar-thalamic-cortico network's may be involved in generating psychotic symptoms across the continuum. This study aimed to investigate this association. All patients (n=42) and a group of age-matched controls (n=20) underwent MRI scanning at presentation. Each participant was subject to detailed clinical interview, neuropsychological testing and functional disability assessment. A composite score was generated to express the degree of psychosis present for each subject. This was calculated from responses during clinical interview and the carer based delusions and hallucinations subcategories of the Neuropsychiatric Inventory (NPI). We then employed voxel based morphometry (VBM) techniques to covary the degree of psychosis to regions of atrophy. Compared to controls the patient group exhibited significant atrophy across regions including bilateral frontal and temporal lobes, the cerebellum, basal ganglia and thalamus (p corrected). A significant association was found between atrophy of subcortical structures and psychotic symptoms across the FTD-MND continuum (p uncorrected). This novel study suggests that subcortical networks are critical for the generation of psychotic features in the FTD-MND continuum. This patient group may benefit from pharmacological therapies aimed at disease burden in these regions.

P.245 Cortical thinning in presymptomatic *C9orf72* mutation carriers without changes in cognitive domain performance

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Abstract: C9ORF72 is the most common genetic cause of familial FTD and ALS. The neuroimaging features of this mutation have been well characterized in affected subjects; however, the progression of structural changes in the presymptomatic stage of the disease remains unknown. In this study, we compared cortical thickness and cognitive domain performance of 8 presymptomatic C9ORF72 mutation carriers with 11 non-carrier family member controls. Presymptomatic mutation carriers were included in the study based on a) a positive family history of FTD, b) positive molecular genetic testing for a C9ORF72 mutation and c) clinical assessment without a diagnosis of dementia. Test scores from the neuropsychological battery were converted into cognitive domain z-scores of working memory, attention, language, nonverbal memory, verbal memory, visuospatial skills and executive function. Between-group differences in cortical thickness were assessed using a surface based vertex-by-vertex model correcting for age, sex, MMSE and years to mean age of family onset. Cortical thickness analyses were performed at three consecutive smoothing levels (10mm, 15mm, and 20mm) with consistently significant clusters reported. Compared to the non-carrier control family members, the presymptomatic C9ORF72 mutation carriers exhibited asymmetrical thinning in the right temporoinsular and left mediofrontal and superior temporal regions, with no significant difference in cognitive domain z-scores. These findings suggest that cortical thinning occurs prior to cognitive decline in presymptomatic C9ORF72 mutation carriers. The early cortical thickness and cognitive patterns appear to differ between C9ORF72 and GRN mutation carriers.

P.246 Decreased performance on cognitive domains in presymptomatic *GRN* mutation carriers without cortical atrophy

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Abstract: The characterization of the presymptomatic stages of genetic forms of frontotemporal dementia is important to the development of early disease interventions. There are some data that suggest that white matter and functional connectivity changes occur prior to grey matter atrophy in presymptomatic GRN mutation carriers, while the onset of subtle neuropsychological changes is not yet characterized. In this study, we compared cortical thickness and cognitive domain performance in 6 presymptomatic GRN mutation carriers with 9 non-carrier family member controls. Presymptomatic mutation carriers were included in the study based on a) a positive family history of FTD due to GRN, b) a positive molecular genetic test for a GRN mutation and c) clinical assessment without evidence of dementia. Between group differences in cortical thickness were assessed using a surface based vertex-by-vertex model correcting for age, sex, MMSE scores and years to mean age of family onset. Test scores from the neuropsychological battery were converted into cognitive domain z-scores of working memory, attention, language, nonverbal memory, verbal memory, visuospatial skills and executive function. Compared to non-carrier controls, the GRN mutation group exhibited poorer performance on domains of working memory ($p = 0.02$) and executive function ($p= 0.01$) with a trend towards reduced language ($p = 0.06$) and visuospatial domains ($p = 0.08$), but did not exhibit any significant difference in cortical thickness. These findings suggest that cognitive changes may precede cortical grey matter atrophy in GRN mutation carriers, however further studies with larger sample sizes are needed.

P.247 A multi-voxel pattern analysis (MVPA) to define neuroimaging markers in granulin disease

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Abstract: In light of future pharmacological interventions, neuroimaging markers able to monitor efficaciously the response to treatment would be key. In Granulin (GRN) disease, preclinical data will prompt pharmacological trials in the near future. Two main points need to be assessed: 1) to identify the target regions to monitor disease progression in the different disease stages and 2) the most accurate functional and/or structural neuroimaging index to be used. To this aim, we have taken advantage of the multivariate approach of Multi-Voxel Pattern Analysis (MVPA) to explore the information of brain activity patterns in a cohort of GRN Thr272fs carriers at different disease stages (14 FTD and 17 asymptomatic carriers) and a group of 33 healthy controls. We studied structural changes with Voxel-Based Morphometry (VBM), functional connectivity by assessing salience, default mode, frontoparietal, dorsal attentional, executive networks, and local connectivity with ReHo, ALFF, fALFF, Degree Centrality and WMHC. In FTD patients with GRN mutation, the most predictive measure was VBM structural analysis, whilst in asymptomatic carriers the best prediction was made by local connectivity measures (fALFF). Taken together, all indexes demonstrated fronto-temporo-parietal damage in GRN pathology, with a widespread structural damage of frontal and temporal regions when disease is overt, and functional impairment limited to parietal regions in the presymptomatic phases. In conclusion, MVPA is of help in identifying the most accurate neuroimaging marker for clinical trials. This approach is able to identify both the target region and the best neuroimaging approach, which will be different in the different disease stages.

P.248 Social cognition and executive performance predicted by network centrality of bvFTD atrophy areas

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Abstract: The core clinical features of the frontemporal dementia (bvFTD) encompass progressive social, behavioral and executive functions. The pattern of atrophy in early stages affects a frontotemporoinsular network that includes anterior cingulate cortex, anterior insula, frontal pole, amygdale and striatum. Some researchers have found that connectivity abnormalities were associated to behavioral symptoms, executive dysfunctions and disease severity. However, none of these studies have employed social cognition tasks to investigate the possible relationship between social deficits and connectivity abnormalities. The aim of our work was to assess whether patients' connectivity might be associated to social cognition evaluation outcomes. Fourteen bvFTD patients and twelve healthy matched controls underwent fMRI resting-state paradigm and we assessed their performance in facial emotion recognition, ToM and executive functions. bvFTD patients presented a significant impaired performance in these three domains compared to controls. We assessed the Network Centrality (NC) of areas comprising the typical pattern of atrophy in bvDFT (involving frontal, insular and temporal cortices). NC was decreased in patients compared to controls. Simple linear regression for the entire sample revealed that the NC predicted participants performance in both social cogniton and executive functions assesstment. Classification methods revealed that patients were discriminated from the control group by the combination of NC values and their social-executive performance. In conclusion, early degeneration in bvFTD alters NC in the frontotemporoinsular network, which is associated with high-level social cognitive and executive profiles. Partially supported by grants from CONICET, CONICYT/FONDECYT Regular (1130920 and 1140114), FONCyT-PICT 2012-0412, FONCyT-PICT 2012-1309, and the INECO Foundation.

P.249 Extended networks for moral cognition in frontotemporal dementia

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Abstract: Moral judgment has been proposed to rely in the ventromedial prefrontal cortex (VMPFC) and its impairments have widely reported in the behavioral variant frontotemporal dementia (bvFTD). Nevertheless, no studies have investigated the structural correlates of moral judgments in bvFTD. This work assessed the gray matter (GM) changes associated with moral judgments in 14 bvFTD patients and 11 controls. We compared the behavioral performance of both groups in a moral judgment task involving scenarios that disentangle the contributions of intentions and outcomes. Moreover, we used voxel-based morphometry to we explore the associations between GM volume and moral judgments, considering a priori selected regions of interest involved in moral cognition. Our results showed that bvFTD patients judged attempted harm as more permissible and accidental harm as less permissible than controls. In both groups, performance in accidental harm was associated with GM volumes in precuneus and VMPFC. In bvFTD, performance was also associated with temporo-parietal junction (TPJ), amygdala and temporal pole. For both groups, performance in attempted harms was associated with GM volume in TPJ. Results suggest that moral judgment abnormalities in bvFTD are related to an impaired integration of intentions and outcomes, which seems to depend on an extended brain network. Thus, crucial areas for inferring intentions and for emotion processing beyond VMPFC seem to account for moral judgment abnormalities in bvFTD. These results have important implications for brain network models associated with moral judgment. (partially supported by grants CONICYT/FONDECYT Regular (1130920), PICT 2012-0412 and PICT 2012-1309, CONICET and INECO Foundation).

P.250 White matter damage across the ALS-FTD continuum

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Abstract: This study aims to investigate the patterns of white matter (WM) damage along the ALS-FTD continuum. We enrolled 14 behavioral variant of FTD (bvFTD) patients, 12 semantic (svPPA) and 11 nonfluent (nfvPPA) primary progressive aphasia patients, 21 progressive supranuclear palsy (PSP) patients, 35 amyotrophic lateral sclerosis (ALS) patients with or without cognitive impairment (14 ALS-plus and 21 ALS-motor), and 28 healthy controls. Tract-based spatial statistics was used to perform a voxel-wise analysis of diffusion tensor (DT) MRI metrics. Fractional anisotropy was the most altered DT MRI metric in all comparisons. The most impaired patients were bvFTD and ALS-plus, with bvFTD showing damage of supratentorial WM and sparing of the internal capsule and infratentorial regions and ALS-cog showing a similar pattern with additional involvement of the corticospinal tracts and cerebellar WM. PSP showed a similar pattern with additional involvement of midbrain, thalami and superior cerebellar peduncles. NfvPPA showed involvement of supratentorial WM, thalami and midbrain with prevalent involvement of left fronto-temporal WM and body of corpus callosum (CC). SvPPA patients showed left frontal and anterior temporal damage with involvement of the entire CC. The least damaged group was ALS-motor, showing alterations in the posterior/middle portion of the body of CC only. Performance at the executive tests correlated with frontal damage. This study shows overlapping WM tract damage across the whole ALS-FTD continuum. In frontotemporal lobar degeneration, WM damage may contribute to symptoms and disease pathogenesis. Funding: #RF-2010-2313220, #GR-2010-2303035, CurePSP#MD505-12_001, ADDF#20131211.

P.251 Mapping regional grey and white matter damage in patients with progressive supranuclear palsy syndrome

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Abstract: This study investigated the pattern of grey matter (GM) atrophy and white matter (WM) damage in patients with probable progressive supranuclear palsy syndrome (PSPs) using MRI. We enrolled 21 patients with probable PSPs and 21 age and sex-matched healthy controls. Patients underwent clinical and neuropsychological evaluation, and brain structural and diffusion tensor (DT) MRI. The regional patterns of brain GM atrophy and WM microstructural damage were assessed using voxel-based morphometry and tract-based spatial statistics, respectively ($p<0.05$ FWE). PSPs patients were in a moderate stage of disease (Hoehn and Yahr score: 3.3) and showed mild to moderate cognitive impairment involving especially attentive-executive functions. PSPs patients did not show GM atrophy relative to controls. On the contrary, they showed a reduction of fractional anisotropy (FA) and an increase of mean, axial and radial diffusivities in the main WM tracts bilaterally, including body and splenium of corpus callosum, cingulum, inferior fronto-occipital, superior longitudinal and uncinate fasciculi, anterior and superior corona radiata, corticospinal tracts, and thalamic radiations. Superior cerebellar peduncles and internal capsules showed a significant increase of diffusivity values, but no FA changes. In PSPs patients, WM microstructural damage is prominent compared to GM atrophy even in the moderate stage of the disease, suggesting that diffuse WM damage in tauopathies is not merely a function of disease severity. Regional differences in DT MRI metrics might reflect a different vulnerability of WM tracts. Our finding might provide new insight in understanding the pathophysiology of the disease and the clinical progression. Funding: CurePSP MD505-12_001.

P.252 Development of a visual rating scale for atrophy of the anterior cingulate, insula and frontal lobes

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Abstract: Studies of frontotemporal dementia (FTD) have shown that brain atrophy occurs earliest in the anterior cingulate, insula and orbitofrontal lobes. Whilst visual rating scales of atrophy in the medial temporal and parietal lobes have been shown to be helpful in the diagnosis of Alzheimer's disease (AD), there have been few studies of such scales in FTD. We developed new visual rating scales (range of scores 0-3) of anterior cingulate (ACA), fronto-insular (FIA) and orbitofrontal atrophy (OFA) to investigate whether they may be helpful in distinguishing FTD from AD, and from cognitively-normal controls, comparing them with previously developed scales of medial temporal atrophy (MTA, range 0-4), posterior atrophy (PA, range 0-3) and anterior temporal atrophy (ATA, range 0-4). Magnetic resonance imaging of 150 subjects (50 FTD, 50 AD and 50 controls) age and gender matched were collected and analysed using visual rating scales by a trained rater. Weighted kappa values for intra-rater agreement were 0.86 for the ACA scale, 0.81 for the FIA scale and 0.89 for the OFA scale. Combining scores for the right and left hemispheres, significant differences were found between FTD and controls, and AD and controls for all scales. Only the OFA (mean (standard deviation) FTD 1.7 (0.9), AD 1.0 (0.7), controls 0.6 (0.6)) and ACA (FTD 1.5 (0.9), AD 1.1 (0.6), controls 0.8 (0.6)) showed significantly higher scores in FTD compared to AD. These easy and reproducible scales can be useful tools in the clinical setting for the discrimination of FTD and AD.

P.253 Using MRI arterial spin labelling to investigate cerebral perfusion in frontotemporal dementia

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Abstract: Earlier studies have used Arterial Spin Labelling (ASL) to detect abnormal perfusion in dorsal brain areas in frontotemporal dementia (FTD). This study investigated whether ASL can also be used to detect the clinically important ventral frontal and temporal abnormalities in FTD (n=13) compared with healthy age-matched controls (n=17). Using a 3T MRI scanner, ASL images were acquired at 4 different time points after labelling (20 slices, voxel size:3.5mmx3.5mmx6mm, TE:21ms, TR:3120ms). Perfusion was calculated with in-house software. Partial-volume correction was applied to perfusion using the 3D MPRAGE T1-derived grey-matter image. Groups were compared with VBM (SPM8) within a single ROI comprising bilateral subcortical, frontal and anterior, as well as medial temporal lobes and insula, using a Family-Wise-Error-corrected threshold of p=.05 at the voxel or cluster level. Lower perfusion was found in patients in three clusters: 1) in the right insula, putamen, hippocampus and superior temporal pole, 2) the left insula, amygdala, anterior fusiform gyrus and superior temporal pole, as well as 3) left superior medial frontal and anterior cingulate cortex. This study demonstrates that ASL is able to detect hypoperfusion in ventral temporal and medial frontal areas and shows potential as a clinical diagnostic tool in FTD.

P.254 Diffusion tensor imaging in primary progressive aphasia and apraxia of speech

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Abstract: Several neurodegenerative conditions have been shown to have specific patterns of white matter (WM) involvement. This study used diffusion tensor imaging to characterize the patterns of WM involvement in a large, prospective cohort of subjects with primary progressive aphasia (PPA) or progressive apraxia of speech (PAOS). Of the 130 included patients, 40 were diagnosed with PAOS, 12 with agrammatic PPA (agPPA), 9 with semantic dementia (SD), 52 with logopenic PPA (LPA) and 17 with PPA-unclassified (PPA-U). PAOS subjects had bilateral frontal involvement, including the precentral WM and superior longitudinal fasciculi. agPPA subjects had similar changes, but prominently limited to the left side. Additionally, agPPA subjects showed more widespread left sided changes, including the inferior frontal, temporal, post-central, and lingual WM. SD subjects had bilateral temporal involvement, extending to the fronto-orbital WM, and the uncinate and inferior occipitofrontal fasciculi. LPA subjects had diffuse and bilateral WM involvement, with posterior aspects of the left temporal WM most involved. PPA-U subjects had widespread and patchy left sided changes. Our findings confirm that PAOS and subtypes of PPA are associated with distinct patterns of WM involvement. The patterns of involvement in specific networks involved in language or speech help explain some of the clinical differences among groups, such as those between PAOS and agPPA or SD and LPA. Some of the differences involved tracts not typically viewed as important for language or speech, which may point to distinct pathological processes.

P.255 Neural correlates of category naming in semantic dementia

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Abstract: Patients with semantic dementia invariably have problems with tasks of naming, although category-specific effects are uncommon. In this study we investigated the presence of such effects in 27 patients with semantic dementia in a confrontational picture naming test with five categories. The neural correlates of category naming were assessed using a voxel-based morphometry (VBM) analysis. Mean disease duration in the patient group was 5.1 (range 2.9-12.8) years. The mean (standard deviation) scores for each subtest (maximum score 10) were as follows: countries (maps) 5.6 (3.7), body parts 6.4 (3.0), colours 7.3 (2.6), animals 3.6 (2.7), and objects 4.3 (3.3). Patients had variable deficits across the subtests, with different patients scoring worse in different subtests. However, naming of countries was correlated with disease duration ($R=-0.50$, $p=0.008$), with patients in the early stages commonly scoring well on this subtest and poorly on other subtests. The VBM analysis ($p<0.001$, uncorrected) showed that object, colour and animal naming were associated with atrophy particularly of the left posterior inferior temporal lobe, whilst body part naming was associated with atrophy of the left dorsal anterior cingulate. In contrast, countries naming was associated with atrophy of the right hemisphere. As there is commonly moderate left temporal atrophy at first presentation, naming of most categories may well be already impaired prior to this. In contrast, the lateralization to the right hemisphere of countries naming leads to a correlation with disease duration, with minimal right temporal atrophy at presentation but increasing atrophy and impaired naming as the disease progresses.

P.256 Neural correlates of verbal and visual semantic processing in dementia

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Abstract: Deficits of semantic processing are prototypical features of semantic dementia, a neurodegenerative disorder within the frontotemporal dementia spectrum. However, semantic impairment is also seen in typical Alzheimer's disease. In this study we investigated the neural correlates of such deficits using a within-modality test of semantic knowledge, the Size/Weight Attribute Test. This assesses attribute rather than associative knowledge of animals and objects in the visual and verbal domains, probing knowledge within a single presentation modality (pictures or written words): participants are required to make the same simple judgment about triads of animal stimuli ("Which is the largest and smallest?") and object stimuli ("Which is the heaviest and lightest?"). The test was performed in 25 patients (19 with semantic dementia, 6 with Alzheimer's disease) with a mean (standard deviation) disease duration of 3.8 (1.7) years. The mean (standard deviation) scores for each of the subtests (maximum score of 30) were as follows: visual animals 24.1 (5.9), visual objects 24.0 (5.1), verbal animals 22.2 (6.2), verbal objects 20.8 (7.5). The VBM analysis ($p<0.001$, uncorrected) showed that the verbal subtests both correlated with atrophy of the left temporal lobe (particularly temporal pole and posterior left fusiform gyrus) without any right hemisphere involvement. In contrast, although the visual subtests correlated predominantly with similar areas in the left temporal lobe, both subtests also correlated with atrophy of the right posterior inferior temporal lobe. The results suggest brain correlates of visual semantic processing are distributed between the temporal lobes while verbal semantic processing is more strongly left-lateralised.

P.257 Accurate diagnosis of PSP and CBD vs Parkinson's disease from supervised machine learning of structural and diffusion magnetic resonance images

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Abstract: The differential diagnosis between progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Parkinson's disease (PD) and other degenerative parkinsonian disorders can be difficult. Accurate early diagnosis is important not only for proactive patient management and care, but also to enable the development and assessment of novel therapeutics that target the distinct pathologies of these disorders. We evaluated machine learning methods in combination with Magnetic Resonance Imaging (MRI) for differential diagnosis of PD, PSP and CBD. Each group comprised of 19 patients, matched for age and UPDRS-III score. Structural MRI images were segmented to generate grey matter (GM) density maps, and the diffusion tensor model was fitted to the Diffusion MRI data to generate Fractional Anisotropy (FA) maps, a measure of white matter integrity. The GM and FA maps were processed separately using principal component analysis (PCA) and support vector machines (SVMs) to construct statistical models for pairwise classification of PD against CBD, PD against PSP and CBD against PSP. The results were validated using a leave-two-out cross-validation strategy. Mean classification accuracies of 88 to 93% were obtained with the FA data, while accuracies of 82 to 88% were achieved with the GM data. These results suggest that this technique could be used in the future to aid the differential diagnosis of PSP and CBD from PD: clinically in conjunction with health care systems' informatics, and as an adjunct to observational and therapeutic trials. Longitudinal and population based studies will determine the how early the MRI based machine learning methods are accurate.

P.258 Network hubs are targeted by multiple neurodegenerative diseases

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Abstract: It is proposed that neurodegenerative diseases progress within networks of brain regions. In Alzheimer's disease highly connected hub nodes are vulnerable to neuropathology (Buckner et al., 2009), in Frontotemporal syndromes, patterns of atrophy mirror the connectivity of pathogenic ?epicentres? (Zhou et al 2012). We test whether hub vulnerability is a generic feature of neurodegeneration using three disorders with different neuropathology and phenotypes: Parkinson's Disease (PD), Progressive Supranuclear Palsy (PSP) and Corticobasal Syndrome (CBS). We predicted that hub regions would show decreased functional connectivity and that brain regions with greater hub characteristics would show the greatest loss in connectivity, correlating in turn with cognitive decline. 150 participants (53 controls, 28 PD, 43 PSP, 27 CBS) underwent task-free functional MRI (3 Tesla, TR 2 sec, minimum 145 volumes). Standard preprocessing was applied and wavelet correlation used to construct networks of 471 brain regions. All three diseases showed decreased functional connectivity compared to age-matched controls characterised by weakening of hub connectivity (PD $p=0.02$, PSP $p=0.05$), and weakening of hub connections (PD $p<0.0001$, PSP $p<0.0001$, CBS $p<0.0001$). We identified a positive correlation between hub characteristics of brain regions in health and loss of connectivity in disease (PD $r=0.58$, $p<0.0001$, PSP $r=0.41$, $p<0.0001$, CBS $r=0.37$ $p<0.0001$). Weighted degree was correlated with verbal fluency in PD ($r=0.52$, $p=0.01$) with similar trends in PSP ($r=0.24$, $p=0.1$) and CBS ($r=0.34$, $p=0.1$) We suggest that cortical hubs are selectively vulnerable to multiple neurodegenerative diseases, and that measurements of hub connectivity may provide a mechanistically and clinically informative disease biomarker.

P.259 Simultaneous imaging of cerebral perfusion and glucose metabolism in FTD

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Abstract: Clinically feasible and sensitive means of detecting early neural dysfunction are needed for FTD patients who do not demonstrate significant brain atrophy. FDG-PET increases the diagnostic accuracy of FTD, but it is expensive and requires exposure to radioactive isotope. Imaging cerebral blood flow (CBF) with non-invasive, radiation-free arterial spin labeling (ASL) MRI might be an alternative. A small number of studies have examined ASL in FTD, but none have directly compared it to FDG-PET. This study evaluated the correlations of simultaneous ASL-CBF and FDG-PET imaging as we hypothesized that ASL-CBF and FDG-PET images would be correlated across major brain regions associated with FTD. Ten FTD patients and two controls were scanned by a hybrid Siemens Biograph PET/MRI scanner. Structural MRI, pseudo-continuous ASL (pCASL) MRI and FDG-PET images were acquired. MR images were segmented and the functional images were registered to the MNI brain with FSL. WFU PickAtlas was used to generated regions of interest (ROIs) in brain regions (frontal and temporal lobes). Correlation analysis of normalized CBF and FDG standard uptake values was performed using SPSS. ASL-CBF and FDG-PET were positively correlated on the normalized mean values across the gray matter, white matter, frontal and temporal lobes, indicating a good agreement between the two imaging modalities. These results suggest that ASL may offer a promising alternative method for detecting regional hypo-perfusion associated with FTD.

P.260 The use of FDG-PET in the early discrimination between frontotemporal dementia, Alzheimer's disease and psychiatric disease

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Abstract: Early discrimination between behavioral variant frontotemporal dementia (bvFTD), early-onset Alzheimer's disease (AD) and psychiatric disease is hampered by frequent overlap in clinical and cognitive symptomatology. FDG-PET could aid early discrimination, visualizing underlying functional brain changes before structural changes become apparent. Our aim was to investigate the discriminative value of FDG-PET in difficult-to-diagnose patients with bvFTD (n = 12), early-onset AD (n = 21) and primary psychiatric disease (n = 15). FDG-PET scans were performed in case of maximal diagnostic uncertainty after standard clinical work-up (90% neuropsychological assessment and 88% structural neuroimaging). Diagnoses used in our analyses were based on clinical follow up (1.3 years average) and lumbar puncture (50% of cases). Quantitative FDG-PET group analyses were performed using SPM8 (threshold $p<0.001$). Comparing metabolic patterns, AD patients showed a posterior hypometabolic pattern known from literature relative to bvFTD, and additional middle frontal lobe hypometabolism relative to psychiatric disease. BvFTD showed hypometabolism in the frontal lobe (orbitofrontal gyrus, rectal gyrus, insula) and cingulate gyrus relative to both AD and psychiatric disease. Psychiatric patients showed a remarkable pattern of thalamus hypometabolism relative to bvFTD and thalamus, orbitofrontal and primary motor cortex hypometabolism relative to AD. Our study shows that patients with maximal diagnostic uncertainty can be distinguished by means of FDG-PET analyses on a group level. In the upcoming months we will perform additional principle-component-analyses in order to evaluate the discriminative value of FDG-PET in bottom up analyses; aiming to generate FDG-PET hypometabolic profiles for patients with bvFTD, early-onset AD and psychiatric disease.

P.261 Hippocampal shape changes in patients with frontotemporal dementia

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Abstract: We investigated hippocampus shape and cortical thickness patterns in subjects with behavioral variant frontotemporal dementia (bvFTD), progressive non-fluent aphasia (PNFA), and semantic dementia (SD) to understand the clinical implication of shape changes in the hippocampus. From the Clinical Research Center for Dementia of South Korea–FTD Registry, 64 patients who fulfilled the diagnostic criteria by Knopman were recruited. All the participants completed thorough neuropsychological tests and 3-tesla brain MRI. Finally, MR data from 29 bvFTD, 11 PNFA, 24 SD, and 17 subjects with normal cognition (NC) were analyzed. The analyses were performed using methods previously described by authors. Institutional review board of the Asan Medical Center approved the study protocol. The hippocampal atrophy patterns were observed in the left hippocampal head (HH) and both hippocampal bodies (HB) in bvFTD, right HH and HB in PNFA, and almost all hippocampi in SD. Compared to bvFTD, the SD patients showed significant atrophy in the left HH and HB. Cortical thinning was observed in both frontal and temporal gyri in bvFTD, bilateral superior and middle frontal gyri and left inferior frontal gyrus in PNFA, and bilateral temporal poles in SD. Cortical thickness patterns in bilateral precuneus were associated with shape changes of the hippocampus in SD. In conclusion, shape changes in the hippocampus possibly serve as additional biomarkers to differentiate the FTD subtypes. A relationship between the cortical thickness and the hippocampal shape will further denote the implication of hippocampal shape changes in patients with FTD.

P.262 Functional MRI signatures of molecular nexopathies

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Abstract: Large-scale brain network disintegration is a unifying theme in neurodegenerative disease but it remains unclear to what extent pathogenic proteins specify network signatures: 'molecular nexopathies'. Here we used activation fMRI of processing information in nonverbal sound to characterise functional network profiles of dementia syndromes with predictable molecular correlates (MAPT mutations, n=5; semantic variant of primary progressive aphasia (svPPA) predicting TDP-C pathology, n=8; logopenic aphasia (LPA) predicting Alzheimer pathology, n=4) in relation to healthy older individuals (n=20). Temporal structure (isochrony), familiarity and episodic encoding of melodies were manipulated in a passive listening protocol. Healthy individuals showed separable signatures of anisochrony processing in posterior superior temporal lobe, melodic familiarity in anterior temporal and inferior frontal cortices and melodic novelty in temporo-parietal cortices. Relative to healthy individuals, auditory stimulation was associated with reduced inferior frontal activation in the MAPT group and enhanced antero-inferior temporal activation in the SD group; isochrony processing was associated with reduced inferior frontal and enhanced hippocampal activation in the SD group; melodic familiarity was associated with enhanced anterior temporal activation in the SD and LPA groups but reduced hippocampal activation in the MAPT group; and episodic encoding was associated with reduced hippocampal activation in the LPA group. Our findings represent the first direct delineation of separable, generic information processing signatures of these diseases using fMRI and suggest that molecular specificities drive complex, bidirectional alterations of network function as well as structural network damage.

P.263 Abstract withdrawn

P.264 Abstract withdrawn

P.265 Differential effect of the serotonin transporter length polymorphism on brain morphology in bvFTD

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Abstract: In multiple psychiatric disorders, the serotonin transporter length polymorphism (5-HTTLPR) short allele (5-HTTLPR-s) has been associated with risk for anxiety and depression via reduced gene expression and subsequent compensatory increases in serotonergic systems that support emotion and behavioral regulation. Studies of 5-HTTLPR-s association with bvFTD, a disease characterized by marked socioemotional dysfunction, have been inconsistent. Our objective was to investigate whether 5-HTTLPR-s is associated with similar or different patterns of gray matter volume in healthy older controls and bvFTD patients. We performed voxel-based morphometry of 169 cognitively normal older adults and 29 bvFTD cases to determine brain changes associated with dose (0/1/2) of 5-HTTLPR-s allele (controlling for severity, education, age, sex, and total intracranial volume). 5-HTTLPR-s frequency did not differ between controls and bvFTD. In controls, carrying more 5-HTTLPR-s alleles was associated with smaller volume in right rolandic operculum (T=4.35, pFWE=0.05), right pars triangularis (T=3.60, puncorruncorrFWE=0.05) in bvFTD only. These results suggest the 5-HTTLPR-s allele confers differential effects on brain morphology in healthy aging and bvFTD. We propose that in healthy aging, carrying more copies of the 5-HTTLPR-s risk allele is associated with smaller brain volumes in emotion-relevant brain regions. However, patients with bvFTD and 5-HTTLPR-s have larger volumes in regions that support socioemotional behavior that may be a developmental or disease-related compensation for altered serotonergic activity.

P.266 Progressive isolation and atrophy of cortical, subcortical, and brainstem intrinsic connectivity networks in progressive supranuclear palsy

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Abstract: Patients with Progressive Supranulcear Palsy (PSP) demonstrate intrinsic functional connectivity reductions within a intrinsic connectivity network (ICN) anchored by the rostral midbrain tegmentum (rMT; Gardner et al., 2013). Nodes of this network participate in control of skeletal and ocular motor structures as well as executive, social-emotional, and speech-language operations, and impairments in this ICN correlate with clinical measures in PSP patients. In this study we examined the longitudinal relationship between ICN dysfunction, structural atrophy, and clinical severity. 15 patients with PSP and 11 age-matched healthy controls received structural MRI and task-free fMRI at two time points separated by 6 months. In patients, Clinical Dementia Rating Sum of Boxes (CDR-SB) score ranged from from 0-6.5. Structural MRI scans were analyzed for longitudinal atrophy. Functional MRI scans were analyzed to determine the network-wise connectivity between 27 brain regions comprising the core rMT-anchored ICN. Overall, PSP patients showed substantially higher functional network modularity ($p < .01$), indicating reduced integration between default mode, salience, and subcortical/brainstem ICNs, a potential substrate for executive dysfunction. Left thalamus showed consistent longitudinal atrophy in PSP patients with a mean annualized rate=-5.4%. The functional connectivity strength between left thalamus and dentate nucleus of the cerebellum at time 1 was highly predictive of thalamic atrophy rate over the next six months ($r=.95$, $p < 10^{-5}$). Connectivity along this pathway appears altered during the rapidly progressing phase of brain atrophy and may anticipate subsequent skeletal motor impairments.

P.267 Neuroanatomical correlates and differences of responses on the social norms questionnaire in frontotemporal dementia vs. Alzheimer's disease

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Abstract: A characteristic of behavioral variant frontotemporal dementia (bvFTD) is a decreased adherence to social norms and conventions. This study evaluated the ability of the Social Norms Questionnaire (SNQ) to distinguish patients with bvFTD (n=15) from those with early-onset Alzheimer's disease (EOAD) (n=11), a common differential diagnostic problem for clinicians. This study further assessed the neuroanatomical correlates of the SNQ with magnetic resonance imaging (MRI), using voxel-based morphometry (VBM) for grey matter volume and diffusion tensor imaging (DTI) for white matter integrity. The results confirmed those with bvFTD, in comparison with EOAD, performed significantly worse overall on the SNQ, and made greater "overadhere" (endorsing appropriate social behaviors as inappropriate) and "break" errors (endorsing inappropriate social behaviors as appropriate). After controlling for age and diagnosis, VBM analyses revealed a significant correlation between increased break errors on the SNQ and lower anterior temporal lobe volume, especially on the right. After controlling for age and diagnosis, DTI analysis showed significant correlations between break errors and white matter deterioration (mean and radial diffusivity measures) particularly in the inferior temporal white matter, as well as in the anterior limb of the internal capsule. In conclusion, the results of this study confirm the value of the SNQ for distinguishing patients with bvFTD from those with EOAD. This study supports the right anterior temporal lobe as a region of social concepts. Further, the impaired adherence to social norms and conventions in bvFTD corresponds to right anterior temporal disease.

P.268 Investigating brain structure in different FTLD subtypes using voxel-based morphometry – data from the multicentric FTLD consortium's study Germany

Karsten Mueller, Sandrine Bisenius, Adrian Danek, Janine Diehl-Schmid, Klaus Fassbender, Hans Foerstl, Armin Giese, Holger Jahn, Frank Jessen, Jan Kassubek, Johannes Kornhuber, Bernhard Landwehrmeyer, Martin Lauer, Albert Ludolph, Markus Otto, Johannes Prudlo, Anja Schneider, Katharina Stuke, Matthias Schroeter, FTLD Study Group Germany

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Abstract: Frontotemporal lobar degeneration (FTLD) is a heterogeneous neurodegenerative disorder. Structural brain differences between different FTLD subtypes need to be further investigated to characterize differential mechanisms of brain pathology. Using a multicenter approach within the German Research Consortium for FTLD, brain structure was investigated in 19 patients with progressive supranuclear palsy (PSP), 20 patients with corticobasal degeneration (CBD), and in 19 patients suffering from amyotrophic lateral sclerosis with behavioral-variant frontotemporal dementia (ALS-bvFTD). To classify different patterns of brain tissue degeneration, potential decrease of grey matter density (GMD) was assessed using magnetic resonance imaging (MRI) and voxel-based morphometry (VBM) including sets of healthy sex- and age-matched controls. All individual grey matter segments were warped to a template and modulated by the Jacobian determinants of deformations introduced by normalization to account for local compression and expansion during transformation. Voxel-wise statistical analyses were performed using the general linear model including total intracranial volume as covariate. Significant GMD differences were obtained using a voxel threshold of $p<0.001$ and a cluster threshold of $p<0.05$, family-wise-error (FWE) corrected. With PSP, reduced GMD was shown mainly in basal ganglia, brainstem, and cerebellum. In contrast, with CBD, reduced GMD was obtained in frontal cortical regions but mostly unilateral within the left hemisphere. Patients with ALS-bvFTD showed bilateral GMD reduction in frontal and temporal cortical regions but also in striatum and hippocampus. In sum, different patterns of brain atrophy suggest specific neuropathological mechanisms in each of the FTLD subtypes that will be validated by biomarkers from cerebrospinal fluid.

P.269 Voxel-based morphometry in behavioral variant frontotemporal dementia – data from the multicentric FTLD consortium's study Germany

Katharina Stuke, Karsten Mueller, Sandrine Bisenius, Adrian Danek, Janine Diehl-Schmid, Klaus Fassbender, Hans Foerstl, Armin Giese, Holger Jahn, Frank Jessen, Jan Kassubek, Johannes Kornhuber, Bernhard Landwehrmeyer, Martin Lauer, Albert Ludolph, Markus Otto, Johannes Prudlo, Anja Schneider, Matthias Schroeter, FTLD Study Group Germany

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Abstract: We used voxel-based morphometry to validate the new imaging criteria for the behavioral variant of frontotemporal lobar degeneration, behavioral variant frontotemporal dementia (bvFTD) (Rascovsky et al. Brain 2011;134:2456-77) in patients enrolled in the multicentric study of the German consortium for frontotemporal lobar degeneration. We compared 16 patients with bvFTD to 16 healthy controls, matched age and gender. Results are reported family-wise error corrected (FWE) with a significance level of $p<0.05$. Significant atrophy for bvFTD was found mainly in anterior insulae, frontomedian and frontolateral cortex, temporal pole, anterior hippocampus and nucleus accumbens. Results support the application of the new imaging criteria as suggested recently. Furthermore, we compared intracenter disease effects with intercenter (scanner and parameter) variability. Different scanning parameters used in different study sites did not influence disease specific results as shown by conjunction analysis, because they were localized in more posterior brain regions different to disease-specific neural networks. Results underline the usefulness of multicentric studies to gather larger sample sizes for the investigation of bvFTD.

P.270 Cortical atrophy in the ALS-FTD spectrum

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Abstract: Amyotrophic Lateral Sclerosis-Frontotemporal Dementia (ALS-FTD) presents with the spectrum of heterogeneous clinical manifestations and pathologic findings of both ALS and FTD. In ALS, cortical atrophy is primarily in the precentral gyrus with variable involvement of extra-motor cortices. FTD presents predominant fronto-temporal cortical atrophy differing between the behavioral and language variants. There are limited evaluations of quantitative cortical thickness analysis in the full ALS-FTD spectrum within one study. We measured cortical atrophy in ALS-FTD and compared with that of ALS and FTD, based on the hypothesis that ALS-FTD reflects cortical atrophy of the disease spectrum and, depending on the clinical presentation, to a larger extent than isolated disease. 3.0 Tesla MRI scans were acquired from 114 controls, 12 ALS-FTD, 10 ALS and 40 FTLD patients (including both language and behavioral variants). We found that in ALS-FTD, atrophy is prominent in the prefrontal and anterior temporal cortices as well as in the anterior cingulate in a pattern similar to that seen in FTD, and extends caudally to include the precentral gyrus. In ALS-FTD, atrophy in the anterior temporal cortical region is less prominent than in FTD. Compared to ALS, in ALS-FTD atrophy is generally more extended and particularly increased in the pre-, medial- and orbito-frontal cortices and temporal region. Further work will investigate whether cortical thickness in a subset of these regions in patients with FTD or ALS alone could predict the development of ALS-FTD and inform about potential cortical and system vulnerability within the full ALS-FTD spectrum of disease.

P.271 bvFTD impairs sensory prediction: implications for learning and behavioural control

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Abstract: The free-energy principle of biological systems provides a principled way to understand many aspects of cortical organisation and behaviour. Dynamic hierarchical models of brain networks provide prior expectations of events that influence perception and behaviour (Friston, 2005). A robust experimental model of such predictions is the auditory 'oddball' task (Garrido et al, 2007), which compares cortical responses to predictable and unpredictable stimuli (the mismatch negativity, MMN). The MMN is sensitive to dementia (Naatanen et al., 2011, Hughes & Rowe, 2013) and in behavioural variant frontotemporal dementia (bvFTD) we propose the impairment is due to reduced frontotemporal feedback. Using magnetoencephalography during an auditory oddball paradigm we examined the impact of bvFTD on cortical predictions of auditory stimuli (bvFTD n=18; Controls n=20). Time frequency analysis and dynamic causal modelling (DCM) were used to test frequency specific network connectivity. Generative models of the induced responses were optimised and compared for a bilateral eight-source network (primary auditory cortex, superior temporal gyrus, inferior frontal and parietal sources). In bvFTD the mismatch negativity was reduced. Time frequency analysis and DCM indicated a loss of frontotemporal feedback connectivity in bvFTD, in the beta frequency band. We propose that impaired prediction of regular sensory events also reduces the response to unexpected (deviant) stimuli in bvFTD. The loss of hierarchical inferences on the causes of events has far reaching implications for cognitive and behavioural control in bvFTD, but also provides a unifying framework for human and translational models of cognitive physiology.

P.272 Disrupted neural networks may influence the pathophysiology of frontotemporal dementia

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Abstract: Much of the pathophysiology of behavioral variant frontotemporal dementia (bvFTD) may be consequent to disruption of white matter (WM) connectivity between cortical regions, reflecting disturbances in neural networks. Diffusion imaging and brain connectivity analyses can assess WM connectivity, using fiber tractography methods to infer neural pathways. In order to investigate the extent and severity of impaired connectivity in bvFTD, we analyzed 1.5-Tesla whole-brain diffusion-weighted magnetic resonance images from 15 patients with bvFTD compared to 30 healthy controls. We reconstructed structural brain connectivity networks focusing on the most highly central and connected cortical regions ("hubs") between bvFTD patients and controls. Our results showed alterations in more than 60% of the connections between cortical regions, and a decrease in fiber density, among the bvFTD patients, compared to the controls. Among the bvFTD patients, the right hemisphere WM was more severely impaired than the left hemisphere WM, particularly in the superior frontal regions (FDR p-value-4). As expected, the most severe alterations were in frontal regions (left and right anterior cingulate, lateral orbitofrontal, rostral middle frontal, and superior frontal regions) (FDR p-value-10). In addition, the left hemisphere insula and pars triangularis and the right hemisphere precentral gyrus were less interconnected in bvFTD, compared to controls (FDR p-value-10). We conclude that bvFTD is characterized by a major disruption of interconnectivity between cortical centers in the frontal lobes, suggesting that the pathophysiology of bvFTD is much more a consequence of disconnection and disturbed neural networks than of focal, modular disease.

P.273 Hypothalamic atrophy in behavioural variant frontotemporal dementia and its relationship to eating behaviour

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Abstract: Abnormal eating behaviours such as hyperphagia and craving for sweet foods are frequently reported in behavioural variant frontotemporal dementia (bvFTD). The hypothalamus is the regulatory centre for feeding and satiety but its role in bvFTD has not been fully clarified, partly due to its difficult identification on magnetic resonance images (MRIs). We aimed to investigate the relationship between hypothalamic volumetry and eating behaviours in a sample of 18 bvFTD patients (including 9 MAPT mutation carriers and 6 C9ORF72 expansion carriers) and 10 cognitively-normal controls (no significant differences in age or gender between groups). All subjects were scanned on a 3T Siemens Trio, and the presence of abnormal eating behaviour was assessed with the revised version of the Cambridge Behavioural Inventory (CBI-R). A novel optimized multimodal manual segmentation protocol of the hypothalamus was developed using 3D T1 and T2-weighted MRIs (intrarater intraclass correlation coefficients ≥0.93). The bvFTD group showed a 17% reduction in hypothalamic volume compared with controls ($p<0.005$): right, mean 397(standard deviation 62) versus 465(46) mm3 and left, 384(53) versus 463(40) mm3, corrected for total intracranial volumes. MAPT mutation carriers showed a trend for lower volumes on both sides compared with C9ORF72 (12% difference). The CBI-R eating habits sum of scores explained the variability in hypothalamic volume in the bvFTD group ($p<0.02$, ANOVA). In summary, bvFTD patients showed lower hypothalamic volumes compared with controls and this finding is associated with the clinical changes in eating behaviour. Moreover, different genetic mutations seem to have a differential impact on the hypothalamus.

P.274 Decreased structural association in regions of the default-mode network in the early stages of Alzheimer's disease

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Abstract: Recent studies have shown that clinical symptoms observed in Alzheimer's disease (AD) patients may reflect variations within specific large-scale brain networks, rather than neural loss in a focal brain region, modeling AD as a disconnection syndrome. The present magnetic resonance imaging study aims to compare the organization of gray matter structural covariance networks between 109 cognitively unimpaired controls and 109 AD patients at the early stages of the disease. Patients were retrieved from the ADNI database. Based on previous studies, the medial temporal lobe (DMN-mtl) and midline core (DMN-mc) subsystems of the default-mode network (DMN), the salience network (SN) and a control network (visual network (VN)), were selected for between-group analysis using voxel-based morphometry. The DMN-mtl was less extended in AD patients in comparison to controls, with a significant decrease in the structural association between the right entorhinal cortex and the left anterior medial prefrontal cortex, the right superior/middle frontal gyrus and the right calcarine gyrus. The DMN-mc was also less extended in AD patients, with a significant decrease in the structural association between the L posterior cingulate cortex and the inferior orbito-frontal gyrus. No significant difference was observed in the structural association of the SN and the VN between the two groups. The observed changes suggest that early disruptions in structural association between heteromodal association cortices and the enthorinal cortex could contribute to an isolation of the hippocampal formation, potentially giving rise to the clinical hallmark of AD, progressive memory impairment.

P.275 Fronto-striatal grey matter integrity in behavioural frontotemporal dementia and progressive supranuclear palsy

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Abstract: Behavioural variant of frontotemporal dementia (bvFTD) and progressive nuclear palsy (PSP) show both frontal atrophy changes and associated clinical features. The striatum is densely connected with the frontal cortical regions affected by bvFTD and PSP, but the impact of these two disorders on the integrity of the striatum has not been compared. The current study set out to address this issue using 3T high resolution T1-weighted scans for 130 participants (54 PSP, 17 bvFTD and 60 controls). The scans were analysed via the FSL-VBM pipeline and were masked for their prefrontal cortex and striatal regions via the Harvard-Oxford probabilistic atlas. We confirmed that both groups had widespread frontal and striatal changes in grey matter compared to controls, involving ventromedial prefrontal cortex (VMPFC), dorsolateral prefrontal cortex (DLPFC), supplementary motor area (SMA) as well as caudate, putamen and nucleus accumbens. The bvFTD patients showed significantly more striatal and frontal atrophy than PSP, particularly for VMPFC, frontal pole, caudate, nucleus accumbens and putamen. By contrast, PSP had significantly more atrophy than bvFTD in SMA and the inferior frontal gyrus laterally on the frontal cortex. PSP atrophy in striatum was not more severe than in bvFTD. These results reveal for the first time that PSP and bvFTD share striatal atrophy patterns similar to their frontal cortical correlates. Interestingly, grey matter changes were more substantial in bvFTD than PSP in the striatum. Future studies are needed to investigate the relationship of these fronto-striatal changes to the symptomology and underlying pathology in both diseases.

P.276 Cortico-striatal network integrity in behavioural variant frontotemporal dementia and Alzheimer's disease

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Abstract: Behavioural variant frontotemporal dementia (bvFTD) has been recently associated with subcortical atrophy, particularly in the striatum, whereas the same regions are relatively spared in Alzheimer's disease (AD). Striatal degeneration in conjunction with cortical atrophy emerges therefore as promising novel diagnostic biomarker to distinguish both diseases. Previous studies have only taken either cortical or striatal atrophy into account when comparing bvFTD with AD. In the current study we establish for the first time a profile of cortico-striatal integrity in both diseases based on the structural connectivity of striatal and cortical regions. Twenty-three progressive bvFTD, 29 AD patients and 50 controls underwent the same MRI protocol. Voxel-based morphometry analyses were performed in using ROI masks of cortical and sub-striatal regions segmented according to their white-matter connectivity. ROI were extracted from the probabilistic Oxford-GSK-Imanova Striatal Connectivity Atlas, resulting in seven ROI: limbic, executive, rostral-motor, caudal-motor (frontal ROIs) and temporal, parietal, occipital ROIs. Comparisons with controls reveal that bvFTD show substantial fronto-striatal and temporo-striatal network changes affecting limbic, cognitive and motor networks. By contrast, AD showed only few fronto-striatal changes, despite having significant cortical atrophy. Contrast of AD and bvFTD revealed significantly more atrophy in the limbic cortico-striatal circuits (ventral striatum and ventromedial prefrontal cortex) in bvFTD. These different profiles of cortico-striatal atrophy in bvFTD and AD suggest that cortico-striatal connectivity is particularly important in determining subcortical changes. Limbic network best distinguished between groups, with bvFTD showing more severe atrophy. Consecutively, deficits in limbic cortico-striatal networks emerge as promising novel diagnostic biomarker for bvFTD.

P.277 Pseudo-continuous arterial spin labeling is sensitive to changes in cerebral blood flow in semantic variant primary progressive aphasia and non-fluent/agrammatic primary progressive aphasia

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Abstract: Structural imaging is valuable for diagnosing and tracking changes in patients with neurodegenerative diseases, but changes in regional brain structure likely occur late in the neurodegenerative process. Cerebral blood flow (CBF) is tightly linked to brain function, and changes in regional CBF may precede changes in structure. We evaluated arterial spin labeled (ASL) perfusion MRI as a method of identifying brain regions showing functional changes in patients with primary progressive aphasia (PPA). We acquired T1 and pseudo-continuous ASL (PCASL) imaging in 17 non-fluent/agrammatic PPA (naPPA) patients, 19 semantic variant PPA (svPPA) patients, and 17 control subjects. ANTs was used to generate mean CBF images from the PCASL data and gray matter (GM) density images from T1 data. We performed whole-brain voxel-wise two-sample t-tests in SPM8 to compare the GM and CBF of naPPA to controls and svPPA to controls. The svPPA group had hypoperfusion relative to controls in anterior temporal lobe and in other frontal and temporal regions. SvPPA patients had atrophy in bilateral anterior temporal and frontal regions. NaPPA patients had hypoperfusion in left dorsolateral prefrontal cortex and other regions and atrophy in frontal cortex and posterior temporal regions. Both patient groups showed hypoperfusion in atrophied cortical regions, as well as in regions not corresponding to atrophy. These findings suggest that PCASL imaging could be sensitive to functional changes in svPPA and naPPA not apparent in structural MRI.

P.278 Strategic problem solving in behavioral variant frontotemporal dementia

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Abstract: Behavioral variant frontotemporal dementia (bvFTD) is the most common clinical syndrome associated with frontotemporal lobar degeneration. BvFTD is characterized by bilateral frontal and temporal lobe atrophy and deficits in executive function, including problem solving. While patients with bvFTD show problem solving difficulty, the neural basis for this deficit remains unclear. We examined strategic problem solving with a simple 20 Questions task in bvFTD (n=23) compared to healthy elderly controls (n=19). Participants were presented with 12 cards, each containing a unique object. Half the cards contained an animal and half a vehicle; each object was one of four colors that were distributed evenly across cards. Participants guessed the target object by asking as few questions as possible. We categorized responses as strategic if they eliminated more than one card and non-strategic if they eliminated a single object. BvFTD patients asked a significantly lower proportion of strategic questions (50%) compared to controls (92%; $p<0.01$), demonstrating impaired strategic problem solving. We then examined gray matter atrophy with high-resolution MRI and used regression analyses to relate performance to atrophy. MRI analysis revealed bilateral frontal and temporal lobe atrophy ($q<0.001$, FDR-corrected) in bvFTD patients relative to a separate control group of healthy seniors (n=31). Regression analysis related strategic limitations to dorsolateral prefrontal cortex, orbitofrontal cortex, and anterior cingulate ($p<0.05$). Neuropsychological correlations revealed that limitations were specific to executive, but not other domains. Dorsolateral prefrontal cortex, orbitofrontal cortex, and anterior cingulate disease contribute to problem solving deficits in bvFTD by limiting mental flexibility and strategic organization.

P.279 Multimodal neuroimaging study in presymptomatic *GRN* mutations carriers

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Abstract: The preclinical stage of frontotemporal lobar degeneration (FTLD) is not well studied. We used a multimodality approach to study the presymtomatic stage of the disease and explore brain metabolism, structural and functional changes in asymptomatic GRN mutation carriers. We studied 12 GRN mutation carriers (GRN+) and 17 controls (GRN-). The mean estimated duration before disease onset was 18 years in GRN+. Voxel-based morphometry (FSL-VBM), cortical thickness (Freesurfer), diffusion tensor images (DTI) (TBSS) and RSfMRI (Integration and Regional Homogeneity) and PET-FDG (SPM8) were performed at baseline and 18 months later. At baseline no differences were found in GRN+ in comparison to GRN- in neuropsychological performances neither in the other multimodalities. However, the performance of Ekman test was correlated with age in GRN+. Cortical thickness decreased more rapidly with age in the left frontal pole in GRN+ than in GRN-. At follow up, a greater reduction of grey matter density was found in the left parahippocampal gyrus, the right rectus gyrus, and in the cerebellum in GRN+ compared to GRN-. In our study, no differences were found between GRN+ and GRN- at baseline suggesting that changes in the different modalities are not easily detected with conventional neuroimaging tools or, more probably, that detectable changes appear in carriers in a shorter delay from the clinical onset. Structural changes detected in the follow up study in prefrontal, orbitofrontal and temporal cortices suggest early alterations in social and emotional processing and could represent a biomarker of progression of the disease.

P.280 Heterogeneity in cerebral PET glucose metabolism in early symptomatic frontotemporal dementia linked to chromosome 3 (FTD-3)

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Abstract: FTD-3 is an autosomal dominantly inherited neurodegenerative disease first described in a Danish family. It is caused by a truncating mutation in CHMP2B (1). FTD-3 is characterized by insidious and progressive changes in personality, behaviour and cognition (2,3). Regional cerebral metabolic rate of glucose (rCMR) was assessed using 18F-flourodeoxyglucose (FDG) and PET. Nine early symptomatic and two pre-symptomatic CHMP2B mutation carriers were PET scanned for 40 minutes after injection of 200 MBq FDG. Images were transformed into a stereotactic space and compared to healthy age-matched subjects (4). Frontal hypometabolism were seen in two patients (FTD like pattern); two patients (PET 1 and 6 years after initial symptom) had posterior deficits in an Alzheimer (AD) like pattern; two (both PET 3 years after initial symptom) showed frontal plus posterior deficits (FTD plus AD like pattern); two (PET 3 and 4 years after onset) had nonspecific cortical deficits indicating neurodegenerative disease. One had no significant deficits despite a clinical FTD diagnosis with estimated symptom onset 4 years before PET. Neither of the two pre-symptomatic cases showed significant PET-FDG deficits. Decreased rCMR was present in 8 of 9 early FTD-3 cases. The pattern of reduced metabolism is very variable ranging from classical FTD to a more Alzheimer-like pattern. Though the causative genetic mutation is identical, functional changes differ considerably, presumably due to other genetic and environmental factors. References: 1) Nature Genetics 2005; 37:806-8. 2) Neurology 2002; 59:1585-94. 3) JNEN 2003; 33: 884-91. 4) J Nucl Med 1995; 36, 1238.

P.281 Prevalence of prefrontal cortical thinning in a prospective cohort of amyotrophic lateral sclerosis

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Abstract: Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) can co-exist. Whether this indicates that all patients with ALS are at potential risk of FTD or that there is only a sub-population in the ALS spectrum that may develop FTD is unclear. This study addressed this question by examining the prevalence prefrontal cortex (PFC) thinning (i.e. excluding motor and premotor areas) in a prospective, consecutive sample of ALS patients (N=105). It also examined whether data in the sample would be normally distributed—suggesting a continuum of prefrontal thinning—or not normal—suggesting the possibility of sub-populations in terms of risk of FTD. Two centers enrolled subjects (Site 1: n=62 ALS patients and 32 controls; Site 2: N=43 ALS and N=24 controls). 8.6% had concomitant clinical FTD. All underwent a common structural MRI protocol: 1mm isotropic, volumetric MPRAGE on a 3Tesla scanner. Mean cortical thickness in the PFC was calculated using Freesurfer. The PFC thickness values were normally distributed in the ALS population. Cortical thickness worse than 1.5 standard deviation from the control population was found in 18% of ALS patients which was significantly higher than would be expected by chance ($Chi2=21.8$, $p<0.001$). Removing those cases with clinical FTD, the result remained significant ($Chi2=9.5$, $p<0.01$). The data suggest that the prevalence of PFC thinning is increased in ALS. The data identified no evidence that the distribution of PFC thickness in ALS is bimodal, as might be the case if only a sub-group of the ALS spectrum were susceptible to FTD.

P.282 Person-based disinhibition in frontotemporal dementia compared to early-onset Alzheimer's disease

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Abstract: Disinhibition is a major behavioural disturbance, but incompletely understood, among patients with dementia. It may result from disturbances in person-based or rule-based neural mechanisms. A deficit in social cognition in behavioural variant frontotemporal dementia (bvFTD), may impair person-based disinhibition and the corresponding neural circuitry for Theory of Mind (ToM). To deconstruct person vs. rule-based elements of disinhibition and their neuroanatomical correlates among patients with bvFTD compared to those with early-onset Alzheimer's disease (eAD), we used caregiver-derived Frontal Systems Behaviour Scale (FrSBe) and tensor-based morphometry (TBM) data of magnetic resonance imaging (MRI) from 28 patients, 12 bvFTD and 18 early-onset Alzheimer's disease dementia (eAD). We then characterized disinhibition into person-based and rule-based subscales and then correlated the severity of the two types of disinhibition, apathy, and executive dysfunction on the FrSBe with the relative grey matter volume on MRI. We found that bvFTD patients had a significant greater decline in person-based disinhibition, but not rule-based disinhibition, compared to the eAD patients ($p=0.004$). The severity of person-based disinhibition correlated with biparietal atrophy ($p<0.05$); with a right-hemispheric dominance; whereas, rule-based disinhibition correlated with left orbitofrontal (OFC) atrophy ($p<0.05$). Our results suggested that person-based disinhibition was more common in bvFTD and it may associated with dysfunction of the neuroanatomical areas representing ToM, possibly through network dysfunction of right parietal areas. In both dementias, dysfunction of the OFC region contributed to rule-based disinhibition. Further work is needed in order to dissect and understand the mechanisms of disturbed behaviour in bvFTD and other neurological diseases.

P.283 Neural correlate of abnormal eating behavior in semantic dementia: a preliminarily semi quantitative analysis

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Abstract: Among frontotemporal lobar degeneration (FTLD), patients with frontotemporal dementia show various abnormal eating behaviors. Semantic dementia (SD) also has serious abnormal eating behaviors such as overeating or food preference change. However, there are few researches focused on eating behaviors in SD. Subjects were selected from consecutive patients who had undergone a medical examination at the Kumamoto University Hospital Dementia Clinic, Japan, from March 2008 to December 2012. Nineteen SD patients, diagnosed by international consensus criteria, participate in this study. All subjects underwent the assessment scale of eating behavior and brain SPECT and MRI. The assessment scale of eating behaviors consists of five domains: swallowing problem, appetite change, food preference, eating habits and other oral behaviors. For assessing regional cerebral blood flow, semi-quantitative methods were used: regional tracer uptake was measured in region of interest (ROI) over the bilateral superior and inferior frontal cortex, lateral and medial temporal cortex, thalamus and cerebellum. The ROIs were manually drawn by an observer, with anatomical information from MRI to guide the placement of ROIs in SPECT by superimposing MRI and SPECT. Data were analyzed in the form of ROI ratios divided by the ROI in cerebellum. Using partial correlation analysis adjusted by duration of illness showed significant correlations between right frontal cortex and increased appetite ($r= -0.512$ $p=0.043$), bilateral temporal cortex and changes of food preference ($r= -0.480$ $p=0.044$, $r= -0.491$ $p=0.039$) , and left frontal cortex and change of eating habits ($r= -0.503$ $p=0.033$, $r= -0.515$ $p=0.029$).

P.284 Magneto-encephalography reveals the reorganization of brain networks in frontotemporal lobar degeneration and Alzheimer's disease subtypes

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Abstract: Several studies have characterised dementia using BOLD-fMRI resting state network activity, but the BOLD-fMRI signal is band limited and an indirect measure of neural activity. To overcome some of these limitations in the study of network function and organisation, we used Magnetoencephalography (MEG) to investigate two Fronto-lobar degeneration dementia subtypes which included (i) behavioural variant fronto-temporal dementia (bvFDT), n=13 and (ii) Progressive supranuclear palsy (PSP), n=15 and a variant of Alzheimer's (iii) Posterior cortical atrophy (PCA), n=9 as well as 15 age matched healthy participants. Eyes closed resting state MEG data were acquired in a magnetically shielded room with a 306-channel Vectorview system (Elekta Neuromag). The data was processed with a novel pipeline that overcomes the technical challenges to connectivity analysis posed by volume conduction seen at the MEG sensor level. Effective connectivity among all sensors was estimated using Partial Directed Coherence (PDC) and combined with a local efficiency measure. We found both Fronto - lobar degeneration groups showed significantly lower local efficiency measures in the beta and low gamma over the left fronto-cortical sensors compared to controls. While the PCA type dementia showed a decrease over the left parietal sensors in the high gamma range compared to healthy controls. The finding suggest that the distribution of changes in resting state effective connectivity and local network efficiency could be determined by the clinical phenotype and anatomical distribution of pathology; and that the temporal dynamics, including effects of disease on specific frequency bands, are characteristic of the pathology rather than phenotype.

P.285 Validation of the new diagnostic imaging criteria for primary progressive aphasia by ALE meta-analyses

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Abstract: In 2011, the diagnostic clinical and imaging criteria for primary progressive aphasia (PPA) had been revised by an international consortium. Here, we use quantitative and systematic anatomical likelihood estimation (ALE) meta-analyses to validate the imaging criteria for the several PPA subtypes. We computed separate meta-analyses for each of the three subtypes of PPA. Additionally, we examined the regional specificity for each PPA subtype in conjunction and subtraction analyses. Further, we investigated whether different imaging criteria should be applied for different imaging modalities by computing separate meta-analyses on FDG-PET and MRI studies on semantic dementia as well as a subtraction analysis between the meta-analyses on both imaging modalities. The meta-analysis on semantic dementia yielded significant atrophy in inferior, middle, and superior temporal gyrus, fusiform gyrus, hippocampus, parahippocampal gyrus, and amygdala. The meta-analysis on progressive nonfluent aphasia showed significant atrophy in putamen, insula, middle and superior temporal gyrus, precentral gyrus, inferior, middle, and superior frontal gyrus. The meta-analysis on logopenic aphasia yielded significant atrophy in middle and superior temporal gyrus, supramarginal gyrus, and cingulate gyrus. Our results validate and refine the current diagnostic imaging criteria for PPA. As shown in the subtraction analyses, the resulting networks of atrophy are highly distinctive for a given subtype of PPA. Interestingly, there was almost no overlap between the results of the meta-analyses on semantic dementia across MRI studies and FDG-PET studies, implicating that (at least for semantic dementia) different imaging criteria should be applied for FDG-PET than for MRI studies.

P.286 Voxel-based morphometry in primary progressive aphasia and its subtypes – data from the multicentric FTLD consortium's study Germany

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Abstract: We used voxel-based morphometry to validate the new imaging criteria for primary progressive aphasia (PPA) in patients enrolled in the multicentric study of the German consortium for frontotemporal lobar degeneration. We compared 30 patients with PPA to healthy controls, and additionally conducted separate analyses for 22 patients with progressive nonfluent aphasia (PNFA), 18 patients with semantic dementia (SD), and 10 patients with logopenic progressive aphasia (LPA) versus groups of healthy controls. All groups of healthy controls were matched for sample size, age, and gender. Results are reported at a false-discovery rate corrected significance level of $p<0.05$. Significant atrophy for PPA was found in inferior, middle, and superior temporal gyri, gyrus rectus, lateral orbital gyrus, hippocampus, amygdala, caudate nucleus, thalamus, insula, cingulate gyrus, supramarginal gyrus, middle occipital, inferior, middle, and superior frontal gyri. The analysis for PNFA showed atrophy in superior temporal gyrus, insula, cingulate gyrus, middle, and superior frontal gyri. For SD, the results showed significant atrophy in inferior, middle and superior temporal gyri, gyrus rectus, fusiform gyrus, hippocampus, amygdala, posterior orbital gyrus, and insula, while the analysis for LPA showed significant atrophy in middle occipital, temporal, and frontal gyri. Furthermore, we computed 2 x 2 factorial ANOVAs in smaller, well-balanced subgroups to investigate whether slightly different scanning parameters used in different study sites influenced the results. The main effect of scanning parameters did not interact with the main effect of the respective disease, thus encouraging the use of multicentric studies to gather larger sample sizes for rare diseases.

P.287 Preclinical evidence for neurodegeneration in *C9orf72* hexanucleotide repeat expansion carriers

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Abstract: Hexanucleotide repeat expansions in C9ORF72 represent the most common genetic cause of familial and sporadic behavioral variant frontotemporal dementia (bvFTD). Compared to sporadic bvFTD, patients with C9ORF72+ bvFTD show similar group-level anterior insula, anterior cingulate and frontotemporal cortex atrophy, but greater parietal, occipital, and thalamic involvement. Whether structural neurodegeneration is detectable in presymptomatic C9ORF72 carriers remains unknown. We studied 13 presymptomatic C9ORF72 carriers (age 45.6 ± 8.9 years, 8 females) and 23 age- and sex-matched healthy controls (age 51.4 ± 8.9 years, 15 females). All participants had a Mini-Mental State Exam (Folstein et al. 1983) score greater than or equal to 27 out of 30. Structural brain MRI was acquired; voxel-based morphometry delineated group differences in gray matter between presymptomatic C9ORF72 carriers and healthy controls using a two-sample t-test with age, sex, handedness, and total intracranial volume as nuisance covariates. We identified significant clusters at a t-threshold corresponding to p C9ORF72 C9ORF72 carriers exhibited reduced gray matter in bilateral dorsolateral prefrontal cortex, left anterior/midcingulate, bilateral temporal cortex, right anterior insula, left mid-insula, left amygdala, and bilateral caudate and thalamus. Our results show that presymptomatic C9ORF72 carriers exhibit reduced gray matter in regions known to atrophy in C9ORF72+ bvFTD, which may represent developmental differences rather than early neurodegeneration.

P.288 Multimodal positron emission tomography in frontotemporal dementia

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Abstract: Positron Emission Tomography (PET) using 11C-dihydrotetrabenazine (DTBZ; VMAT2), 11C-raclopride (RAC; dopamine D2 receptors), 11C-PMP (acetyl cholinesterase), and 11C-PIB (β-amyloid) was performed on patients with Frontotemporal Dementia (FTD, n=14). The subytpes included behavioural variant FTD (bvFTD, n=5), semantic dementia (SD, n=5), progressive non-fluent aphasia (PNFA, n=2), logopenic variant primary progressive aphasia (LvPPA, n=1), and dementia of Alzheimers type with a family history of FTD (DAT, n=1). C9orf72and progranulin gene mutations were identified in 1 patient each (n=12), no mutation in MAPT gene was seen(n=7). On 11C-DTBZ imaging, 1 patient (bvFTD) had reduced binding in the right caudate and right putamen. RAC imaging revealed reduced binding in 2 patients in right caudate (1 bvFTD who also had reduced DTBZ binding, 1SD), and bilateral putamen in 1 patient (PNFA); increased binding was seen in 1 patient in right caudate (SD), 2 patients each in bilateral caudate (1SD, 1LvPPA), bilateral putamen (1SD, 1LvPPA), and left putamen (1SD, 1DAT). Cholinergic activity was found to be within mean±2SD of normative data in all studied brain regions, consistent with lack of benefit seen with cholinesterase inhibitors in FTD. 11C-PIB was normal in all subjects, except one patient with LvPPA, which might suggest underlying or concurrent Alzheimer's pathology; normal binding in the patient with DAT suggests non-amyloid pathology. Reduction in 11C-DTBZ binding suggests dopaminergic denervation. Reduced RAC binding suggests post synaptic striatal pathology; increased binding may reflect reduced striatal dopamine release. This preliminary study describes alterations in the dopaminergic system of patients with FTD.

P.289 Left parietal cortex tDCS enhances gesture processing in corticobasal syndrome

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Abstract: Corticobasal Syndrome (CBS) is characterized by higher cortical dysfunctions associated with asymmetric onset of levodopa-resistant parkinsonism, dystonia and myoclonus. One of the most typical and distressful features of CBS is limb apraxia, which is associated with parietal atrophy. Up to now, no successful treatments for apraxia are available. Transcranial direct current stimulation (tDCS) is a non-invasive procedure of cortical stimulation, which represents a promising tool for cognitive enhancement and neurorehabilitation. The present study investigated whether anodal tDCS over the parietal lobes would improve limb apraxia in CBS patients. Fourteen CBS patients with upper limb apraxia were enrolled. Each patient was randomly subjected to three types of stimulation: tDCS over the right parietal cortex, tDCS over the left parietal cortex, and placebo tDCS. Anodal tDCS at 2 mA intensity, delivered for 7 minutes, was administered. Apraxia was assessed before and after each session using the De Renzi apraxia test. A significant improvement of De Renzi apraxia test score was observed after active anodal stimulation over the left parietal cortex (□□= 17.6, P= 0.0005), while no significant effect was noticed over the right parietal cortex (□□= 7.2, P=0.07). By stimulating left parietal lobe, a significant improvement of praxis performances of both right (mean De Renzi improvement, real stimulation vs. sham, 2.0±1.6 vs. -0.3±2.9, P=0.03) and left (3.5±2.8 vs. 0.1±3.0, P=0.01) limbs was observed. These results suggest that anodal tDCS applied over the left parietal cortex can modulate praxic abilities in CBS patients and might represent a promising tool for future rehabilitation approaches.

P.290 Targeting the autophagic/lysosomal pathway to restore progranulin levels in FTD-GRN.

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Abstract: Progranulin (PGRN) is an important neurotrophic growth factor needed to maintain neuronal health. Mutations in the GRN gene, which encodes PGRN, cause a ~50% reduction of the protein and cause age-related frontotemporal dementia (FTD), while smaller reductions in PGRN are reported to increase the risk for Alzheimer's disease. GRN mutations are one of the most common causes of FTD, however no effective treatments exist. Interestingly, complete loss of PGRN in mice and humans produces pathological features of neuronal ceroid lipofuscinosis, a lysosomal storage disease, suggesting PGRN has a functional role in the autophagic/lysosomal pathway. It is currently unknown how loss of PGRN leads to neuronal death, but boosting PGRN expression in the brain is an attractive therapeutic strategy. Unfortunately, there are no clinically effective drugs to boost PGRN in FTD-GRN cases. Towards overcoming this therapeutic gap, we have discovered that small molecule inhibitors of the mechanistic target of rapamycin (mTOR) robustly increase intracellular and secreted levels of PGRN in cultured cells. mTOR is a critical kinase that plays a key regulatory role in cellular energy metabolism and autophagy. Importantly, lysosomal function is unaffected at doses of mTOR inhibitors that increase PGRN. mTOR inhibitors were also able to restore PGRN levels in human fibroblasts from GRN mutation carriers. Ongoing experiments are testing if mTOR inhibition rescues PGRN levels in neuronal models of PGRN haploinsufficiency derived from mice or FTD-GRN patient iPSCs. Taken together our research suggest that mTOR inhibitors, or related compounds, are novel drug leads to treat FTD-GRN patients.

P.291 Gender differences in emerging cognitive-behavioral change in amyotrophic lateral sclerosis suggest a neuroendocrine model for treatment

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Abstract: ALS is associated with frontotemporal lobar degeneration (FTLD) in ~50% of patients, characterized by primary progressive aphasia and/or behavioral decline. Our published work (N=106) demonstrated gender differences that included more males with the Disinhibited behavioral subtype (impulsivity, jocularity, poor insight). Within the Apathy subtype, more women evidenced Personal Neglect. We generated a theory of FTLD onset involving midbrain circuitry of dominance and motivation. We now hypothesize a neuroendocrine model of neuroprotection whereby estrogen replacement may forestall disease progression in peri-menopausal ALS females with emerging FTLD. We investigated gender differences (N=356) in pattern of emergence, and their relationship to estrogen levels. We found a significantly greater number of males with Disinhibition (p=.014) and Stereopathy (p=.048). Within apathy, females evidenced a greater incidence rate of moderate-severe Personal Neglect (6.9%) relative to males (4.5%). Medication records review of female estrogen status for patients aged 31-74, showed a strong relationship to both higher executive functioning capacities [similarities (p=.005), judgment (p=.018), letter fluency (p=.004)], and attenuation of Apathy (p=.022), the latter unrelated to age (p=.076). Gender differences are present in emerging ALS/FTLD, and relate to estrogen status. These findings evidence the potential of estrogen as a therapeutic agent in emerging ALS-FTLD. Given the overlap in genes associated with ALS, FTLD and breast cancer, gonadal steroidal hormones likely serve as immuno-modulatory agents. Estrogen analogs are needed to attenuate neurodegeneration while inhibiting over-activation in the breast and uterus, akin to the selective estrogen receptor modulators currently applied as therapeutics in the treatment of breast cancer.

P.292 Effects of antipsychotic and antidepressant medication on neuropsychiatric symptoms and carer burden in FTD

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Abstract: Prescription of antipsychotic or antidepressant medication in FTD is prevalent. However, the efficacy of such medications on neuropsychiatric symptoms and carer burden in FTD has been virtually unexplored. The current study investigated: i) the rate of medication prescription across FTD subtypes and ii) its potential impact on behavioural symptoms and carer burden. Fifty-one patients (bvFTD=20; PPA-sv=18; PPA-nfv=13) with detailed medication usage record, carer burden data (ZBI) and behavioural data (CBI-R) were included. Rates of drug prescription were: bvFTD (30% antipsychotics only; 50% antidepressants only; 35% both; 40% no medication); PPA-sv (29% antidepressants only; 11% both; 71% no medication); PPA-nfv (8% antidepressants; 92% no medication). Analyses was performed on bvFTD and PPA-sv groups only due to the low medication rates in PPA-nfv. Splitting groups by antidepressant prescription showed no difference for behavioural symptoms and carer burden in bvFTD or PPA-sv. Similarly, splitting bvFTD patients by antipsychotics prescription showed no difference for behavioural symptoms and carer burden, with the exception of disinhibition which was significantly higher in the bvFTD patients on antipsychotic medication. The findings show that rates of drug prescription vary greatly across clinical FTD subtypes, with bvFTD having the highest prescription rates and PPA-nfv the lowest. Medication appears to have little effect on neuropsychiatric symptoms or carer burden in FTD subtypes. The results highlight the urgent need for better disease-tailored pharmacological and non-pharmacological treatment strategies. Future studies are needed to investigate on/off medication modulation within-patients to corroborate our findings.

P.293 Conducting clinical drug trials in frontotemporal dementia: problems and challenges

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Abstract: The initial phase II and III studies in frontotemporal dementia (FTD) that are currently under way bring to light several problems and pitfalls when conducting a clinical drug trial with this particular patient group: Problems with study design clearly include the lack of reliable biomarkers. The measures and assessments of cognition and functional impairment of activities of daily living as well as the clinical global impression of change may be more dependent on the degree of the patients' motivation and cooperativeness rather than their actual cognitive or functional ability. Assessments of behavior are not able to reliably detect any improvement. Study conduct is hampered by problems with patient recruitment. Given the low prevalence of FTD it is difficult to identify patients who are willing and able to take part in drug trials. Lack of insight into their disease and non-compliance with the study procedures appear to be major reasons for screening-failures and drop-outs. Particularly disinhibited or aggressive patients are unable to comply with protocol requirements. Therefore, a selection bias favoring quiet, apathetic patients is likely. Untrained staff is often overwhelmed when severe behavioral disturbances occur. Adverse event reporting proves to be difficult as some patients seem not to have any insight in somatic symptoms. Often it is necessary to initiate sedative or antipsychotic drugs during the course of the trial. Particularly in drug trials that require genetic testing in symptomatic or even presymptomatic probands important ethical issues need to be considered.

P.294 Progranulin is modulated by a sortilin receptor antagonist: structural modelling and the identification of lead molecules for the treatment of frontotemporal disease

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Abstract: Mutations in the progranulin (GRN) gene are a frequent genetic cause of frontotemporal disease. All mutations in GRN lead to a functional loss of progranulin (PGRN) or haploinsufficiency. Restoration of progranulin, a growth factor, in the brains of affected individuals is an attractive therapeutic strategy. We have used in silico molecular modelling of a progranulin receptor, sortilin 1 (SORT1), to identify potential antagonists which may act to prevent uptake of circulating progranulin. SORT1 is a toric protein that exists as a beta-propeller structural type. Blocking the binding of PRGN to SORT1 may lead to an increase in extracellular PGRN and restoration of function. We have used structural bioinformatics approaches to identify sortilin antagonists. Screening of compound databases containing over 20,000 small molecules using high-resolution molecular docking algorithms yielded six candidate molecules that bind to the PRGN binding site of SORT1. One of these lead molecules (BCG1) generated a significant ($p<0.05$) increase on PGRN levels in mouse neuronal cell cultures. BCG1 was superior among these compounds, and was chosen for further testing in mice. In silico methods predicted a binding constant (Kd) in the nanomolar range. BCG1 produced a modest, but significant ($p<0.05$), increase of PRGN in mouse brain tissue. These data indicate that molecular dynamics competition experiments may be used to identify small bioavailable molecule that have a desirable biological effect – the modulation of PGRN in vitro and in vivo. Additional medicinal chemistry is required to identify novel congeners that possess improved biological qualities including a higher binding constant.

P.295 Improving impulsivity in bvFTD: a pharmacological magnetoencephalography study of response inhibition

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Abstract: Behavioural variant frontotemporal dementia (bvFTD) is characterised by disinhibited or impulsive behaviours, inflexibility, socially inappropriate conduct and stereotypical or perseverative actions. Behavioural inhibition depends on serotonergic systems in frontal cortico-striatal networks, as evidenced by human functional brain imaging, electrophysiology and comparative models. We therefore examined response inhibition in bvFTD, and the potential restoration of function by serotonergic treatment, using a 'Go-NoGo' task with MEG and EEG. 12 patients with bvFTD were tested in a double blind cross over placebo controlled study after (i) 30mg oral citalopram and (ii) placebo. Twenty age matched controls completed a single session for normative data with no drug. Cortical sources of successful trials were identified using MEG and EEG during three time windows: 100-200ms, 250-350ms and 400-500ms. Peak amplitudes and latencies in the electrophysiological ERP of two key components for inhibition were analysed: the NoGo-N2 and the NoGo-P3. During the first two time windows, NoGo trials in health activated right temporal and inferior frontal gyrus (IFG). bvFTD reduced these source responses in the right temporal cortex and IFG. Citalopram in patients restored responses in the right IFG 250-350ms ($p<0.05$ FWE, Citalopram vs placebo). Concomitant reductions were observed in the N2 and P3 amplitudes in bvFTD. Critically, citalopram normalised the P3. These results reveal that bvFTD impairs the neurophysiological function of critical regions for response inhibition, which can be reversed by serotonergic treatments. Optimisation of serotonergic strategies for impulsivity will require clinical trials, and identification of factors that determine individual differences in therapeutic efficacy.

P.296 Behavioral varient frontotemporal dementia treatment

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Abstract: Frontotemporal dementia (FTD) is a heterogeneous group of disorders characterized by progressive, focal degeneration of the frontal and/or temporal lobes. Behavioral variant frontotemporal dementia (bvFTD) is a subtype of FTD that presents with progressive changes in behavior and personality. Cognitive impairment in bvFTD appears later in the course of disease progression. There is limited but potentially effective treatments for bvFTD. The focus of this poster is to present behavioral interventions, pharmacologic treatments, and caregiver/family education to effectively treat bvFTD. Any effective treatment requires a multidisciplinary team and flexibility. One behavioral intervention for caregivers and families is the antecedent-behavior-consequence (ABC) model. Caregivers and families look at patters of behavior to figure out what might be causing them in order to minimize exacerbating events. Pharmacologic interventions are limited. There are no FDA approved treatments. Pharmacologic interventions are tailored to treating symptoms and behaviors. Anosognosia and lack of insight into symptoms and behaviors is common which may results in refusal to take medications. The serotonergic system is affected early in the course or bvFTD due to decrease in serotonin receptors in the fontotemporal region as well as neuronal loss in the raphe nuclei. Thus, many medications shown to be effective in treating bvFTD affect the serotonin system such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). The dopaminergic system is also affected in bvFTD, so stimulants sometimes used. Regarding education, The Association of Frontotemporal Degeneration (AFTD) is a first line resource for caregivers and families to learn about bvFTD and treatment options.

P.297 Naming treatment in three cases of primary progressive aphasia

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Abstract: Primary Progressive Aphasia (PPA) is a neurodegenerative syndrome with impaired language as most prominent symptom, in particular impaired word retrieval at the early stage, yet still without established treatment. We evaluated the efficacy of a therapy for word retrieval in PPA using a series of single case experimental designs in three patients. We predicted that treated items should be retrieved more easily, compared to untreated items, bearing in mind that the default pattern in a neurodegenerative condition is for a worsening of performance. The patients were 59, 64, and 69 years old and had been diagnosed with svPPA (2 cases) and lvPPA, respectively, after extensive diagnostic work-up (including CSF analysis, cMRT, FDG-PET, FBB-PET). Items for treatment (n≥120) were selected individually for each patient. Two matched sets of words (n≥30 each) were trained with an errorless learning technique using delivery via PC for two (one set) and successively four weeks (other set). The remaining stimuli (n≥60) served as control set. Outcome measures were accuracy of confrontation naming for treated and untreated items and carry-over into spontaneous speech, assessed in a semi-structured interview. One patient (svPPA) showed significant improvement in naming performance for treated but not for untreated items. He continued practicing for another six months, resulting in further improvement of naming. The other two patients (svPPA & lvPPA) showed no significant change. Our study suggests that in a minority of patients naming skills may benefit from dedicated treatment, even if the ecological validity of this effect remains to be proven.

P.298 Isoform specific RNA interference as a gene therapeutic strategy for FTD-3

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Abstract: Frontotemporal dementia (FTD) is the second most common form of young-onset dementia after Alzheimer's disease, and several genetic forms of FTD are known. A rare genetic variant is caused by a point mutation in the CHMP2B gene located on chromosome 3, hence FTD-3. The mutation is located in the splice acceptor site of the last intron resulting in two aberrant transcripts termed CHMP2B Intron5 and CHMP2B Δ10. Both transcripts are translated into proteins that lack the final 36 amino acids of the C-termini and due to mis-splicing are replaced with either 1 or 29 aberrant amino acids. CHMP2B is a member of the Endosomal Sorting Complex Required for Transport (ESCRT), a multi-protein complex required for the delivery of endocytosed proteins to lysosomes. Mutant CHMP2B causes abnormal trafficking of endosomes that can be observed as abnormal endosomal structures in patient brains and cultured fibroblasts, suggesting that the endosomal pathway is central in the pathogenesis. In this study we developed artificial miRNA lentiviral vectors that efficiently and specifically knock down the mutant isoforms of CHMP2B in patient fibroblasts in order to pursue a gene therapy approach for treating FTD-3. Additionally, we tested if knock down of the mutant forms of CHMP2B in primary patient fibroblasts can alleviate the key endosomal phenotype associated with CHMP2B mutations. Finally, we recloned our most effective knock down cassette into an adeno associated vector for efficient in vivo delivery into mice to test if rescue of pathology could be achieved in our transgenic CHMP2B mutant mouse model.

P.299 The experience and coping strategies of spouses of people with an early-onset dementia

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Abstract: The goal of this qualitative, grounded theory study was to understand the experiences of spouses of people who have frontotemporal dementia and early-onset Alzheimer's disease, throughout the disease trajectory. I conducted semi-structured interviews with 30 participants; 17 had partners with frontotemporal dementia and 13 had partners with early-onset Alzheimer's disease. Spouses were recruited with the intention of capturing various stages of the caregiving career. The participants ranged all the way from spouses of people who were newly diagnosed, to individuals who had already been placed in long term care. Three themes emerged from the data analyses initially: (1) issues related to life-stage, (2) disease invisibility and (3) living with continuous uncertainty. These themes led to a fourth theme of caregivers feeling like they were falling through the cracks of the healthcare and social support systems since there are no appropriate services/policies set up for younger people affected by dementia. Finally, a core theme of surviving chronic crises emerged as spouses described how they coped with the continuous challenges related to their partner's dementia. Spouses live through series of crises that they need to constantly manage, leading to a feeling that they are barely surviving. The most common coping strategies that spouses employed through the illness trajectory included: advocacy, reframing, self-care and spirituality. Over the caregiving trajectory, spouses adapted to the impact of having a partner with early-onset dementia. The applicability of the findings is that they point to the timing, to the types of clinical interventions and to policy initiatives.

P.300 Italian frontotemporal dementia network (FTD Group SINDEM): sharing clinical and diagnostic procedures in Frontotemporal Dementia in Italy

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Abstract: In the prospect of improved disease management and future clinical trials in Frontotemporal Dementia (FTD), it is desirable to share common diagnostic procedures. To this aim, the Italian FTD Network, under the aegis of the Italian Neurological Society for Dementia (SINDEM), has been established. Currently, 77 Italian Centres involved in dementia care are part of the network. Each Centre completed a questionnaire about the local clinical procedures, focused on i) clinical assessment, ii) use of neuroimaging and genetics; iii) support for patients and caregivers; vi) an opinion about the prevalence of FTD. A preliminary analysis of the results showed that presenile onset and a positive family history for dementia and/or psychiatric disorders are additional elements considered in the diagnostic work-up. Co-occurrence of motor neuron disease is also widely considered. The majority of FTD centers require a comprehensive neuropsychological evaluation (95.3%) and a structural (90.7%) neuroimaging exam for diagnostic purposes. In most of the cases (73.3%) functional neuroimaging is also requested. In the half of cases, genetic (55.8%) and cerebrospinal fluid (52.3%) analyses are available, along with genetic counseling. About half of centers plan patient/caregiver support and cognitive rehabilitation. Early onset FTD is considered to be as prevalent as early-onset AD.The general scenario from these data documented a comprehensive clinical and instrumental approach to FTD patients and their caregivers, with about 900 newly diagnosed cases per year.Future goals will be directed to implement the network between tertiary referral Centres and participating primary care Centres, with the aim to improve FTD diagnosis and management.

P.301 S.Y.D. – Service for younger people with dementia – supporting the diagnosed, their families and beyond in North Wales

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Betsi Cadwaladr University Health Board

Abstract: Since 2004, Betsi Cadwaladr University Health Board (BCUHB) has supported services for younger people with dementia (YOD aka early-onset dementia) in North East Wales. Identified and ongoing challenges include the surprise of early onset age, and poor awareness leading to a lack of specialist services, evidenced by government papers stating that dementia only sometimes affects people under 65. 2010 saw the Welsh Minister for Health promise £0.5million to develop YOD services in Wales, in line with publication of the National Dementia Strategy and The National Dementia Vision for Wales for 2011. Consequenlty, since 2011, BCUHB, the Welsh Minister for Health, and national programs have mandated services for YOD, supporting 3 additional nurses to cover North Wales and North Powys, the only health board in Wales offering such a service. Previously YOD service has been “make do” at most. Current projects include education, including national festivals, local primary and secondary schools, translating a Canadian children’s Activity book about Frontotemporal dementia into Welsh, developing a bilingual pamphlet on dementia for children, and collaborating "Seasons", a charity to support grieving children. The development of this “virtual team” along with Government drive to develop Dementia communities brings about publicity and greater public drives to raise awareness.

P.302 Assessing the needs of frontotemporal degeneration helpline users: a social ecological framework

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Association for Frontotemporal Degeneration

Abstract: AFTD is the national advocacy organization in the United States for frontotemporal degeneration (FTD). AFTD's HelpLine provides information and support for anyone living or working with FTD and can be contacted via phone, email, or AFTD's website. This analysis describes the characteristics and needs of AFTD HelpLine users employing the Social-Ecological Model (SEM) framework. The SEM allows a multilevel analysis of the relationship between an individual's personal circumstances, their environment, and their health. An SEM coding manual was written, refined and pretested for AFTD HelpLine cases. HelpLine cases from July 1, 2012 – June 30, 2013 (n=1661) were coded by four reviewers for the presence of 5 SEM levels: intrapersonal, interpersonal, institutional, community, policy/society. Additional demographic information was compiled and summarized where available. Our data indicate that primary caregivers were the most frequent caller type (37.9%). The majority of cases contacted the HelpLine via the toll-free number (36.8%). Intrapersonal (59.1%), Institutional (49.0%), and Community (36.0%) were the most common SEM levels present in the HelpLine cases. Most cases were coded with one (56.1%) or two (31.3%) different SEM levels. By identifying the levels most often present in HelpLine cases, the SEM model worked well to describe and categorize the varied needs of HelpLine callers. Our findings suggest further analysis of HelpLine data with the SEM and an exploration of how the SEM levels interact could increase understanding of the needs of people coping with this rare, younger-onset dementia and aid the development of FTD-specific supports, resources, and interventions.

P.303 Clinical application of understanding conversation in primary progressive aphasia

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Abstract: Primary Progressive Aphasia (PPA) is a clinical syndrome resulting from neurodegenerative diseases, the most prominent feature being gradual dissolution of language with initial sparing of other cognitive domains. Much has been written describing the cognitive and linguistic impairments in PPA and their neural and pathological bases but the question of how these impact conversations has been largely neglected. In the absence of pharmacotherapies, behavioural interventions that promote quality of life are needed. For the individual with PPA and their family, approaches that facilitate successful conversation despite significant language impairment can be beneficial. We aim to describe the clinical application of better understanding of conversation breakdown in the variants of PPA. We previously studied trouble and repair in the conversations of two dyads with a partner with PPA (nfvPPA and lvPPA). The analysis of data from the svPPA dyad is in progress. The patterns of trouble and repair during the conversations of people with PPA were unlike those of people with dementia and diverse patterns were observed in the nfvPPA and lvPPA individuals. It is anticipated that as svPPA has unique language characteristics, unique patterns will also be observed in the svPPA trouble and repair behaviour. Generic advice about strategies to facilitate success in conversation will not adequately meet the needs of individuals with PPA and tailored approaches for each variant of PPA are required. Understanding the nature of conversation breakdown in PPA may improve the effectiveness of behavioural interventions and promote quality of life for individuals with PPA and families.

P.304 Characteristics and caregiver evaluations of a behavioral variant frontotemporal/primary progressive aphasia educational seminar

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Mayo Clinic

Abstract: Caregiver education is critical in the management and support of patients and families affected by behavioral variant frontotemporal dementia and primary progressive aphasia (FTD/PPA). To promote education/support and awareness of disease management options, the FTD/PPA Educational Seminar was developed at Mayo Clinic Rochester. We present the evolution of the program, outline of the 7 hour session, and the results of caregiver evaluations. The seminar began in 2008 and occurred every 3 months with 4-10 families participating. It expanded to involve 50-100 participants and has occurred every 12 months since 2012. Activities for each seminar has proceeded as follows: staff and family introductions, the basics of FTD/PPA, integrating and expanding the health care team, current research and genetics, questions and answers session, lunch, separate focus group sessions for FTD and PPA (including coping and communication strategies as well as FTD and PPA patient sessions occurring concurrently with separate session for their care partners and group summary/conclusions). Caregiver evaluations over 3 annual seminars (n=72 completed surveys) revealed that 74% rated the content and quality of the program as “excellent.” In addition, five topic sessions were rated as “excellent” by 70-89% of the attendees. These findings suggest that caregivers view educational sessions with other patients and their families and key health care team members as highly desirable and informative. Additional research is needed to determine if educational sessions improve patient/caregiver quality of life, reduce need for hospitalization, delay need for institutionalization, reduce expenditure of health care costs, etc.

P.305 The burden of care in FTD: the under-reported impact on child-carers

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Abstract: Little is known of the impact of FTD on children of patients affected by it. Most of the focus of carer research has been on the impact of FTD on spouses, who are usually the primary carers. This study investigated (1) whether a difference in carer burden exists between spouses and children; (2) whether differences in burden exist between children living with or away from the affected parent; (3) which variables are associated with burden in children. Ninety carers of individuals with FTD were included (spousal-carers=43; child-carers=47). Carers were assessed with the Zarit Burden Interview, Depression, Anxiety and Stress Scale-21 and Social Network Index. Bond between patient and carer, and dementia severity were also measured. A multiple regression analysis was run for each group separately, to identify the variables contributing to burden. Spousal-carers and child-carers experienced similar levels of burden, depression, anxiety and stress (all p values>0.05). Spousal-carers had significantly ($p<0.001$) richer social networks than the child-carers. Child-carers living with the patient had smaller ($p<0.05$) social networks than those living separately, and also had significantly higher levels of burden ($p<0.01$). Importantly, factors influencing carer burden differed between spousal-carers (77% variance explained by dementia severity and carer depression) and child-carers (51% variance explained by carer depression). Child-carers of a parent with FTD share a similar level of carer burden as spousal-carers. However, factors associated with this burden differ and should be considered for future provision of FTD carer support services, where interventions targeting child-carers are much needed.

P.306 Differences in carer burden are not associated with use of coping styles in FTD

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Abstract: There is scarce knowledge of the potential impact of carer coping styles on levels of carer burden reported in FTD, and in comparison to AD. This study investigated whether differences or similarities in carer burden in the three main FTD variants were associated with carers' coping styles. Data from 148 carers (bvFTD=48; PPA-sv=30; PPA-nfv=29 and AD=41) were included. Coping styles were classified via the Brief COPE questionnaire, which identifies a number of coping strategies considered functional (Active; Planning; Positive Framing; Acceptance; Religion; Self-Distraction) and dysfunctional (Using Emotional Support; Using Instrumental Support; Denial; Venting Emotions; Substance Use; Behavioural Disengagement). Burden was measured with the ZBI; carer demographics were also examined. Carers from all groups were well matched for age and education; the proportion of female carers was greater in the AD group. Rates of burden were similar between bvFTD and PPA-sv carers ($p=0.115$), but greater in the bvFTD group in comparison to PPA-nfv and AD carers (both p values<.05). Use of functional coping styles did not differ between carers from different diagnostic groups, nor did use of dysfunctional coping styles (no group effect for both conditions). Dementia carers seem to apply very similar coping styles, regardless of dementia subtype. Burden of care does not seem to be associated with the type of coping style used. The complexity of factors involved in high levels of carer burden in bvFTD and PPA-sv needs to be further investigated to ensure the development of novel and efficacious non-pharmacological carer interventions in FTD.

P.307 Caregiver challenges and strategies with FTD

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Abstract: Caregivers of individuals with Frontotemporal Degeneration (FTD) are challenged with symptoms different from those caring for someone with Alzheimer Disease (AD). The purpose of this presentation is to highlight the unique stressors caregivers face in FTD and discussing potential interventions garnished from our work at the Alzheimer Outreach Services with the caregivers. Research indicates that caregivers with a spouse diagnosed with FTD experience higher levels of depression and anxiety than spouses of persons diagnosed with AD. Many dementia specific programs tend to incorporate persons with FTD and their caregivers into programs designed for caregivers dealing with AD with minimal or no recognition of the unique needs of the FTD group. A blended group can limit the benefits of mutual learning since behaviours and symptoms can differ widely. Information on strategies coping with AD is widely available but there still is a dearth of information for FTD. In this presentation we discuss some general principles in dealing with the behavioural symptoms of FTD and some specific interventions that can be utilized at various stages of the disease. Video clips with three spouses who are at different stages of their FTD journey will illustrate their own insights and learning. The experiences of two caregivers coping with the language variant of FTD are in the video along with comments from the person diagnosed with semantic dementia. This presentation shines the spotlight on the unique demands of families coping with FTD and the pressing need to continue developing better strategies.

P.308 Therapeutic Touch TM in a geriatric palliative care unit - a retrospective review

Helen Senderovich

Baycrest Health Sciences

Abstract: Introduction: Complementary therapies are increasingly used in palliative care as an adjunct to the standard management of symptoms to achieve an overall well-being for patients with malignant and non-malignant terminal illnesses. A Therapeutic Touch Program was introduced to a geriatric Palliative Care Unit in October 2010. Two volunteer Therapeutic Touch Practitioners offer the therapy to patients who have given verbal consent. Objective: To conduct a retrospective review of Therapeutic Touch services provided to patients in an in-patient geriatric palliative care unit to better understand the impact of the Therapeutic Touch Program on patient care. Methods: A retrospective medical chart review was conducted on both patients who received Therapeutic Touch as well as a random selection of patients who did not receive Therapeutic Touch. Client characteristics and the Therapeutic Touch Practitioners' observations of the patient's response were collected. Descriptive analyses were conducted on all variables. Results: Patients who did not receive Therapeutic Touch tended to have lower admitting Palliative Performance Scale scores, shorter length of stay and were older. Based on the responses provided by patients and observed by Therapeutic Touch practitioner the majority of patients receiving treatment achieved a state of relaxation or sleep. Conclusions: The results of our chart review suggest beneficial effects for significant numbers of participants and deserve a more robust comparison study in future. Recommendations also include revising the program procedures to improve processes and documentation, and ensure all or most patients are offered the therapy.

P.309 Family adaptation to living with behavioural variant fronto-temporal dementia

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Abstract: Behavioural variant fronto-temporal dementia (bvFTD) has distinctive impacts upon empathy, awareness and social relationships. However, in-depth understanding of how families, including the person with dementia, experience and adapt to living with bvFTD are missing. This presentation will provide data from an on-going longitudinal qualitative study, focused on the emotional experience and impact of bvFTD upon relationships, and the strategies families use to make sense of and cope with FTD-related changes. The study includes interviews at 4 time points over 2-3 years with 7 families (19 people, including 5 living with FTD). This paper focuses on findings from narrative and thematic analysis of the first 2 time points. We derived four key themes: Making sense of what's happening captures the struggle of family members, including those with bvFTD, to understand; Relationship quality reflects changes in relationships in particular; It's not so much husband and wife these days, shows a (sometimes shared) regret about changes in couple relationships; and Cumulative effects of changes reflects longer-term impact. An influential variable was the positioning of the person with bvFTD in the family, which affected processes of adaptation, blame and striving to maintain the status quo. Verbatim examples will be given of each theme, and each process. Our study illustrates the interaction between (i) attitudes, life expertise, and family cultures, (ii) changes brought by bvFTD and (iii) other current pressures – all of which contribute to how families adapt as bvFTD progresses. We will draw out the implications for support and interventions for families with bvFTD.

P.310 FTD talk - a website providing jargon free research updates for the whole frontotemporal dementia community

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Abstract: Research in frontotemporal dementia (FTD) is hugely important in being able to better understand the disorder and move forward towards clinical trials of disease-modifying therapy. The ability to engage with patients and their families is paramount to the success of FTD research and yet the lay FTD community often find it difficult to stay up to date or understand exactly what new research means. It is therefore imperative that FTD researchers find the optimal methods that allow them to interact with patients and the wider FTD community. With this in mind, we set up a new website called FTD talk (www.ftdtalk.org) which aims to provide accurate, up to date and accessible information on the latest FTD research. The site has basic information and downloadable factsheets about FTD but its main aim is to publish short articles on recently published scientific papers or relevant dementia conferences. It is currently available only in English and as well as the three editors there are almost twenty contributors from FTD research groups across the UK, Australia, Canada and the US. To engage as widely as possible though social media, information from FTD talk is available on Twitter (@FTDtalk) and Facebook (www.facebook.com/FTDtalk). Launched in March 2014, over 1000 people visited the site in its first month. We hope that FTD talk can serve as an important link between researchers and the FTD community, allowing both to learn from the interaction.

P.311 Phone call frequency to FTD clinicians before and after participation in a frontotemporal dementia caregiver educational and support program

Laura Allen, Bradley Boeve, Brendon Boot, Keith Josephs, Meredith Wicklund, Jack Thomas, Glenn Smith, Charlene Martin-Lillie, Angela Lunde, Marla Bruns, Daniel Drubach, David Jones, Suzanne Kennebeck

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Abstract: Caregiver distress in frontotemporal dementia (FTD) is substantial. Individually-developed, multicomponent interventions that include education and support services might decrease this distress, improve quality of life, and enable caregivers to provide at-home care for longer periods. We sought to evaluate the number of phone calls to a subspecialty behavioral neurology practice – a presumed indirect measure of caregiver distress – over the 12 months prior to and 12 months subsequent to participation in an FTD caregiver education and support program. For programs conducted 2009-2013 involving 50 unique patients plus their caregivers and relatives, the overall call frequency decreased 26% (range 9-80% decrease for 4 years and increased 250% for 1 year). These findings suggest that education and support programs specifically designed for FTD patients and families empower caregivers and may modestly decrease caregiver distress. Future analyses are planned to better delineate how caregiver distress and quality of life are impacted by education/support programs.

P.312 Coping strategies but not satisfaction predict PPA caregiver psychological wellbeing

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Abstract: Little is known about the psychological wellbeing of caregivers of persons with Primary Progressive Aphasia (PPA), but because the syndrome has a younger onset and selectively impacts communication, PPA caregivers experience a unique set of circumstances and warrant focused study. We investigated the role of caregivers' positive appraisals of satisfaction and coping strategies in predicting their psychological wellbeing. Forty-four Australian PPA caregivers completed questionnaires for analysis. PPA severity was measured with the Addenbrooke's Cognitive Examination-Revised, satisfaction with the Carer's Assessment of Satisfaction Index, psychological wellbeing with the Depression Anxiety and Stress Scale (DASS-21) and the Positive and Negative Affect Schedule (PANAS) and problem-focused, emotion-focused and dysfunctional coping strategies with the Brief COPE and COPE Inventory. Severity of PPA was not predictive of caregiver satisfaction or psychological wellbeing. Caregivers' appraisal of satisfaction was unrelated to caregiver depression, positive affect, or coping strategies. Satisfaction also did not mediate the relationship between PPA severity and psychological wellbeing. Instead, problem-focused coping uniquely predicted caregiver reduced depressive symptoms ($p < .05$), with younger caregivers at risk of adopting more dysfunctional coping. Our results suggest that although PPA caregivers endorse satisfaction in their caregiving role, this satisfaction is not protective of their psychological wellbeing. Rather, the coping strategies they adopt are central to their psychological wellbeing and should therefore be a focus of intervention. Further research is needed on PPA caregivers, particularly the interaction between satisfaction and burden in predicting positive and negative aspects of psychological wellbeing.

P.313 Clinical diagnostic phenotyping and therapeutic targeting of neuropsychiatric symptoms in FTD: initial results with an expanded version of the Neuropsychiatric Inventory Questionnaire (NPI-Q2)

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Abstract: Recent consensus diagnostic criteria for behavioral variant frontotemporal degeneration (bvFTD) include neuropsychiatric, cognitive, motor, and vegetative signs and symptoms. The Neuropsychiatric Inventory Questionnaire (NPI-Q), a derivative of the parent NPI interview to provide a more brief clinical assessment, assesses 4/6 criteria (apathy, disinhibition, aberrant motor behaviors and appetite / eating alterations. Although the brevity of the NPI-Q has led to it being adopted for use in multicenter studies of Alzheimer disease, each symptom domain is rated categorically without identifying specific manifestations. The NPI includes specific symptoms within each domain for rating purposes, but these are not included in the final scoring. In an attempt to enhance the utility of the NPI-Q, representative items from each symptom domain on the NPI were added as check boxes under each domain-screening question to create the NPI-Q2 (validation study ongoing), We present data on 50 FTD subjects (33 bvFTD, 17 primary progressive aphasia), focusing on FTD-spectrum symptoms and other potentially significant signs and symptoms. Apathy (82%), aberrant motor behaviors (60%), disinhibition (56%) and appetitive changes (56%) were present in a majority of subjects; aberrant motor and agitated behaviors were more common in bvFTD subjects. Appetitive and nighttime behaviors had among the highest overall severity ratings, and were also commonly associated with severe caregiver distress. Change in food preferences and excessive daytime somnolence were the most frequently reported signs in these respective domains. Our preliminary data suggest that the NPI-Q2 may help identify clinical diagnostic features and other potential symptom-based therapeutic targets in FTD.

P.314 The savvy caregiver program: a psycoeducational support program for dementia caregivers

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Abstract: The “Savvy Caregiver” program is a six week, 12 hour psychoeducational series for caregivers of people with various forms dementia, including frontotemporal degeneration (FTD). The central concept is the notion of strategy; throughout the program caregivers learn, develop and modify strategies that will be used to accomplish goals for their particular caregiving situation. Another tenet of the program is to have the loved one be active and contented. 93 caregivers attended Savvy Caregiver series from 2011 to 2014. FTD, Alzheimer’s disease (AD), vascular dementia, FTD, Lewy body dementia and Korsakoff Syndrome caregivers participated. Every group member was given a post series evaluation to fill out. Nine caregivers identified FTD as their loved one’s diagnosis, 7 Bv FTD, and 2 primary progressive aphasia. Six caregivers were spouses; two were daughters and one sister and sister in law. Seventeen males and 32 females completed evaluation. The majority of family caregivers were referred by physicians from an affiliated memory/dementia clinic. 74 evaluation forms were completed. Overall satisfaction with program, usefulness of information presented, whether the program met expectations were rated on a 0 (=did not meet expectation) to 2 (=exceeded expectations) scale. Expectations were met or exceeded for all respondents in all categories. Participants’ comments about the program indicated decreased caregiver burden: “(helps) me further understand my husband and the disease”, “This information is a lifesaver for me”, and “(I can) better cope with the demands of caregiving”. This program demonstrates the need for structured caregiver education and support.

P.315 Frontotemporal dementia caregiver support groups: benefits and challenges

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Abstract: Research shows frontotemporal dementia (FTD) caregivers experience higher distress levels than Alzheimer's disease (AD) caregivers due to challenging behavioral symptoms. FTD caregivers compared to AD caregivers find less information and support services within the healthcare system. Furthermore, FTD symptom onset typically occurs at a younger age than AD, thus disrupting family and occupation earlier in life. Families caring for someone with FTD need supportive and educational services that cater to their specific needs. The Indiana Alzheimer Disease Center (IADC) and the Northwestern University (NU)-CNADC offer monthly psychoeducational caregiver support groups. To determine the groups' impact, a cross-sectional survey of current group members from both IADC and NU-CNADC was conducted in Spring 2014. Unique challenges by faced by FTD caregivers include significant legal, financial, social and relational problems due to marked changes in reasoning, judgment, and personal and emotional conduct. Among the most beneficial aspects of attending the groups are learning care management strategies and feeling a sense of solidarity with others - knowing they are not alone. Suggestions to improve the groups included planning social activities and offering more educational sessions. Barriers to group attendance included finding care for the patient, in addition to the scarcity of FTD support groups requiring some families to drive several hours each month to attend the groups. Offering caregiver support groups designed to address the unique challenges faced by FTD caregivers meets a critical need. Future plans include exploring technological options to increase access to FTD education and support in the Midwest US region.

P.316 The Australian FTD association: on the road to a brighter future

Melissa Kettle

The Australian Frontotemporal Dementia Association

Abstract: In November 2012, the Australian Frontotemporal Dementia association (AFTDA) was established as a National carer-driven charitable organisation. The AFTDA has now raised sufficient funds to appoint a National Clinical Coordinator role, with the goal of establishing collaborative partnerships and a National FTD registry. Given FTD is a rarer form of dementia, this will be critical to increasing FTD research opportunities in Australia and to provide FTD-specific support services that overcome the vast distances between Australia's major cities and remote communities. This poster will highlight the AFTDA's outcomes to date: A scoping project undertaken across all states/territories identifying existing FTD services and service gaps. Alzheimer's Australia, the National Dementia Behaviour Management Advisory Service and 5 national younger onset dementia clinics/research centres have committed to supporting the AFTDA with; education programs, meeting space, assistance with fund raising and consultation with the AFTDA on younger onset dementia initiatives, research and projects FTD education to Alzheimer's Australia's newly established " Younger Onset Dementia Key Worker " staff 6 additional FTD carer support groups established across 4 remote states/territories. A collaborative project with the Eastern Cognitive Disorders Clinic and the Cognition and Memory Clinic in the Northern Territory (NT), has built capacity for FTD tele-health case consultation opportunities for clinicians supporting people with FTD in the NT's remote and indigenous communities. Ongoing production of an Australian FTD caregiver documentary. Review of the Australian FTD toolkit and AFTDA website to include a directory to newly identified and establishing FTD support services around Australia.

P.317 Words over time: maintaining benefits of word retraining in semantic dementia

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Abstract: Recent research shows that patients with Semantic Dementia (SD) can improve their naming ability through word retraining, with good retention 1 month later. Improvements often fade beyond this time period, yet no studies have focused on methods to maintain performance. Nine SD patients completed a 2-month word training program and were subsequently monitored over a period of 6 months: first, for 2 months without training, followed by a further 4 months, where revision training sessions were provided if required. All patients improved their naming immediately post-intervention ($p < .001$). After 2 months without practice, a significant decline was observed in 4 of the 9 patients. To sustain at least 80% of their post-intervention performance at 6 months, 4 patients required a minimal level of revision (less than 10 sessions), 2 required regular weekly or biweekly sessions, with the remaining 3 patients requiring no additional sessions. During this period, group results indicated some decline in words that were initially known, but were not trained. Overall, results demonstrated that improvements in naming can be sustained in SD patients, with the support of less intense, but ongoing revision. In addition, our findings indicate that training words that are still known may be of value, in order to help prolong knowledge of these words.

P.318 When a little knowledge can be dangerous: false positive diagnosis of bvFTD among community clinicians

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Abstract: Background: Clinical diagnosis of behavioral-variant FTD is difficult, even for specialists. However, the degree to which community clinicians understand and accurately apply consensus diagnostic criteria remains uncertain. We examined referrals to a dementia clinic at UCSF to determine referring clinicians' diagnostic accuracy. Method: We reviewed charts and referral letters for the 3578 consecutive patients for whom such letters were available and who had received a definitive diagnosis at UCSF. We evaluated referral diagnoses, symptoms, demographic data, and MMSE, CDR, and NPI scores. Result: False positive diagnosis of bvFTD by community physicians was alarmingly high. Of 361 patients referred with bvFTD as one of multiple options on the differential, only 18% were diagnosed with bvFTD by UCSF. 247 subjects were referred with a definitive diagnosis of bvFTD alone, but 60% did not have bvFTD according to specialists. Falsely diagnosed patients were more likely to be depressed and non-Caucasian, had less euphoria, apathy, disinhibition, and abnormal eating behaviors, had milder disease severity and better overall cognition than true bvFTD patients. In contrast, potentially due to the referral bias inherent in UCSF being an FTD specialty center, false negative rates were lower. Of 194 subjects diagnosed as true bvFTD at our center, 86% had bvFTD mentioned in the referring differential. bvFTD was more likely to be missed in males. Conclusion: Despite greater awareness of bvFTD among clinicians, our data suggest they remain undereducated about the disease's diagnostic criteria and specific clinical characteristics, and are at high risk for falsely assigning a definitive bvFTD diagnosis.

P.319 The caregiver burden and wear in behavioral variant frontotemporal dementia and Alzheimer disease

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Abstract: Specific problems of bvFTD caregivers include delayed diagnosis, young age of patients, behavioral problems, lack of suitable care facilities, and poor self-care.We compared caregiver burden in Behavioral variant Frontotemporal Dementia (bvFTD) and Alzheimer Disease (AD). 2. We examined which factors contribute to bvFTD and AD caregivers' burden and wear. Sixty-two caregivers, aged 55 or older and with at least two years of formal education, were invited to participate. Among patients, 31 diagnosed with bvFTD and 31 with AD. Protocols: Short Zarit Burden Inventory; caregiver wear and patient´s neuropsychiatric and behavioral symptoms from the Neuropsychiatric Inventory (NPI); Disability Assessment for Dementia (DAD) and Cornell Depression Scale in Dementia. Patients: Addenbrooke's Cognitive Examination-Revised (ACE-R); Executive Interview (EXIT-25); Direct Assessment of Functional Status (DAFS-BR), and Geriatric Anxiety Inventory (GAI). Caregivers of patients with AD and bvFTD did not significantly differ according to age, schooling and sex. In the NPI, bvFTD caregivers reported higher presence and severity of neuropsychiatric symptoms, as well as caregiver distress, when compared to the AD group. In the bvFTD group only, DAD-Total and DAFS-BR sub-scores were strongly correlated with caregiver burden (ZARIT). bvFTD caregivers seem to experience higher levels of burden and wear than AD caregivers. Patients' cognitive and functional limitations, as well as their psychiatric symptoms seem to be associated with higher burden and wear in bvFTD caregivers.These findings are relevant for the planning and delivery of support for families, reinforcing the need for tailored caregiver support that should take into account the disease characteristics.