International Dementia with Lewy Bodies Conference
Fort Lauderdale, Florida, USA; December 1 – 4, 2015

Table of Contents

Oral Presentations

Day 1 DLB Review & Update (Tuesday Dec. 1)

Day 2 New DLB Research I (Wednesday Dec. 2)

Day 3 New DLB Research II (Thursday Dec. 3)

Day 4 Hot Topics/Controversies/Harmonization (Friday Dec. 4)

Poster Presentations

Tuesday Dec. 1 and Wednesday Dec. 2

TUESDAY DECEMBER 1, 2015

Session 1: DLB Update – Clinical

O.1

DLB History, Differential Diagnosis and Diagnostic Features

Ian McKeith

Newcastle University, Newcastle, UK

Although case reports of dementia associated with LB pathology can be traced back to the early part of the twentieth century, its recognition as a common and possibly, separate entity was much more recent. The DLB Consortium first met in 1995 to bring together the handful of researchers interested in the disorder, to harmonise the various competing appellations and to evolve the DLB concept. A brief historical account of this and subsequent developments will be offered as a starting point for the current meeting. DLB cases can be usefully divided into typical and atypical presentations. Typical cases correspond to the DLB profile described by Consensus criteria with one or more of fluctuating confusion, recurrent visual hallucinations, mild extrapyramidal features, RBD, autonomic dysfunction or neuroleptic sensitivity. In such cases the differential diagnosis includes Alzheimer's disease, Parkinson's disease with dementia, vascular dementia or delirium. Although guidelines recommend neuroimaging investigations to aid diagnostic discrimination, since >80% of clinically typical cases are found to have cortical LB disease at autopsy, current biomarkers can add only a limited amount. More problematic are atypical presentations with complaints of memory dysfunction, apathy, low mood and general functional decline but lacking core features of DLB and corresponding to what was previously called the Lewy body variant of Alzheimer's disease. Cognitive testing reveals deficits across multiple domains and in the absence of further history taking, the most frequent diagnosis made is of Alzheimer's disease or mild cognitive impairment (MCI). It is in such cases that systematic questioning about prodromal features suggestive of LB disease are most helpful and these should form part of the routine history taking of all patients being assessed for the cause of cognitive decline. It is also in this group that neuroimaging and other biomarkers may most increase diagnostic confidence.

O.2

Key Clinical, Epidemiologic, Neuropsychologic and Imaging Features of DLB

Bradley F Boeve

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Dementia with Lewy bodies (DLB) is a clinical syndrome characterized by dementia associated with two or more of the following features: recurrent fully-formed visual hallucinations, fluctuations in cognition, spontaneous parkinsonism and REM sleep behavior disorder (RBD). The evolving data indicates that the clinical manifestations of DLB encompass many other features spanning the cognitive, neuropsychiatric (e.g., delusions, apathy, depression, etc.), motor, sleep (e.g., hypersomnia, fragmented nocturnal sleep, etc.), autonomic (e.g., constipation, orthostatic hypotension, sexual dysfunction) and sensory (e.g., reduced smell and color vision) domains. DLB is not only the second most common cause of degenerative dementia syndrome (after Alzheimer's disease or AD), some of the clinical features are similar to both AD and Parkinson's disease, underscoring the relatively high prevalence as well as the complexity in terms of diagnosis and phenomenology. Neuropsychological assessment typically demonstrates impairment in attention, executive functioning and visuospatial functioning, with more preserved functioning in memory and confrontation naming – this profile is different than that typically present in individuals with AD. Neuroimaging studies are also useful in differentiating DLB from other disorders, with the characteristic findings being preserved hippocampal volumes on MRI, posterior cerebral hypometabolism and the "posterior cingulate island sign" on FDG-PET imaging, reduced striatonigral uptake on ioflupane SPECT imaging, and reduced cardiac uptake on MIBG imaging. Medical management can be particularly challenging in DLB, as certain medications which are effective for some of the manifestations can worsen other features, yet a comprehensive approach addressing the most problematic features can result in significant clinical improvement and quality of life in some patients. Characterizing prodromal DLB is a high priority as early diagnosis may lead to management strategies being used that could impact symptoms and clinical course more. Prodromal DLB patients will also be attractive candidates for clinical trials as potential disease modifying therapies are refined.

O.3

DLB Tools for the Clinician

James E Galvin

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Introduction**:** Dementia with Lewy bodies (DLB) is a challenge to diagnose with long delays leading to significant patient and caregiver burden. We developed two brief instruments to assist diagnosis and staging of dementia in the clinic setting. The Quick Dementia Rating Systems (QDRS) is a 10-item questionnaire provides a rapid assessment of the presence and severity of dementia. The Lewy Body Composite Risk Score (LBCRS) was developed from autopsy-verified cases to improve the ability to detect DLB as the cause of dementia. Methods**:** The QDRS and LBCRS were validated in a consecutive series of patients compared with the Clinical Dementia Rating (CDR) and gold standard measures of cognition, motor, function, and behavior. Psychometric properties including floor and ceiling effects; validity, and internal consistency were determined. Receiver operator characteristic curves were used to test discrimination properties of QDRS across CDR stages and the ability of LBCRS to differentiate DLB from other causes of cognitive impairment. Results**:** QDRS scores increased with higher CDR and poorer neuropsychological performance. The QDRS demonstrated excellent validity across CDR stages; differential scores by dementia etiologies; and discriminated controls from dementia (AUC=0.911 (0.86–0.96). LBCRS scores were significantly different between DLB and AD (6.1$\pm$2.0 vs. 2.4$\pm$1.3, p<.001) and between MCI-DLB vs MCI-AD (3.2$\pm$0.9 vs. 1.0$\pm$0.8, p<.001). The LBCRS was able to discriminate DLB from other causes of dementia with AUC for DLB vs. AD=0.93 (0.89-0.98), and for MCI-DLB vs. MCI-AD=0.96 (0.91-1.0). Discussion: The QDRS validly and reliably differentiates individuals with and without dementia and accurately stages dementia. The LBCRS increases diagnostic probability that Lewy body pathology is contributing to the dementia syndrome. Combined, the QDRS and LBCRS provides a rapid method to determine presence and severity of dementia and determine whether DLB is the likely underlying cause. These instruments should improve clinical detection and enrollment for clinical trials.

Session 2: DLB Update – Imaging/Biomarkers

O.4

Structural Imaging Changes in Lewy body Dementia

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In contrast to the marked functional imaging changes in Lewy body dementia, in particular striatal dopaminergic loss and parieto-occipital hypometabolism, early MRI studies showed relative structural preservation in both dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD). This was especially so when compared to Alzheimer's disease, where focal atrophy of the hippocampus and medial temporal lobe is characteristic, and relative preservation of the medial temporal lobe was adopted as a supportive diagnostic marker for DLB in the 1996 and 2005 Consensus Criteria, subsequently validated by autopsy. Autopsy studies indicate that when medial temporal atrophy occurs in DLB it may reflect concurrent Alzheimer type changes, especially tangle pathology. While MRI is widely available, it is not universally so in many countries and coronally reconstructed CT was recently shown to have good diagnostic accuracy in separating DLB from AD. The advent of more sensitive methods of imaging analysis, including cortical thickness, has demonstrated changes in frontal, temporal and parieto-occipital studies in DLB and PDD. Some studies have shown quite marked changes on diffusion imaging in posterior white matter in Lewy body dementia, suggesting this may be an early marker of disease which may predate grey matter atrophy, though this remains to be confirmed. Serial imaging studies also show relatively little structural change over time periods of a year, in contrast to AD. Studies in early disease, when Parkinson's disease associated with mild cognitive impairment or "Prodromal" DLB, suggest that early structural changes can be demonstrated, for example the insula in early DLB and frontal and association cortical areas in PD-MCI. Further work will determine the relationship between structural and functional imaging changes and symptoms, and combined with imaging markers of tau and amyloid will allow pathophysiological relationship to be examined in vivo across the disease process.

O.5

Functional Imaging Changes in DLB

Nicolas Bohnen

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Occipital hypometabolism and hypoperfusion were one of the first recognized functional imaging features distinguishing DLB from Alzheimer's disease. Although the occipital feature has overall high specificity its sensitivity is limited. Additional metabolic and flow changes include the so-called posterior cingulate island sign and relative sparing of mesiotemporal lobe activity in DLB compared to Alzheimer's disease. Presynaptic dopaminergic nerve terminal imaging provides a robust diagnostic tool to distinguish DLB from Alzheimer's disease. There is increasing interest in multimodal presynaptic dopaminergic nerve terminal and fibrillary β-amyloid imaging to provide a differential diagnostic algorithm to distinguish DLB from not only Alzheimer's disease but also the frontotemporal lobar degenerations that may prove to outperform clinical diagnostic criteria. Such imaging algorithms are expected to improve with the anticipated advent of tau and α-synuclein ligands. Cholinergic ligand imaging remains an investigational tool that based on brainstem pedunculopontine-thalamic nerve terminal imaging may be highly accurate to distinguish DLB from prototypical Alzheimer's disease. Imaging algorithms to identify subjects with incidental or prodromal Lewy bodies remain to be defined but may include cholinergic abdominal or cardiac sympathetic nerve terminal imaging.

O.6

Electrophysiologic correlates of Dementia with Lewy bodies

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There is a clear need to identify biomarkers of DLB in order to: (1) expedite early diagnosis and accurate differential diagnosis; (2) improve our understanding of how DLB progresses; (3) provide objective measures of therapeutic response; and (4) ultimately help develop disease-modifying interventions. One potential biomarker modality which has previously been neglected in DLB is that of electrophysiology, which includes approaches such as electroencephalography (EEG), magnetoencephalography (MEG) as well as non-invasive stimulation techniques e.g. transcranial magnetic stimulation (TMS).A barrier to the use of electrophysiological techniques in DLB such as EEG has been their lack of diagnostic specificity, a dearth in expertise in their use and, previously, the tendency for the use of electrophysiology to be eclipsed in dementia, both clinically and research-wise, by neuroimaging. However electrophysiology is currently undergoing a renaissance in neuroscience as a result of increases in computational power and advances in electrophysiological hardware (e.g. high density EEG) which allow for complex data modelling, improved spatial resolution, and the development of novel neurophysiological protocols that can probe different neural systems. In my presentation I will provide an overview of electrophysiological approaches and their application in DLB. I will demonstrate emerging evidence for the utility of EEG in the differential and early diagnosis of DLB as well as show how electrophysiology can provide mechanistic insights into core symptoms of DLB including cognitive fluctuations and visual hallucinations. I will also describe how neurophysiological stimulation protocols can be used as probes of therapeutic response. I will finish with a look to the future and how complex multimodal electrophysiological approaches may help us understand the patho-aetiological basis of DLB and ask whether TMS, non-invasive electrical stimulation e.g. transcranial direct current stimulation (tDCS), and deep brain stimulation may be useful therapies for DLB.

Session 3: DLB Update – Neuropathology/Genetics/Basic Science

O.7

Historical Perspective of Lewy Body Disease, Including DLB

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The history of Lewy body disease (LBD) including PD and DLB is briefly presented. Since Lewy reported Lewy bodies in the brain stem nuclei of the PD brains in 1912. Lewy bodies have been considered an essential pathological finding for the diagnosis of PD. It had been, however, considered that there were almost no Lewy bodies occurring in the cerebral cortex. In 1976, we reported our first autopsied case showing numerous Lewy bodies in the cerebral cortex as well as in the brain stem. In 1978, we reported the detailed characteristics and distribution pattern of cortical Lewy bodies, based on our three autopsied cases showing diffuse Lewy body disease (DLBD), a term that we proposed in 1984. We also reported two German autopsied cases showing DLBD in 1979, which were the first DLBD cases reported in Europe. In 1980, we also proposed the term Lewy body disease and classified it into three types: brain stem type, transitional type and diffuse type. The brain stem type is the same as PD, and the diffuse type was later designated DLBD. In 1996, we added the cerebral type. In 1990, we reviewed all the 37 DLBD cases reported in Japan and classified DLBD into two forms: a common form with more or less Alzheimer pathology and a pure form without such pathology. The term DLB was proposed at the first international workshop held in 1995. CDLB guidelines were published in 1996, and the CDLB guidelines=revised were reported in 2005. In the revised guidelines in 2005 and in the paper of the International workshop in 2006, the term "Lewy body disease" was used as a generic term that included DLB, PD and PDD, as we had insisted since 1980. LBD has neuropathological characteristics whereby numerous Lewy bodies are present in the central and sympathetic nervous systems, and it is a type of alpha-synucleinopathy.

O.8

Neuropathologic Aspects of Dementia with Lewy bodies

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Dementia with Lewy bodies (DLB) is a clinical syndrome characterized by mid-to-late life dementia associated with visual hallucinations, Parkinsonism, and fluctuation in alertness or level of consciousness. Sleep disorders, particularly rapid eye movement sleep behavior disorder (RBD), and autonomic dysfunction are also common. Lewy body disorders are associated with neuronal cytoplasmic inclusions – within perikarya (Lewy bodies) and neuronal processes (Lewy neurites) – composed of α-synuclein and include not only DLB, but also Parkinson's disease (PD) and Parkinson's disease dementia (PDD). Neurons vulnerable to Lewy body pathology include dopaminergic neurons in the substantia nigra, noradrenergic neurons in the locus ceruleus, serotonergic neurons in raphe nuclei, and cholinergic neurons in the basal nucleus of Meynert. Other brain regions that are especially vulnerable to Lewy body pathology include the olfactory bulb, amygdala, hypothalamus, mesopontine tegmentum, and dorsal motor nucleus of the vagus. Involvement of cerebral cortex, especially the allocortex and anterior temporal neocortex, is characteristic of DLB and PDD, while neocortical involvement is minimal in PD. Neuronal loss in the substantia is a *sine qua non* for PD and PDD, but variable in DLB. Basal forebrain cholinergic neuronal loss is consistent and often marked in DLB and PDD. Because Lewy body disorders often occur in mid-to-late life, they frequently, but not always, have concomitant Alzheimer type pathology, especially senile plaques composed of Aβ protein. Alzheimer type neurofibrillary degeneration composed of tau protein is variable in DLB, PDD and PD. When Alzheimer type pathology is severe, the clinical presentation usually resembles Alzheimer's disease (AD) rather than DLB. Currently, a neuropathologic diagnosis of DLB is expressed as a probability statement that takes into account the relative contribution and severity of both Lewy body pathology and Alzheimer type pathology. The greatest certainty that observed pathology would have been associated with DLB is with severe and widespread Lewy body pathology and minimal Alzheimer type pathology.

O.9

Genetic Perspectives of DLB

Jose Bras

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Dementia with Lewy Bodies (DLB) is perhaps the most underserved common disorder. This is surprising since it is also the second most common form of dementia following Alzheimer's disease. Over the last few years, genetic studies in DLB have been focused on small cohorts or single families and, crucially, testing small numbers of genetic markers. In general, Results from these studies have been underwhelming. Recent advances in technology have enabled us to assess the genome of large numbers of individuals with great resolution. These technologies have started to be applied to DLB recently, with results shedding light on novel aspects of the genetic architecture of this disease. Through a worldwide network of collaborators we have brought together a cohort of >1,400 neuropathologically proven DLB cases. Within this network we are performing a genome-wide association study and also exome-sequencing in this large and well-characterized cohort. Novel loci and specific common markers have been identified to modulate risk for disease and the effects of rare genetic variability are starting to be uncovered. Importantly, these results also allow us to undertake detailed comparisons with Parkinson's and Alzheimer's disease genetics, hopefully enabling us to tease out differences and similarities at the most basic level between these disorders. Although preliminary, these results are encouraging and represent an important achievement towards our goal of a complete understanding of the genetic architecture of DLB.

O.10

Transmission of Misfolded α-Synuclein in Synucleinopathies

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The accumulation of pathological α-synuclein is found in a number of neurodegenerative diseases including Parkinson's disease, multi-system atrophy and dementia with Lewy bodies. Misfolded α-synuclein can be propagated from cell-to-cell through the template recruitment of endogenous normal α-synuclein to form Lewy body and Lewy neurite-like aggregates. Moreover, pathological aggregated α-synuclein propagated along major central nervous system (CNS) pathways to regions far beyond injection sites and appear to follow neuroanatomical interconnectomes. This spreading of α-synuclein pathology is progressive and leads to behavior impairments and eventually compromises neuronal survival but immune therapy reduces the spread of pathology, rescue behavior phenotypes and neuron loss. Other studies also showed differences in the conformations of human versus mouse α-synuclein that lay the foundation for the concept of strains in synucleinopathies. Our findings open up new avenues for understanding the mechanisms of disease progression and for developing novel therapeutics.

Session 4: DLB Update – Therapeutics

O.11

Cholinesterase Inhibitors and Memantine

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At present, there are no disease-modifying treatments for dementia with Lewy bodies (DLB) or Parkinson's disease dementia (PDD). Although cholinesterase inhibitors (CHEI; rivastigmine, donepezil and galantamine) and memantine are frequently used in DLB and PDD, at present only rivastigmine is licensed for PDD and donepezil for DLB in Japan. Compared to Alzheimer's disease, there have been relatively few randomized controlled trials (RCTs) in DLB and PDD. The best evidence for CHEI comes from 5 RCTs, 3 conducted in DLB and 2 in PDD. Rivastigmine moderately benefitted cognition on ADAS-cog and MMSE, neuropsychiatric symptoms (NPS) and activities of daily living in PDD (Emre, N Engl J Med, 2004), whereas another large RCT of donepezil produced mixed results (Dubois, Mov Disord, 2012). A modestly sized RCT of rivastigmine in DLB showed significant improvement on NPS but not on cognitive measures (McKeith, Lancet Neurol, 2000). However, donepezil in two Japanese RCTs (Mori, Ann Neurol, 2012; Ikeda, Alz Res Therap, 2015) showed dose-dependent improvement on cognition but less convincing results for NPS. There have been 2 modestly sized RCTs looking at the effect of memantine for PDD and DLB (Aarsland, Lancet Neurol, 2009; Emre, Lancet Neurol, 2010). The Aarsland study did not separate DLB and PDD, but overall, memantine had a positive effect on global impression of change. The Emre study also showed a positive effect of memantine on global impression of change for DLB patients but not for PDD patients. A meta-analysis of CHEI and memantine produced small benefit on global impression of change, but only CHEI and not memantine conferred significant benefit on cognition (Wang, 2015, JNNP). All 4 drugs have good safety profile, but rivastigmine has slightly higher rate of mild to moderate side effects. In conclusion, CHEI and memantine slightly improve global impression of change, however only CHEI enhance cognitive function.

O.12

Antipsychotics

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The harms associated with antipsychotics in people with dementia have been a key topic. Most work has focused on Alzheimer's disease, where modest benefits and significant safety risks including mortality, stroke and accelerated cognitive decline have led to regulatory warnings. Paradoxically, although the dangers of antipsychotic use in people with Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) were reported much earlier, with severe neuroleptic sensitivity reactions described in the early 1990's, there has been less subsequent development of the evidence base. Building on several case series, a more robust cohort study identified severe neuroleptic sensitivity reactions in 25-50% of people with PD, PDD and DLB respectively. There has been very little focus on other safety outcomes, although risperidone, olanzapine and aripiprazole are poorly tolerated in PD. Two recent studies show that atypical antipsychotics are associated with a significant increase in mortality and other key adverse outcomes in PD. RCTs in PD psychosis have suggested that quetiapine is ineffective. There is only one RCT of quetiapine in DLB/PDD, which also fails to demonstrate benefit. Trials in PD psychosis suggest that clozapine does confer benefit over short term treatment (4 weeks), but there are no RCTs in DLB or PDD. Although not antipsychotics, both rivastigmine and donepezil improve psychosis, particularly visual hallucinations, in DLB and PDD patients. Mechanistic data highlighting the importance of the serotonergic system and 5HT2A receptors in particular for psychosis in PD heralded the development of the novel antipsychotic pimavanserin, a 5HT2A inverse agonist with a good tolerability profile in PD; and a recent pivotal RCT highlighted significant benefit in the treatment of PD psychosis over 6 weeks. Of particular relevance with respect to DLB and PDD, the sub-group of individuals with significant cognitive impairment had an even greater benefit in psychotic symptoms from pimavanserin treatment.

O.13

Antiparkinsonian Agents

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This review of the treatment of Dementia with Lewy Bodies (DLB) with antiparkinsonian agents will consider three essential issues: (1) The requirement for these drugs (that is, the frequency and impact of parkinsonism in DLB); (2) The efficacy of antiparkinsonian drugs in DLB; and (3) The potential adverse effects associated with the use of these drugs in DLB. Parkinsonian signs are present in around 60% of DLB cases at diagnosis and increase in frequency during the disease course. Their presence is predictive of mortality and long-term care and is associated with greater functional impacts. There have been four uncontrolled trials evaluating the efficacy of levodopa in DLB, yielding findings suggestive of both acute and chronic benefits. A greater than 10% improvement in motor UPDRS score is reported in 32-55% of cases, while a response to acute levodopa treatment appears to predict subsequent clinical drug response. There is some evidence that levodopa efficacy may wane over 12 months in DLB. The relative toxicity of antiparkinsonian drugs in DLB may be considered as a continuum with: levodopa (least toxic), dopamine agonists, and anticholinergics (most toxic). Anecdotally, rasagline is probably safer than selegiline, because of amphetamine-like side effects of the latter. There probably is a low frequency of levodopa related dyskinesias associated with DLB, related in part to the low cumulative drug doses exhibited in a majority of cases. Levodopa is generally well tolerated by people with DLB. Exacerbation of neuropsychiatric symptoms and excessive daytime somnolence, or the precipitation of a toxic confusional state, probably occurs in a minority. Pragmatic prescription advice should, however, be to "start low and increase slow" and to continually review the requirement for an antiparkinsonian agent.

WEDNESDAY DECEMBER 2, 2015

Session 5: CLINICAL I

O.14

Cognitive Neuroscience Approach to DLB

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Neuropsychological studies show that patients with autopsy-proven DLB perform significantly worse than those with "pure" AD on tests of visuospatial ability and executive functions, but better on certain aspects of episodic memory. To explore the cognitive and neurological processes underlying these disproportionate deficits, we have carried out a series of studies using approaches and models from cognitive neuroscience. Visual processing abilities of patients with DLB were assessed psychophysically using a simple horizontal motion discrimination task that engages the dorsal visual processing stream. Participants indicated the left or right direction of coherently moving dots that were embedded within dynamic visual noise provided by randomly moving dots. Motion discrimination thresholds of DLB patients were significantly higher (i.e., worse) than those of patients with AD (which were normal). When visual search was tested in patients with DLB, target detection time in a single-feature (finding a black dot among white dots) task was not influenced by the number of distractors (i.e. "pop-out" effect), whereas it increased abnormally as the number of distractors increased in a feature-conjunction (finding a black dot among white dots and black squares) task. This deficit in feature binding is consistent with abnormalities in networks involving the dorsal occipito-parietal cortex. Interactions between working memory and secondary memory were assessed with recognition memory span tasks that required retention of increasing amounts of verbal, spatial, or visual object information across trials. Spans were lower in patients with DLB than in those with AD, despite similar deficits on independent measures of secondary memory. The disproportionate vulnerability of recognition memory span in DLB compared to AD may be due to both medial temporal lobe and fronto-striatal involvement in DLB and a corresponding decrement in cooperative interaction between the two systems. Further cognitive neuropsychological analysis may identify *in vivo* neurobehavioral markers that differentiate DLB from AD.

O.15

Disease Trajectory and Cognitive Profiles of Three Pathologic Subtypes of DLB

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Background: The neuropathology of Lewy body disease includes varying degrees of α-synuclein, tau and amyloid-β deposition. We examined whether 3 pathologic subgroups of DLB show differences in baseline clinical presentation and disease trajectory. Methods: Clinical and neuropathologic assessment was carried out on prospectively followed patients with probable DLB (n=46) at Mayo Clinic Florida. Distribution and quantitative image analyses of percentage burden was obtained for cortical and limbic α-synuclein (LB509), tau (PHF-1) and amyloid-β (4G8). Groups included transitional and diffuse LBD (TLBD, DLBD), and the DLBD group was further divided on the basis of tau burden (PHF-1 < 6%) using a frequency distribution. Clinical features of TLBD (PHF-1 < 6%), DLBD-L (PHF-1 < 6%), and DLBD-H (PHF-1 ≥ 6%) were compared. A linear mixed model examined group differences in rate of decline using Mini Mental State Examination (MMSE), Dementia Rating Scale (DRS), and Global Deterioration Scale (GLDS). Results: Pathologic groups (TLBD, DLBD-L, DLBD-H) did not differ in demographics, number of visits, parkinsonism severity, number/duration of core clinical features, or baseline dementia severity (mean GLDS 3.1 ± 0.8, mean MMSE 24 ± 3, mean DRS 121 ± 14). All patients had dementia and each group had comparable attention and visuospatial deficits. Memory and naming were significantly worse in DLBD-H compared to DLBD-L and TLBD (p<0.01). Although duration of illness was shorter for both DLBD groups compared to TLBD (9.3 ± 3 vs. 6.5 ± 2 years, p<0.01), rate of decline using MMSE, DRS, and GLDS was most rapid for DLBD-H, intermediate for DLBD-L, and slowest for TLBD (p<0.05). Conclusions: All three DLB pathologic groups had comparable core clinical features and baseline dementia severity. TLBD and DLBD-L had similar cognitive profiles, while DLBD-H had greater baseline memory and naming deficits. Rate of dementia progression was fastest for DLBD-H, intermediate for DLBD-L and slowest for TLBD.

O.16

Visual Hallucinations in DLB

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When considered from a trans-diagnostic perspective, visual hallucinations may be caricatured as 'Good' and 'Bad'. Prototypical 'Good' hallucinations occur in eye disease (the Charles Bonnet Syndrome) where they do not predict cognitive decline and, while distressing for a minority of patients, do not seem associated with a change in care needs. In contrast 'Bad' hallucinations predict cognitive decline and are associated with the move from independent living into care. Bad hallucinations are found in Parkinson's disease (PD) and Alzheimer's disease (AD), with the visual hallucinations of DLB assumed 'Bad' although their high prevalence makes comparative studies of patients with and without visual hallucinations challenging. What are the neurobiological differences between susceptibility to Good and Bad hallucinations and between patients with Bad hallucinations across the clinical contexts of DLB, PD, AD and posterior cortical atrophy and what do such differences tell us about visual hallucinations as prognostic biomarkers? In this talk I will present evidence to suggest that, across all clinical contexts, susceptibility to visual hallucinations is associated with visual cortical atrophy. What distinguishes susceptibility to Bad hallucinations is additional atrophy outside visual cortex in the frontal lobe and hippocampus (Carter and ffytche, 2015). Impaired function in this wider network is likely to be responsible for the more rapid cognitive decline and move to care associated with Bad hallucinations, although the cognitive changes or behaviours mediating the transition are unclear. A key unanswered question is whether reduced occipital blood-flow and metabolism marks the mechanism of Bad hallucinations in DLB as distinct from other conditions. From a clinical perspective, I will describe how phenomenological differences between Good and Bad hallucinations may help distinguish prodromal DLB with prominent hallucinations from Charles Bonnet Syndrome and current treatment options for visual hallucinations. Carter R, Ffytche DH. On visual hallucinations and cortical networks: a trans-diagnostic review. J Neurol. 2015;262(7):1780-90.

O.17

Does Abnormal Ventral Visual Stream Function Underlie Recurrent Complex Visual Hallucinations in Dementia with Lewy Bodies?

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Background: The recurrent complex visual hallucinations (RCVH) frequently seen in DLB typically present as well formed scenes or animate objects. From an anatomical and functional perspective this would suggest an involvement of the ventral stream of visual processing, where objects and scenes are interpreted by successive linked locations from the primary visual cortex through the inferior occipital cortex to the inferior temporal lobe. Key to object perception is the fusiform gyrus, which is responsible for storage of object representation and shows specific responses to recognisable objects. We have previously found evidence of altered interneurone function in the primary visual cortex in DLB, thus changes to visual stimulus processing within the primary visual cortex may result in altered perception of objects as a result of aberrant coupling to proximal or distal parts of the ventral stream resulting in RCVH in DLB. Design: We comprehensively analysed the fusiform gyrus in post-mortem tissue taken from DLB patients to determine its role in the generation of RCVH. Results: In accordance with findings in the primary visual cortex, stereological investigations showed no changes in interneurone number. However, selective changes were found in markers of interneurone function in the fusiform gyrus in DLB, with a loss in the major biosynthetic enzyme GAD1, along with reductions in gephryin, radixin and GABARAP, as well as the synaptic markers, N-ethyl maleimide sensitive factor, SNAP25, synataxin and synaptotagmin. Such changes, however, were not found in other visual processing regions, the inferior occipital cortex (V4) or frontal eye fields. Conclusion: These changes suggest abnormalities exist in a structurally intact network including the fusiform gyrus, and RCVH result from a combination of altered outflow from the primary visual cortex to an altered fusiorm gyrus and this may itself be causative in the biology of the RCVH in DLB.

O.18

Neuropsychological Performance Identify Impending Dementia with Lewy Bodies in Rapid Eye Movement Sleep Behavior Disorder

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Rapid eye movement sleep behavior disorder (RBD) is a parasomnia considered as a risk factor for neurodegenerative disorders, such as dementia with Lewy bodies (DLB) and Parkinson's disease (PD). As a specific and sensitive prodromal syndrome, RBD allows the investigation of potential preclinical markers, such as cognition. The purpose of this study is to follow-up a large cohort of idiopathic RBD patients to find cognitive markers of neurodegeneration. Seventy-six polysomnography-confirmed idiopathic RBD patients underwent a baseline neuropsychological and neurological assessment and were followed for a mean of 3.6 years. At follow-up, thirty-four RBD patients (45%) developed a neurodegenerative disorder, including 19 with parkinsonism only and 15 with DLB. Neuropsychological characteristics were compared between groups with t-tests. Receiver operator-characteristic (ROC) curves were performed to assess the sensitivity and specificity of cognitive tests. The cognitive performance of 39 healthy controls were used to determine cutoff values.RBD patients who developed DLB were significantly impaired at baseline on neuropsychological tests (in attention and executive functions, verbal memory, and visuospatial abilities tasks) when compared to patients who developed parkinsonism only. Moreover, they were more frequently diagnosed with a mild cognitive impairment (93% vs 42%, p=.002). Two subtests yielded the best ratio between sensitivity and specificity : 1) a normality cutoff of 42.00 for the Rey Auditory Verbal Learning Test (sum of trials 1-5), with sensitivity (93%), specificity (87%), and 91% correct classification; and 2) a normality cutoff of 27.00 for the Verbal Phonetic Fluency, with sensitivity (90%), specificity (87%), and 92% correct classification. This study showed that cognitive impairments in idiopathic RBD patients were predictive of specific conversion to DLB 3.6 years before diagnosis on average. Neuropsychological testing might be a marker for an increased risk of DLB in idiopathic RBD patients and may be used as a tool in future neuroprotective trials.

Session 6: CLINICAL II

O.19

Sleep Issues in DLB, Including Prodromal DLB

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Sleep disorders affect about 60-80% of the patients with DLB and include insomnia, circadian rhythm disorder with early awakening, hypersomnia due to frequent napping, and REM sleep behavior disorder (RBD) which is a parasomnia characterized by dream-enacting behaviors, unpleasant dreams and polysomnographic detection of REM sleep with increased electromyographic activation. Obstructive sleep apnea and restless legs syndrome may occur but are no more common than in the general population of similar age. The origin of sleep disorders in DLB is multifactorial and related-factors include degeneration of the brain areas that modulate sleep, the symptoms of the disease (dementia, parkinsonism, anxiety, depression, hallucinations) and the effect of some medications. Therapy of sleep disorders should be individualized in DLB. Detection of RBD in an individual with comorbid dementia point toward DLB, because the parasomnia is rare in the setting of other dementias like Alzheimer disease. RBD occurs in up to 80% of the DLB patients, predominates in men, has short duration of dementia, early onset of parkinsonism and visual hallucinations, and little Alzheimer disease-related pathology on autopsy. In patients with DLB, RBD may be difficult to distinguish from both visual hallucinations and confusional awakenings associated with agitation and wandering, only using clinical history even with the help of the spouse or caregiver. Video-polysomnography is able to identify and distinguish these disorders. RBD is one of the components of the prodromal stage of DLB. RBD antedates the onset of dementia in approximately 70% of the DLB patients with comorbid RBD. Most of the patients with the idiopathic form of RBD are eventually diagnosed with a neurological disease, mainly DLB and Parkinson disease. Idiopathic RBD patients who are later diagnosed with DLB develop a stage of mild cognitive impairment characterized by executive, visuospatial and memory dysfunction; the interval between mild cognitive impairment and dementia onset is about two years. Patients with idiopathic RBD with or without MCI are candidates to test disease-modifying therapies to interrupt the underlying neurodegenerative process.

O.20

Motor and Autonomic Issues in DLB, Including Prodromal DLB

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Parkinsonism is one of the diagnostic hallmarks of DLB. In DLB, parkinsonism tends to be more prominently akinetic-rigid, rather than tremor-dominant. This is analogous to studies in PD, which suggest that tremor-dominant patients have lower dementia risk. Parkinsonism in DLB clearly can improve with levodopa, although response is less notable than in PD without dementia. This may reflect diffuse neurodegeneration in motor systems outside the substantia nigra pars compacta. Moreover, side effects of dopaminergic therapy such as somnolence and hallucinations are much more common. Within DLB a variety of autonomic symptoms can occur. Most prominent is orthostatic hypotension, which is present in the majority of DLB patients. Its recognition has important clinical implications, as many patients are treated with antihypertensives. Failure to recognize OH can cause syncope and falls, and there have been preliminary suggestions that allowing blood pressure to rise can result in cognitive improvement. Prevalence of constipation and urinary dysfunction have not been systematically studied in large surveys, but certainly occur quite frequently. It has become clear that both motor and autonomic changes can predict future development of PD. Studies in idiopathic REM sleep behavior disorder have demonstrated clear motor abnormalities in the prodromal stage of DLB. These problems appear to start approximately 5 years before onset of dementia. Interestingly, motor abnormalities appear to predict DLB equally as well as PD. Among autonomic findings, OH clearly predicts development of DLB in PD. Moreover, very recent studies have shown that up to 40% of patients with idiopathic OH develop neurodegenerative synucleinopathy, including DLB. Within idiopathic RBD, autonomic findings are able to identify those at higher risk of developing neurodegeneration. The large majority of iRBD patients have abnormalities, indicating that autonomic findings occur very early in the course of DLB.

O.21

Prodromal Symptoms in Dementia with Lewy Bodies: The Newcastle LewyPro Study

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Background: Prodromal Alzheimer's disease has been extensively studied, but little is known about the prodromal phase of dementia with Lewy bodies (DLB). The Newcastle LewyPro Study is an ongoing prospective study which aims to characterise the clinical and biomarker profile of prodromal DLB. Methods: Patients with MCI and symptoms suggestive of Lewy body (LB) disease were recruited. Each patient had a comprehensive clinical and neuropsychological assessment and striatal dopaminergic ^{123}I-FP-CIT imaging. Following this subjects were classed as 'probable Lewy body MCI (LB-MCI)', based on the presence of two or more core or suggestive features of DLB, or 'other-MCI' if no or only one core or suggestive feature was present. Results: Forty-two patients have been recruited to date, with 27 classed as LB-MCI and 15 classed as other-MCI. LB-MCI subjects were more likely to report depressive symptoms (p=0.01) and symptoms associated with parkinsonism, such as a change in handwriting (p=0.01). They also displayed some neuropsychological similarities to established DLB, with slower cognitive processing during computerised reaction time tasks (p=0.02) but better delayed recall (p=0.03). Symptoms of autonomic nervous system dysfunction were common in both groups. Conclusions: It is possible to identify patients with features of LB disease during the MCI phase. MCI subjects with core and suggestive features of DLB display some clinical and neuropsychological features seen in established DLB. These patients will be followed-up longitudinally in an effort to clarify their diagnosis and identify predictors of progression to dementia.

O.22

Cognition in At-Risk Lewy Body Disease

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The Parkinson Associated Risk Syndrome (PARS) study identified a cohort of healthy adults with hyposmia and dopamine transporter (DAT) binding reduction (using [^{123}I]β-CIT single photon emission computed tomography (SPECT) to characterize individuals at risk for Parkinson's disease (PD). Individuals age >50 years without PD were recruited. A total of 225 participants completed cognitive testing and were included in the final analysis. A neuropsychological test battery was administered and normative scores created for global cognition and five domains: memory, executive function/working memory, processing speed/attention, visuospatial abilities, and language domains. Other non-motor symptoms (constipation, depression, anxiety, and REM sleep behavior disorder) were assessed through questionnaires. Individuals with both hyposmia (scoring ≤15th percentile based on age and sex study-specific norms) and reduced DAT binding (≤80% age-expected lowest putamen [^{123}I]β-CIT uptake)(n=38) had lower mean scores for global cognition, executive function/working memory, and memory compared with all other participants (n=187). In separate multivariate logistic regression models, lower global cognition (odds ratio=1.97, p=0.004), and specifically executive function/working memory (odds ratio=1.84, p=0.004), scores were associated with membership in the hyposmia plus DAT reduction group. Combining hyposmia with relative impairment on specific cognitive domains increased the odds of DAT binding reduction compared to hyposmia alone, with the greatest increase in odds for hyposmia plus executive function/working memory relative impairment (68% increase in odds from 4.14 to 6.96). Changes in global cognitive abilities, and specifically executive function/working memory, are present in individuals at risk for PD. Combining non-motor features, including cognition, improves prediction of dopamine transporter binding reduction. In additional longitudinal analyses, in hyposmics lower baseline putamen DAT predicted long-term decline in attention (significant p value) and global cognition (trend p value), and partial correlation showed a trend association between change in age-adjusted putamen DAT and change in attention score over time.

O.23

Prodromal Electroencephalogram Slowing in Rapid Eye Movement Sleep Behavior Disorder

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Background: REM sleep behavior disorder (RBD) is strongly associated to the subsequent development of Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Therefore, identifying markers of neurodegeneration in RBD could have major clinical implications. In a previous study, we noted that waking EEG slowing was associated with mild cognitive impairment in RBD. The aim of the present study was to assess the usefulness of waking EEG spectral analysis at baseline for predicting development of a neurodegenerative disease in RBD patients. Methods: A total of 54 RBD patients, 28 of which developed PD, DLB or MSA (mean follow-up: 3.5 years) and 30 healthy subjects underwent a waking EEG recording in a resting state with eyes closed and a neuropsychological assessment at baseline. Analysis of the absolute spectral power was performed for five frequency bands (delta, theta, alpha, beta1, beta2) in five cortical regions (frontal, central, parietal, temporal and occipital). The slow-to-fast $[(\delta+\theta)/(\beta)]$ power ratio for each of the five cortical regions was calculated as a specific index of global cortical slowing. Mixed-design analyses of variance (Group x Band and Group x Region) were used to compare the three groups. Results: RBD patients who developed disease showed higher absolute delta and theta power in all five cortical regions compared to disease-free RBD patients and controls. The slow-to-fast power ratio was higher in all regions in patients who developed disease than in the two other groups. Disease-free RBD patients only showed higher absolute delta power in frontal and occipital regions compared to controls. Conclusions: This study indicates the presence of greater EEG abnormalities (slowing) in wakefulness in RBD patients who will develop a neurodegenerative disease. Our results suggest that these disturbances could be a marker of more severe and extensive neurodegeneration in RBD.

Session 6: Imaging

O.24

Imaging-Pathologic Correlations in DLB

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Patients who meet the clinical criteria for dementia with Lewy bodies (DLB) often have overlapping Alzheimer's and Lewy body (LB) disease pathologies, and patients with AD dementia may have mixed LB disease pathology at autopsy. The underlying pathology is frequently complex in patients with DLB, and it is clinically challenging to determine the contributions of multiple pathologies to the dementia syndrome. Current advances in development of disease-modifying treatments for AD, and responsiveness of DLB patients to cholinesterase inhibitor treatment generate a need for imaging biomarkers to detect the presence of LB - and AD-related pathologies and follow their progression. In this symposium, we will discuss promising multimodal imaging biomarkers such as structural MRI, amyloid PET, F18-fluorodeoxyglucose (FDG) PET and I-123 ioflupane SPECT for distinguishing patients with AD pathology, LB disease pathology and mixed (DLB/AD) pathology. Determining the pathologic correlates of imaging findings is critical for diagnosis and treatment planning in patients with DLB.

O.25

Imaging in Prodromal Dementia with Lewy Bodies

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In recent years increasing attention has been paid to early diagnosis and relatedly to mild cognitive impairment (MCI) and the diagnosis of prodromal dementia. To date most of the discussion has focused on Alzheimer's disease (AD) with little focus on the pre-dementia stage of cognitive decline which culminates in Dementia with Lewy bodies (DLB). Proposals for early AD and MCI-AD have been published and these have included the use of imaging biomarkers. It is likely that such biomarkers will be important in identifying and defining prodromal DLB (pDLB). Accurate identification of pDLB involves both the exclusion of other major causes of early cognitive impairment, in older people these are predominantly the pathologies of AD and vascular cognitive impairment, and the inclusion of evidence of the synucleinopathy and associated neurochemical changes characteristic of DLB. Potential imaging biomarkers may therefore be divided into two types, negative and positive. Negative biomarkers include: MRI hippocampal atrophy and extensive white matter hyperintensities and infarcts; cerebral amyloid on PET-amyloid; hypometabolism in temporo-parietal and posterior cingulate areas on PET-FDG. Positive imaging biomarkers include MIBG scans showing cardiac denervation and FP-CIT evidence of dopaminergic deficits. This presentation will contain two main elements. First, a review of the evidence for potential imaging biomarkers for pDLB, drawing on research from early DLB, PDD and AD. Second, FP-CIT data will be presented from the ongoing Newcastle LewyPro study, which is a longitudinal study of pDLB. Although imaging evidence can provide positive and negative evidence supporting pDLB, since changes in early disease are necessarily more minor then multimodal imaging may be required for high sensitivity and specificity.

O.26

Predicting Survival in Dementia with Lewy Bodies with Hippocampal Volumetry

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Background: Dementia with Lewy bodies (DLB) is associated with shorter survival compared to Alzheimer disease (AD) dementia, but antemortem predictors of disease duration are unknown. Our objective was to determine whether smaller hippocampal volumes (associated with greater neurofibrillary tangle pathology) are associated with shorter survival in DLB. Methods: For 167 consecutive DLB patients with 1.5 or 3T MRI from the Mayo Clinic Alzheimer's Disease Research Center, regression models were fit predicting hippocampal volumes using age at MRI and total intracranial volume. Using residuals, patients were trichotomized into low (0-33.3%), medium (33-66.7%) and high (66. 7-100%) hippocampal volume categories. Cox proportional hazard models were performed for survival from age of onset. The models were adjusted for APOE e4 status and age of cognitive onset. Results: The median age at cognitive onset was 68 years (interquartile range (IQR): 63, 74), and 80% were male. The median time from estimated first cognitive symptom to death was 7.34 years (IQR: 5.4, 9.7). Low (Hazard ratio 1.66 (95% CI 1.05-2.62, p=0.03) and medium hippocampal volumes (Hazard ratio 2.01 (95% CI 1.22-3.331, p=0.006) were associated with higher risk of death compared to high hippocampal volumes. The predicted median survival for subjects with onset of cognitive symptoms at age 68 was 11.72 years (95% CI 9.59-15) for APOE e4 negative, high hippocampal volume subjects, 10.2 years (8.11-14.54) for APOE e4 positive, high hippocampal volume subjects, 8.77 years (7.82-11.08) for APOE e4 negative, low/medium hippocampal volume subjects, and 7.84 (7.1-9.77) years for APOE e4 positive, low/medium hippocampal volume subjects. Conclusions: Among patients with clinically diagnosed DLB, those with hippocampal volumes in the highest tertile have longer survival. Hippocampal volumes may improve our ability to predict survival in DLB patients. Therefore among DLB patients, concomitant AD pathology may be associated with a shorter duration of illness.

O.27

Quantitative correlation between cardiac meta-iodobenzylguanidine uptake and remaining axons of the cardiac sympathetic nerve in Lewy body disease

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Objectives: Meta-iodobenzylguanidine (MIBG) cardiac scintigraphy is a useful imaging tool that possibly differentiates Lewy body disease (LBD) including Parkinson's disease (PD) and dementia with Lewy bodies (DLB) from other related disorders. Reduced cardiac MIBG uptake and loss of cardiac sympathetic axons, as its possible anatomical substrate, are both recognized in LBD, while their direct correlation has so far remained speculative. Increasing availability of autopsy-confirmed patients of LBD prompts us to quantify residual cardiac sympathetic axons to establish their relationship to cardiac MIBG uptake. Methods: We collected cardiac tissue samples from 23 patients with autopsy-confirmed LBD (8 PD and 15 DLB) and two non-LBD control patients (one Alzheimer disease and one multiple system atrophy) who underwent MIBG cardiac scintigraphy in life. Samples of the left ventricular anterior wall were stained with anti-tyrosine hydroxylase (TH) and anti-neurofilament (NF) antibodies as markers of cardiac nerve axons. We quantified the immunolabelled areas and assessed their correlation to standardised heart to mediastinum (H/M) ratios of MIBG cardiac scintigraphy. Results: Cardiac MIBG uptake in the early and delayed phases was reduced in 90.9% and 95.7% of patients with LBD, respectively. The area of TH-immunoreactive axons correlated significantly with the H/M ratio in the early ($p=0.036$) as well as in the delayed ($p=0.018$) phases. The area of NF-immunoreactive axons also correlated with the H/M ratio in the early ($p=0.003$) as well as in the delayed ($p=0.001$) phases. Conclusions: A strong quantitative correlation between cardiac MIBG uptake and corresponding loss of sympathetic axons in LBD provides a scientific basis to confirm the reliability of MIBG cardiac scintigraphy as a powerful imaging tool to detect loss of these axons as a biomarker for the presence of LBD.

O.28

PiB and T807 PET imaging of amyloid and tau pathology in dementia with Lewy bodies

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Background: Deposits of beta-amyloid and tau are common in dementia with Lewy bodies and Parkinson disease and may contribute to their course. PET radioligands that label paired helical filaments of tau (PHF-tau), such as [F18]T807, have recently been developed. Together, amyloid and PHF-tau imaging provide a means to evaluate, antemortem, the contribution of these co-pathologies to DLB and PD. We hypothesized that beta-amyloid would accelerate cognitive decline in DLB and PD dementia (PDD) and that PHF-tau deposition would be elevated in DLB and contribute to cognitive impairment. Methods: 16 DLB and 17 PDD subjects underwent [C11]PiB PET and annual neurologic and neuropsychological assessments for an average of 3.3 visits. To date, 4 DLB, 4 PD with normal cognition, and 6 PD with cognitive impairment have undergone [F18]T807 PET and have been compared with 30 healthy control subjects (HCS). [C11]PiB retention was expressed as the distribution volume ratio with cerebellar reference. [F18]T807 retention was expressed as the SUVR using cerebellar gray matter reference. Groups were similar in age. Results: Greater baseline cortical PiB retention was associated with faster cognitive decline in DLB and PDD, as measured with the MMSE, but not with motor decline. Cortical [F18]T807 binding varied widely across subjects and was prominent in the inferior temporal region. Inferior temporal [F18]T807 binding was higher in DLB than in HCS (p=0.001, t-test) and was intermediate and heterogeneous in the PD groups. We are exploring the relation of [F18]T807 retention to group status, cognitive function, and PiB retention. Conclusions: These Results suggest that amyloid accelerates cognitive decline in DLB and PDD. In addition, our preliminary Results in a small number of subjects suggest that PHF-tau deposition may be elevated in some cases of DLB. Multimodal PET imaging of amyloid and PHF-tau holds promise for evaluating the contribution of these common co-pathologies to DLB and PD.

THURSDAY DECEMBER 3, 2015

Session 9: Neuropathology/Molecular Biology

O.29

Models of Pathogenesis in Lewy Body Disease

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Lewy bodies are intraneuronal cytoplasmic inclusions made of many proteins, but the core fibrils are made from the abnormal aggregation of α-synuclein. Lewy bodies in the brains of longitudinally studied brain donors with dementia with Lewy bodies (DLB), Parkinson's disease (PD), and controls without neurological or psychiatric diagnoses have been analysed in many studies. Within individual neurons, Lewy bodies form from a build-up of punctate membrane aggregates of phosphorylated α-synuclein that coalesce into loosely packed filaments that undergo ubiquitination and "mature" by compaction. The dynamics of how these inclusions form within individual neurons, infiltrate the brain, and interact with the main age-related pathologies are different between Lewy body diseases, although the factors influencing these dynamics largely remain to be determined. A slow pace of relatively restricted regional Lewy body involvement occurs in PD, while the most rapid and spatially expansive molecular involvement occurs in patients with DLB. There is a build-up of brain tissue changes overtime that precede and propagate Lewy body inclusions, including reduced glucocerebrosidase, increased phosphorylation of α-synuclein and autophagy impairment. These changes have been able to be modeled in laboratory animals. Lewy bodies occur in animal models when different forms of synucleins are overexpressed, when lysosomal enzymes (GBA1, LIMP2, cathepsinD) are reduced or dysfunctional, with the use of certain neurotoxins (rotenone, fenpropathrin), and when key inflammatory molecules are reduced (interferon-β) or overexpressed (TLR2). In contrast, dysfunctional mitochondria and protease inhibitors do not consistently produce Lewy bodies in animal models. Lewy pathology has also been shown to be transmitted between vulnerable neurons in humans and in new animal models. These models confirm that changes in synuclein levels and/or forms, lysosome dysfunction and associated inflammation contribute to neuronal Lewy body formation.

O.30

Cell to cell transmission of synucleinopathies

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When the first reports on Lewy pathology in grafted dopamine neurons Parkinson's disease patients were made in 2008, few people subscribed to the idea that this could be due to alpha-synuclein (a-syn) acting in a prion-like fashion. Even when combined with the insight provided by the neuropathology studies by Braak and colleagues, the evidence to suggest that misfolded a-syn could propagate from one neuron to another was just tentative. The notion that misfolded alpha-synuclein can act in a prion-like fashion remains a working hypothesis, but today it has significant support from numerous studies performed in many independent laboratories. For example, there is strong supporting evidence from cell cultures and animal models showing a-syn transfer between cells (including neurons, astrocytes, oligodendrocytes and microglia). The molecular mechanisms that underlie spreading of a-syn aggregates are also beginning to be dissected. Some studies have illustrated how a-syn aggregates can spread between brain regions over long distances. Furthermore, of great clinical relevance, several experiments suggest that a-syn derived from the brains of patients with Parkinson's disease and Multiple System Atrophy can seed a-syn aggregation in animals after intracerebral injection. In this presentation, I will discuss how these findings are relevant to Dementia with Lewy Bodies. I will also pose the questions whether differences between synucleinopathies with regard to cellular and anatomical pathology could be, at least in part, due to variation in the types of a-syn aggregates that are formed and / or the anatomical site at which the first a-syn misfolding takes place. In closing, I will outline experiments that can shed light on these important questions. Ultimately, improved understanding of possible differences in the prion-like behavior of a-syn in the different diseases can result in the discovery of targets for therapies that slow the progressive worsening of symptoms. It might also have important implications for how the ongoing immunotherapy trials are conducted.

O.31

Pathological and Synaptic Correlates of Cognition and Behaviour in Lewy Body Dementia

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Lewy body dementias, including Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB), are common disorders with both cognitive dysfunction behavioural and mood disturbances. In addition to cortical pathology featuring alpha synuclein there is also a considerable but variable Alzheimer pathology. The relative contributions of these different pathologies and synaptic pathology to particularly disturbances of mood and behaviour are not well understood. One hundred and thirty brain were available for this study; 25 controls, 34 PDD, 55 DLB and 16 AD. Using standard diagnostic protocols for Alzheimer's disease and alpha synuclein pathology semi-quantitative scores for plaques, tangles and alpha synuclein pathology were obtained for frontal (BA9), parietal (BA40), temporal (BA21) and anterior cingulate (BA24) cortices (each scored as 0-3). A range of pre-and post-synaptic proteins including synaptophysin, PSD95, ZnT3, and SNARE proteins were determined by western blotting. Pathological scores and synaptic levels were correlated with scores for cognition (MMSE) and behaviour/mood scores for depression, agitation/aggression, hallucinations and delusions. Of the pathological scores the most significant correlate of cognition was alpha synuclein pathology in the temporal cortex. In terms of synaptic proteins PSD95, ZnT3, Munc18 and CAMKII were reduced in DLB/PDD whereas syntaxin 1 was increased. ZnT3 reductions correlated with worsening cognition while Munc18 reductions related to depression. Taken together these data indicate that both pathological features and changes in synaptic proteins contribute to the clinical features of DLB/PDD and provide opportunities for biomarker development and novel treatment targets.

O.32

Prevalence of Esophageal and Submandibular Gland Synucleinopathy in Dementia with Lewy Bodies and Other Lewy Body Disorders

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Background: The clinical diagnosis of dementia with Lewy bodies (DLB) is inaccurate when core clinical features are lacking. Previously, we conducted a large autopsy survey, indicating that the lower esophagus and submandibular gland (SMG) are the two sites offering the most promise for a peripheral biopsy diagnosis of Lewy body disorders. We have completed two clinical trials of SMG needle core biopsy in 60 PD and control subjects with no serious complications. Here, we report an extension of our studies in 227 autopsied subjects from the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND). Methods: Included were 145 cases with CNS Lewy-type synucleinopathy (LTS), with 34 DLB, 55 PD, 14 incidental Lewy body disease (ILBD), 40 Alzheimer's disease with Lewy bodies (ADLB) and 2 with progressive supranuclear palsy and Lewy bodies (PSPLB). Eighty-two control subjects, defined as those without CNS LTS, included 51 normal elderly, 15 AD, 12 progressive supranuclear palsy, 2 corticobasal degeneration and 2 multiple system atrophy subjects. Immunoperoxidase staining was performed using a well-characterized antibody to p-serine 129 alpha-synuclein, demonstrating SMG and esophageal LTS in formalin-fixed, paraffin-embedded sections. Results: SMG LTS was found in 21/31 (68%) of DLB, 42/46 (91%) of PD, 4/35 (11%) of ADLB and 1/10 (10%) of ILBD subjects. Esophageal LTS was found in 25/34 (74%) of DLB, 48/55 (87%) of PD, 3/40 (7.5%) of ADLB and 1/14 (7%) of ILBD subjects. None of the 82 CNS-LTS-negative control subjects had SMG or esophageal LTS. Conclusions: These results provide support for additional clinical trials of SMG diagnostic needle biopsy for PD and DLB. The lower esophagus has a similar LTS prevalence but is less accessible. In addition to aiding subject selection for clinical trials, an accurate peripheral biopsy diagnosis would be advantageous when selecting subjects for invasive therapies or for verifying other biomarker studies.

O.33

The Role of the Visual Thalamus in the Visual Hallucinations in Dementia with Lewy Bodies

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Background: Complex visual hallucinations occur in 70% of dementia with Lewy bodies (DLB) cases and significantly affect patient wellbeing. Visual cortical and retinal abnormalities have been recorded in DLB cases and may contribute to visual hallucinations. The visual thalamus plays a vital role in relaying and modulating sensory input. In particular, the lateral geniculate nucleus (LGN) and pulvinar nucleus play important roles in relaying optical input and visual attention, respectively. This study therefore determined whether pathological and molecular changes occur in the LGN and pulvinar nucleus in post-mortem tissue taken from DLB patients. Methods: The LGN from six DLB, seven AD and seven control cases was serially sectioned for quantitative analyses of cellular populations using stereology and neuropathological lesions using densitometric analysis. Frozen pulvinar tissue from 12 DLB cases was compared with tissue from 12 control cases using a range of protein expression assays. Results: In DLB, the LGN was found to be relatively intact, while greater cell loss and neuropathological lesions were found in AD cases. However, substantial, significant reductions have been found in an array of synaptic proteins, including synaptophysin, gephyrin and PSD-95 in the pulvinar nucleus in DLB cases. Conclusions: These results suggest that the pre-cortical primary visual pathway is structurally intact in DLB cases but that the secondary visual pathway, routed through the pulvinar, may be impaired. Damage to the pulvinar nucleus may lead to attentional issues either directly or through alterations in interplay between top-down and bottom-up processing, both of which have been postulated to underlie visual hallucinations in DLB.

Session 10: Genetics/Biofluid

O.34

Alpha-Synuclein Oligomers as a Biomarker Candidate for Lewy Body Diseases

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Developing effective treatments for neurodegenerative diseases is one of the greatest medical challenges of the 21st century. Parkinson's disease (PD) and dementia with Lewy bodies (DLB) are very common neurological disorders of the elderly. Although many of these clinical entities have been recognized for more than a hundred years, it is only during the past fifteen years that the molecular events that precipitate the diseases have begun to be understood. Mutations in the alpha-synuclein gene cause early-onset PD, often associated with dementia, and one an alpha-synuclein mutation segregated with pure DLB (with no Alzheimer's pathology). Neuropathologically these diseases are characterized by the presence of Lewy bodies, intraneuronal inclusions mostly composed of alpha-synuclein protein fibrils, cementing the notion that this protein has a central role in Lewy body diseases (LBD). Despite the progress that has been made in understanding the underlying disease mechanisms of LBD, there remains an urgent need to develop methods for use in diagnosis. The development of reliable surrogate markers for the presence and abundance of alpha-synuclein lesions (Lewy bodies) in the brain would naturally facilitate a more streamlined work-up during the early care of PD and DLB patients, and importantly, allow for the biologically guided evaluation of future drug trials aimed at neuroprotection in the synucleinopathies. In this seminar, I will present the progress which has been made so far by our group to explore the use of CSF alpha-synuclein species, specifically its oligomeric forms as a biomarker for LBD.

O.35

Blood-Based (Protein) Biomarker Efforts in Parkinson's Disease and Alzheimer's Disease: Potential Applicability to DLB

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Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Dementia with Lewy Bodies (DLB) have several key common features. They are progressive, they affect a relatively inaccessible organ, they will affect an increasing number of people as the world population ages, and we have no disease-modifying therapies for them. For these brain-based diseases, current diagnosis and evaluation of disease severity rely largely on clinical examination. Yet, these clinical categories have remained grossly unchanged for a century, they may provide only a rough approximation of disease state, and they are, by definition, somewhat subjective. Thus, the development of biomarkers -- objective, relatively easily measured, and precise indicators of pathogenic processes -- could improve patient care and accelerate therapeutic discovery. This session will review (1) candidate vs. unbiased approaches to biomarker discovery, (2) existing national and international biobanking efforts in PD and AD, and (3) blood-based biomarkers that have been evaluated in multiple cohorts in these two diseases. Using the example of plasma epidermal growth factor, we will also trace how one may go from discovery to replication in cohorts that span clinical sites and disease stages, and how biomarkers may span PD and AD. Finally, we will discuss implications for similar biomarker research in DLB.

O.36

APOE ε4 is Associated with Risk of Dementia with Lewy Bodies Irrespective of Severity of Alzheimer's Disease Pathology

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Background: To evaluate the association between apolipoprotein E (APOE) ε4 and risk of dementia with Lewy bodies (DLB) and to examine whether this association is consistent for Lewy body disease cases with varying levels of Lewy body (LB) and Alzheimer's disease (AD) pathology. Methods: A total of 393 clinical DLB patients, 337 autopsy-confirmed Lewy body disease cases, and 719 clinical controls were genotyped for APOE. Four different Lewy body disease groups classified as high likelihood DLB: Braak neurofibrillary tangle stage 0-II & transitional Lewy body disease (N=69), Braak 0-II & diffuse Lewy body disease (N=65), Braak III & diffuse Lewy body disease (N=107), and Braak IV& diffuse Lewy body disease (N=96). Braak stage V and VI cases cannot be classified as high likelihood DLB and were thus excluded from analysis. Autopsy-confirmed Lewy body disease cases were examined regardless of clinical presentation. Results: APOE ε4 was strongly associated with an increased risk of clinical DLB (Odds ratio [OR]=2.63, P=2 x 10-14) and autopsy-confirmed Lewy body disease cases (OR=2.85, P=8 x 10-13). The association between ε4 and Lewy body disease was highest for Braak IV cases (OR=4.89, P=6 x 10-13), followed by Braak III (OR=3.61, P=6 x 10-9) and Braak 0-II (OR=1.58, P=0.021). Regarding Braak 0-II cases, no association with ε4 was observed for the transitional Lewy body disease subgroup (OR=0.94, P=0.84), whereas a strong association was observed for the diffuse Lewy body disease group (OR=2.42, P=0.0003). No association between APOE ε2 and risk of DLB or Lewy body disease was observed. Conclusions: APOE ε4 is significantly associated with risk of Lewy body disease regardless of severity of AD pathology, suggesting that ε4 may affect risk of clinical DLB through an influence on both AD and LB pathology.

O.37

Four Cases of Probable Dementia with Lewy Bodies with Anti-N-Methyl-D-Aspartic Acid Type Receptor Antibodies

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Dementia with Lewy bodies (DLB) exhibits progressive dementia and core features including cognitive fluctuation, parkinsonism and visual hallucinations. The clinical diagnosis is supported by reduced cardiac Iodine-[123]-metaiodobenzylguanidine (^{123}I-MIBG) uptake and/or occipital hypoperfusion on single photon emission computed tomography (SPECT). Anti N-methyl-D-aspartic acid type glutamate receptor antibodies (anti-NMDA antibodies) are known to be detected in the patients with autoimmune encephalitis. We experienced 4 cases of probable DLB with anti-NMDA receptor antibodies in their cerebrospinal fluids (CSF). The patients are Japanese, three female and one male, aged 59-78. All cases presented progressive dementia, cognitive fluctuations and parkinsonism. Three cases exhibited recurrent visual hallucinations. Two cases exhibited rapid eye movement sleep behavior disorder. Two cases exhibited dysesthesia. Three cases exhibited catatonia. All cases exhibited autonomic dysfunctions such as constipation and excessive sweating. All cases needed admission for treatments to psychiatric symptoms such as visual hallucination, irritability, excessive anxiety or catatonia. Three cases had anti thyroid antibodies in their serum. Reduced cardiac ^{123}I-MIBG uptake was found in two patients. Occipital hypoperfusion on SPECT was found in two patients. No malignancies were detected in all cases except a giant ovarian cyst in one case. Evaluation for anti-NMDA antibodies was conducted due to catatonia or early onset dementia. Methyl prednisolone pulse therapy and oral prednisolone intake were performed for three cases, and their general functions were improved after the immunotherapies. The one without immunotherapy exhibited catatonia, and modified electro convulsion therapy improved that state. All cases left hospital and remained good psychiatric condition back at home. Cognitive functions were improved but remained mild impairment in three cases. One case remained dementia. Although it is unclear whether anti-NMDA antibodies emerged secondarily to the neurodegeneration, something immunological process would be suggested to affect the clinical features of these cases.

O.38

Comparative Genetic Analysis of Dementia with Lewy Bodies and Parkinson's Disease with Dementia

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Objective: Case-control studies have revealed several susceptibility loci for Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB). We sought to assess the extent to which genetic determinants for these two disorders overlap. Methods: Subjects were classified as having DLB (n=348) or PDD (n=102) using both clinical information and neuropathological assessments. All subjects were genotyped for the APOE ε2/ε3/ε4 polymorphism, SNCA rs356219, and the MAPT H1/H2 haplotype, and screened across the entire coding region for mutations in the GBA gene. Logistic regression was used to test for differences in allele frequency between groups under a dominant (APOE/GBA) or additive model (MAPT/SNCA) adjusting for sex and age at autopsy. Results: The frequency of APOE ε4 carriers was significantly higher in DLB (61.9%) than in PDD (41.2%; p=3.9 x 10-4) even after adjusting for Braak and CERAD staging (p=0.03), whereas the frequency of GBA mutation carriers was lower in DLB (5.4%) than in PDD (17.7%; p=0.036). There was a marginally significant overrepresentation of the SNCA rs356219 "C" allele in PDD (45.9%) compared to DLB (38.5%; p=0.06). MAPT H1 haplotype frequencies did not differ significantly between groups. Conclusions: Our findings suggest that there are substantial differences in the genetic architecture of DLB and PDD, and provide further support for the nosological distinction between these two entities. Large-scale comparative studies will be needed to more fully understand the degree to which DLB and PDD share genetic determinants.

O.39

Dementia with Lewy Bodies and Alzheimer's Disease: An Unfortunate Couple

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Objective: To investigate whether concomitant Alzheimer(AD)-pathology, reflected by CSF-biomarkers, has clinical impact on Dementia with Lewy Bodies (DLB) in terms of clinical presentation, cognitive decline, nursing home admittance (NHA) and survival. Methods: From the Amsterdam Dementia Cohort, patients with probable DLB and CSF available were selected and divided into a DLB/AD+ and DLB/AD- group, based on the AD-biomarker profile. DLB-AD+ was defined by the ratio of tau to $A\beta42 > 0.52$. Clinical characteristics and neuropsychological measures were compared between groups using logistic regression analyses with adjustments for age, sex and education. Difference in global cognitive decline was investigated using linear mixed models with random effects. Kaplan-Meier curves and Cox regression analyses were used to investigate effects of AD-biomarker profile on time to NHA and time to death. Results: 111 DLB-patients were included, 42 (37.8%) had AD-biomarker profile. Patients with DLB/AD+ significantly performed worse on memory tasks (OR= 0.457 (95% CI 0.233 – 0.933) and experienced more delusions (7/31, 22.6%, p-0.043) and hallucinations (17/31, 54.8%, p-0.022). No difference was found in cognitive decline during follow-up. Survival data were significantly worse in DLB/AD+. Mean time from diagnosis to NHA was 69.35 ± 31.95 (SE) versus 99.47±4.50 (HR=11.70, 95% CI 3.74-36.55) and mean time to death 59.43±10.47 versus 76.71 ±4.79 (HR=3.13, 95% CI 1.57-6.24). Conclusion: This study shows that concomitant AD-pathology has clinical impact in DLB-patients in terms of disease manifestation and survival. For clinical practice this could implicate that a DLB-subgroup can be identified by CSF-biomarkers that has poorer prognosis. In future DLB-AD+ patients could be selected for trials testing disease-modifying drugs targeting AD-pathology.

Session 11: Novel Therapeutics

O.40

Novel Therapeutics for Synucleinopathies: Clues from Model Systems

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Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) are neurodegenerative disorders of the aging population characterized by progressive accumulation of α-synuclein. Alterations in the balance between synthesis, clearance, aggregation and extracellular release/uptake of α-synuclein might play a central role in the pathogenesis. Therefore approaches targeting α-synuclein are currently at the forefront of experimental disease modifying therapies. Studies in chemical and genetic animal models of PD/DLB have shown that reducing α-synuclein synthesis using anti-sense, miRNA's or small molecules regulating the promoter region might be protective. Likewise, research in animal models of synucleinopathy have shown that active and passive immunization against α-synuclein reduce the propagation of α-synuclein from neuron-to-neuron and diminish the accumulation of intracellular α-synuclein aggregates, possibly via direct neutralization and clearance through autophagy and microglia engagement. Moreover, antibodies targeting particular epitopes of α-synuclein appear to be more effective in cell based and animal models resulting in improved behavioral performance, reduced neurodegeneration, and inflammation. Recent studies have also explored targeting various α-synuclein aggregates utilizing specific monoclonal antibodies and tagged single chain antibodies that direct aggregates to lysosomal degradation. More recent studies in animal models, have shown that novel therapies with small organic molecules that reduce α-synuclein aggregation either by functioning as chaperons to neutralize α-synuclein toxin species, to enhance clearance or by reducing aggregation ameliorate the behavioral and neurodegenerative pathology. Based on these pre-clinical studies there are 2 phase I clinical trials completed using immunotherapy and a few other underway. Even though considerable progress has been achieved with current animal models additional work is needed as models do not fully reproduce the disease and could have low predictive value, so for example developing biomarkers in the animal models that can be more reliably translated to patients might enhance the usefulness of animal models. Supported by grants from NIH, Prothena and Neuropore Therapies.

O.41

Novel Therapeutics: Human Trials and Next Steps

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Currently there is only one medication, donepezil, approved by any regulatory agency in the world for the treatment of dementia with Lewy body (DLB). In the United States, rivastigmine has been approved for dementia associated with Parkinson's disease (Parkinson's disease dementia, PDD), but there are no medications that have been approved by the US Food and Drug Administration for the treatment of DLB. Thankfully, recently several new medication trials been proposed to specifically treat DLB. Clearly there is a great need for new medication trials in DLB and ultimately for more effective therapeutics. This presentation will briefly review common off-label treatments used for DLB, and then a more detailed examination of current or planned treatment trials for either the cognitive or behavioral effects of DLB. Because of the relevance to DLB, new treatments aimed at Parkinson's disease associated cognitive or behavioral disturbance will also be reviewed. Finally, potential new avenues of treatment will be examined, based on new theories around the pathogenesis of the Lewy body disorders.

O.42

Efficacy Results of a Phase 2b Study of RVT-101, a Neurotransmitter-Targeted Therapy, in Mild-to-Moderate Alzheimer's Disease

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Background: RVT-101 (formerly known as SB-742457) is a potent antagonist of the 5-hydroxytryptamine 6 (5-HT6) receptor, in development for the treatment of patients with Alzheimer's disease and Dementia with Lewy Bodies. The drug is administered orally and dosed once-daily, and works by promoting the release of acetylcholine and other key neurotransmitters in the brain. RVT-101 has been evaluated in over 1,250 Alzheimer's disease patients and healthy subjects across 13 clinical studies to date. We present the results of a 48-week Phase 2b study in mild-to-moderate Alzheimer's disease, in which RVT-101 was tested on a background of stable donepezil therapy. Methods: This 48-week placebo-controlled study randomized 684 subjects with Alzheimer's disease to receive 35 mg RVT-101, 15 mg RVT-101, or placebo on top of donepezil. Subjects had MMSE scores between 10 and 26, and were on a stable dose of donepezil for at least two months prior to the start of the study (and on any dose of donepezil for at least six). We present the results of the pre-specified Mixed Model Repeated Measures (MMRM) analysis of the intent-to-treat population, as well as the results of an analysis of covariance (ANCOVA) analysis of completers. Conclusion: RVT-101 was effective in improving cognition and function in a Phase 2b study in mild-to-moderate Alzheimer's disease. RVT-101's mechanism of action, safety profile, and efficacy in patients with Alzheimer's disease support its development in patients with Dementia with Lewy Bodies.

O.43

Impact of Armodafinil Therapy on Quality of Life in DLB Patients and Caregivers

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Background: Dementia with Lewy bodies (DLB) is the second most common neurodegenerative dementia. Both the symptom burden on patients, and caregiving burden on caregivers, can have a negative impact on their quality of life (QOL). We describe QOL in patients and caregivers in a pilot investigation of a wake promoting agent (Armodafinil) to improve somnolence in patients with DLB. Design: We conducted a 12-week open label study of armodafinil 250 mg taken orally with a primary specific aim to assess its efficacy on daytime somnolence in DLB patients. In this abstract we present secondary outcome measures of caregiver and patient QOL at baseline and end of treatment (week 12) using the Linear Analogue Self-Assessment Scale (LASA), a 10-item self-report on a 10-point Likert scale, ranging from 1="As bad as it can be" to 10="As good as it can be," to assess overall QOL ("During the past week, including today, how would you describe your overall quality of life?") and QOL domains of physical, emotional, spiritual, mental, and social well-being; pain frequency and severity, and coping. Last-Observation-Carried-Forward (LOCF) method was used to impute the few missing data. Results: Twenty subjects (16 male) median age 72 years completed baseline assessments, of which 17 subjects completed the 12-week protocol. At the end of treatment, patients endorsed improvement of physical (p=0.002), emotional (p=0.032), and mental (p=0.014) well-being, but no significant difference in overall QOL. In contrast, caregivers' overall QOL improved (p=0.001), but there were no significant differences found with other QOL domains. Conclusions: In our DLB patients treated with Armodafinil therapy, overall QOL was maintained, and QOL domains of physical, emotional, and mental well-being improved. Caregivers showed improvement in overall QOL. Our findings suggest benefit for both patients and caregivers based on significant improvement of QOL in different domains.

Session 13: Hot Topics

O.44

Can Genetics Assist in Predicting the Conversion from REM Sleep Behavior Disorder to Dementia with Lewy Bodies and Other Synucleinopathies?

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Background: Dementia with Lewy Bodies (DLB) and other synucleinopathies often occur after a prodromal stage of REM sleep Behavior Disorder. The contribution of genetic factors to RBD and to its progression to DLB and other synucleinopathies is still unknown. Methods: As a 'proof-of-concept', an initial genetic screening was performed, for markers that are known to be associated with synucleinopathies, among 265 RBD patients and 379 controls, followed by full sequencing of the GBA gene. Subsequently, we performed a genome wide association study (GWAS) and next-generation sequencing of 51 known or suspected synucleinopathy genes, using molecular inverted probes (MIPs) in 1850 individuals with RBD, PD or controls. Results: In the initial analysis, two SNPs in loci associated with synucleinopathies, rs6812193 (annotated to the SCARB2 gene, OR=0.67, p=0.004) and rs12185268 (annotated to the MAPT gene, OR=0.43, p=0.001) were associated with RBD. Kaplan-Meier survival analysis in a subset of RBD patients who were followed up (n=56), demonstrated that homozygous carriers of the USP25 rs2823357 had progressed to synucleinopathies faster than the others (Log-rank p=0.003). GBA mutations were associated with RBD (OR=2.63, p=0.0052 for all variants, and OR=3.46, p=0.0045 for pathogenic variants). Initial analysis of the GWAS data identified two potential novel loci that are associated with RBD, and the next-generation sequencing identified novel mutations in novel as suspected genes that are associated with RBD. Conclusion: Our results suggest that RBD is associated with at least a subset of synucleinopathy-associated genes. Furthermore, it is possible that by combining genetic and prodromal clinical data, we will be able to identify individuals that are about to develop synucleinopathies in a much earlier stage.

O.45

Protein Biomarkers in Dementia with Lewy Bodies

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Introduction: Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) commonly have pathological overlap but patients with DLB who respond to cholinesterase inhibitors have fewer AD-like imaging biomarkers (cingulate island sign, hippocampal atrophy, amyloid-β PET deposition). Blood-based biomarker profiles show AD can be distinguished from Parkinson's disease and normal controls using a multi-level classification approach. We examined a blood-based biomarker profile in detecting and differentiating DLB treatment responders from AD and normal controls. Methods: We identified 35 probable DLB patients at Mayo Clinic Florida who had good response to cholinesterase inhibitors. These were matched by age and gender with AD patients (n=39) and cognitively normal individuals (n=48). Plasma samples were assayed in duplicate via a multi-plex biomarker assay platform using ECL on the SECTOR Imager 2400A from Meso Scale Discovery (MSD; http://www.mesoscale.com). Markers included sVCAM1, IL5, IL1, IL6, IL7, IL10, adiponectin, MIP1α, TNFα, sICAM, CA125, SAA, CRP and eotaxin 3. Age, education and gender were entered into the models. Random forest (RF, dichotomous) and support vector machine (SVM, multi-category classification) were used to generate biomarker profiles. Results: A multi-marker, multi-level classification approach using SVM yielded 100% accuracy when simultaneously detecting and distinguishing between DLB, AD and normal controls with five-fold cross validation. The area under the receiver operating characteristic curve (AUC) was 0.81 when distinguishing DLB from normal controls, and 0.56 in differentiating DLB from AD. Conclusions: Current results provide the first evidence that a plasma-based biomarker profile approach detects DLB treatment responders and distinguishes them from AD and normal controls. Future studies are needed for confirmation and to determine if these findings can be extended to include other Lewy body disease subgroups.

O.46

The Influence of DLB Feature and ^{123}I-FP-CIT SPECT Scan on Diagnosis at 6-months Follow-up

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Introduction: Dementia with Lewy bodies (DLB) is diagnosed according to Consensus clinical criteria. To make a diagnosis of DLB patients must have dementia and one or more characteristic features. These features are divided into Core, Suggestive and Supportive depending on their diagnostic weight. Core features (greater diagnostic weight) are fluctuating cognition, spontaneous parkinsonism, and visual hallucinations. Our aim was to investigate the contribution of different diagnostic features to clinical diagnosis in combination with FP-CIT (DaTSCAN). Methods: As part of a European multicentre randomized study we recruited 114 patients with possible DLB (dementia plus one core or one suggestive feature) who underwent DaTSCAN imaging. No patients had neuroleptic sensitivity and all patients had DaTSCAN as part of the protocol. We determined the contribution of the different diagnostic features of DLB in combination with the imaging result in 106 patients that completed 6-months follow-up. Results: At baseline the frequency of fluctuations was 32%, visual hallucinations 22%, parkinsonism 27%, and REM sleep Behavior Disorder (RBD) 20%. Changes in diagnostic category were more frequent in patients with a positive (abnormal) scan. In patients with an abnormal scan, 85% with fluctuations, 100% with hallucinations, 85% with parkinsonism and 86% with RBD had a change in diagnostic category. The corresponding percentages for normal scans were 67%, 86%, 56% and 27%. In patients with an abnormal scan there was no significant difference in frequency of change in diagnostic category across the different features. There was a difference between these features and change in diagnostic category to non-DLB in patients with a normal scan. The difference was statistically significant for RBD. Conclusion: In the presence of a negative DaTSCAN, in patients with possible DLB, different features have a variable influence on the diagnosis. In particular, in patients with RBD and negative DaTSCAN, clinicians remain uncertain about the diagnosis.

O.47

The SYNERGY Mouse: A Model of Bi-Genic Risk to Develop Dementia with Lewy Bodies and Parkinsonism

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Background: We created a mouse model of dementia with Lewy bodies (DLB) and Parkinson disease (PD) that is informed by genetic susceptibility and clinicopathological insights in humans. SYNERGY mice harbor changes at two loci for elevated risk of DLB and PD [GBA1, SNCA]. Our goal was to recapitulate the evolution of biochemical and pathological features of DLB/PD leading to detectable motor and cognitive deficits during ageing and examine these in the context of α-synuclein- (SNCA) and sphingolipid-associated changes. Methods: SYNERGY mice carry D409V knock-in mutations in Gba1 and four insertions of PAC-human SNCAA53T on a murine snca-null Background : We are performing age-dependent analyses to correlate specific changes in behavioural performance with altered SNCA and lipid metabolism. [Xu et al. 2003; Kuo et al. 2010]. Results: SYNERGY mice develop SNCA-dependent motor and sensorimotor impairments as early as 6 weeks that persist with age. Compared to wild-type mice, SYNERGY mice consistently under-perform on challenging motor tasks, including the Rotarod and Pole tests. Beginning at 3 months-of-age, they progressively worsen in Nest Building, which tests integrated sensorimotor functions and motor planning. At 6 months-of-age, SYNERGY mice show cognitive impairment in Cued Fear Conditioning. These changes are associated with: a PAC-SNCA-dependent ~2.5-fold increase in total human SNCA level in the brain compared to wild-type mice; a further ~18% rise in SNCA expression due to homozygous mutations in Gba1; and the presence of proteinase-K resistant SNCA in 3 brain regions. Gba1 activity is reduced to 30% of wild-type mice. Lipid analysis and studies in older mice are ongoing. Conclusions: We posit that SYNERGY mice represent an etiologically relevant model for DLB and PD. Our overall goal was to create a platform to study changes in biochemistry, pathology and behaviour that leads to neurodegeneration in humans, and a pre-clinical tool for drug testing.

Session 14: Controversies

O.48

Maintain the 1-Year Rule in PD/PDD and DLB: Yes

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There is a saying which goes: "If it isn't broken then don't fix it". The Queen Square Brain Bank (QSBB) Criteria for Parkinson's (PD) have served us admirably over the years, and are widely regarded as the gold standard in academic publications for inclusion of study participants with a high likelihood of Parkinson's. Subsequent to the QSBB Criteria emerged Consortium Criteria for the diagnosis of dementia with Lewy bodies. As a movement disorder specialist this author initially struggled with the so-called "one-year rule" which served to differentiate people with PD and then the onset of dementia (after 12 months or more, thus labelling them as PD with dementia, PDD), from those whose dementia preceded, or was indeed accompanied by, the onset of spontaneous (i.e. not drug-induced) parkinsonism, giving a label of dementia with Lewy bodies (DLB). Indeed, he was heard to state in lectures that: "Biology does not work in straight lines". But with the passage of time, the opportunity to reflect upon the current state of play, and catalyzed by the emergence of newly proposed MDS PD criteria, this author recognizes that the one year rule actually DOES serve a useful purpose. The MDS-PD criteria do not consider dementia as an exclusion criterion for PD, regardless of when it occurs in relation to parkinsonism onset, and invoke (conveniently!) an optional PD (DLB) subtype. This issue is more than semantics, and a parsimonious way of tidying up a rule that has been challenging us to be broken since its inception. It is a question of what is best for the patient. Care pathways differ between those presenting with primarily dementia and those already in movement disorder clinics who subsequently become demented. Furthermore, parkinsonism in DLB is not inevitable; will such cases be known as the DLB (non-PD) subtype? If it isn't broken, don't fix it – the one year rule serves our patients well and is grounded on both practical and tried and tested diagnostic criteria.

O.49

Maintain the 1-Year Rule in PD/PDD and DLB: No

Ron Postuma

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For decades, movement disorders and behavioral neurology have been advancing on parallel tracks. In behavioral neurology, we now recognize dementia with Lewy bodies as highly prevalent, with specific identifying clinical markers. In movement disorders, improved motor treatment has led to the recognition that dementia will be experienced by the majority of PD patients. We now know that dementia can occur at any time point in PD, and parkinsonism at any time point in DLB. The striking similarities between PD dementia and DLB are easy to list. Clinically, both have hallucinations, fluctuations, somnolence, and parkinsonism. Both have a neuropsychological profile characterized by the same prominent visuoperceptual dysfunction, improvement of memory with cues, etc. They have a highly similar prodromal state, with REM sleep behavior disorder and olfactory loss as key markers. Their neuroimaging profile, from functional MRI, to whole-brain glucose utilization imaging, to dopaminergic imaging, to cholinergic imaging is similar. They have similar underlying genetic causes; of note, different patients with the same mutation can have either condition. Finally, they are indistinguishable on autopsy; both have indistinguishable patterns of synuclein deposition at death. Our new understanding of the essential role of synuclein leads to a paradox; the most prototypical 'dementia with Lewy bodies' (i.e. PDD) is not even considered as DLB. Disease boundaries are constructs; borders that we use to help prognosticate, treat clinically, and most critically, develop new pathophysiological-based treatments. No two patients with any disease are identical; every patient has their own disease. Each person with dementia and Lewy bodies travelled a different clinical path to get there. So, the question is not whether PD and DLB are identical, rather whether it is wise to consider PD dementia and DLB as mutually-exclusive diseases. Rules that keep our two fields apart will impair further progress; the one-year rule should be abandoned.

O.50

Should Antipsychotics Be Used in DLB? Yes

Clive Ballard

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The harms associated with antipsychotics in people with dementia have been a key topic. Most work has focussed on Alzheimer's disease, where modest benefits and significant safety risks including mortality, stroke and accelerated cognitive decline have led to regulatory warnings. The dangers of antipsychotic use in people with Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) were reported even earlier, with severe neuroleptic sensitivity reactions described in the early 1990's and more recent studies have demonstrated that atypical antipsychotics are associated with a significant increase in mortality and other key adverse outcomes in PD. Against this background it appears paradoxical to be arguing for the use of antipsychotics in people with DLB. However, psychotic symptoms are much more intrusive, much more persistent and much more distressing in people with DLB than they are in people with other dementias. This level of distress cannot be ignored, particularly when the usual clinical course is for these symptoms to persist for a year or longer if untreated. Clearly a careful clinical decision needs to be made, and benefits and harms need to be balanced for each patient. In addition, given evidence that the cholinesterase inhibitors rivastigmine and donepezil do confer some benefit in the treatment of psychosis in DLB patients, this should be the first line pharmacological therapy. However, for patients with severe and distressing psychotic symptoms that are not responsive to cholinesterase inhibitor therapy, atypical antipsychotics remain the only evidence based treatment option. In particular there is clear evidence supporting the value of clozapine treatment in people with PD, and whilst further RCTs in people with DLB are a priority, this should probably be the preferred treatment based on current evidence.

O.51

Should Antipsychotics Be Used in DLB? No

Daniel Weintraub

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Up to 60% of Parkinson's disease (PD) patients experience psychosis, 80% develop dementia, and the use of antipsychotics (APs) in PD is common. The use of APs in dementia patients in the general population is associated with increased mortality, but it is not known if this risk extends to PD patients. National Veterans Affairs (VA) health system administrative data (1999-2010) was used to examine the risk associated with AP use in a cohort of idiopathic PD patients with recent stable physical health. We compared 180-day mortality rates in those patients initiating an AP with matched non-AP users (matched on age (+/- 2.5 years), gender, race, index year**,** presence and duration of dementia, PD duration, delirium, hospitalization, Charlson Comorbidity Index, and new non-psychiatric medications. Cox regression models were used with both intent-to-treat (ITT) and exposure period only analyses. There were 7,877 matched PD pairs. AP use was associated with more than twice the hazard ratio (HR) of death compared with non-use (ITT HR=2.35, 95% CI=2.08, 2.66, p<0.001). The HR was higher for typical compared with atypical AP use (ITT HR=1.55, 95% CI=1.24, 1.92, p<0.001). Among atypical APs, HRs relative to non-use of APs in descending order were olanzapine (HR=2.79, 95% CI=1.97, 3.96), risperidone (HR=2.46, 95% CI=1.94, 3.12) and quetiapine (HR=2.16, 95% CI=1.88, 2.48). In conclusion, AP use is associated with an increased mortality risk in PD patients, after adjusting for measurable confounders. This finding highlights the need to use APs cautiously in PD patients. Future studies should examine the role for non-pharmacologic strategies in managing psychosis in PD. In addition, new pharmacologic treatments that do not increase mortality in patients with neurodegenerative diseases need to be developed. Additional analyses showed that AP use in PD is also associated with increased morbidity (e.g., ER visits) in those patients who did not die during the observation period.

Session 15: Toward Global DLB Research Harmonization

O.52

DLB Research in North America

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The goal of this session is to review briefly recent consensus efforts in diagnostic guidelines and research priorities. I will review the National Institute on Aging (NIA)-Alzheimer's Association diagnostic guidelines for the neuropathologic assessment of Alzheimer's disease and related dementias, including Dementia with Lewy bodies. In addition, I will highlight the major research recommendations from the 2013 Alzheimer's Disease-Related Dementias conference organized by the National Institute on Neurological Disorders and Stroke (NINDS) and NIA, and the NINDS 2014 Parkinson's disease conference.

O.53

DLB Research in Europe

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DLB research has a long history in Europe. UK researchers were instrumental in directing academic and clinical interest towards DLB. In particular, the group in Newcastle, led by Ian McKeith, played a key role, and was heavily involved in the development and subsequent revisions of the clinical and pathological consensus diagnostic criteria. In a second phase, single-centre studies were conducted in many other European countries. In addition, several industry-sponsored multicentre studies were completed, including clinical phase 3 trials of rivastigmine, followed by a phase 3 (and subsequent phase 4) biomarker trial (dopamine transporter imaging), and multicentre clinical trials of memantine. A recent third phase is characterised by extensive international academic collaboration that led to the formation of the European DLB study (E-DLB). E-DLB was partly funded by a grant from the EU Joint Programme for Neurodegenerative Diseases, which enabled the development of a harmonized protocol for multicentre clinical and biomarker cohort-studies in DLB. The basic protocol should be feasible for use in clinical practice at specialized centres. We also attempted to streamline the design with other multicentre studies such as PPMI and ADNI in order to facilitate collaboration. E-DLB has rapidly grown in size and now includes 25 centres from 11 European countries, which are loosely connected in this research network. The E-DLB has two over-arching goals: 1) to establish a database including clinical and biomarker data from existing DLB patients, and 2) conduct a prospective cohort study with a comprehensive biomarker collection, based on the agreed protocol. The first objective is ongoing, and has successfully collected data on more than 1300 DLB patients. Several papers have been submitted or are being submitted based on this large database, and several of these studies will be presented at this conference. Examples include studies on longitudinal course, CSF markers, and EEG, and data collection on structural and functional imaging and genetics is ongoing. Future aims include the need for additional funding for centralized biobanking and biomarker analysis.

O.54

DLB Research in Asia

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In 1976, Kosaka et al. reported the first autopsied case with diffuse Lewy body disease from psychiatric hospital in Japan. Thirty years later, the Fourth International Workshop on DLB and PDD was held in Japan in 2006. Dr. Kosaka established a Japanese society for DLB research in 2007, and multicenter studies subsequently confirmed the diagnostic utility of ^{123}I-meta-iodobenzylguanidine (MIBG) scintigraphy and the efficacy of donepezil and yokukansan, a traditional Japanese medicine, as pharmacotherapy in DLB. Treatment using donepezil, the diagnostic use of MIBG scintigraphy and dopamine transporter imaging in DLB are approved by the Japanese government. In Asian countries, research regarding prodromal DLB is increasing. Although clinical cohort studies of idiopathic REM sleep behavior disorder (RBD) are underway, there is limited information on the prodromal DLB state without preceding RBD symptoms. Based on the clinicopathological relationship between REM sleep without atonia (RWA) on polysomnography and neurodegenerative disorders, the concept of subclinical RBD is attracting attention for early detection of underlying neurodegeneration. A community-based Korean longitudinal study revealed the prevalence of subclinical RBD (4.95%) in elderly people over 60 years of age. RBD has been also increasingly reported in patients with psychiatric disorders, especially major depressive disorder (MDD). In Hong Kong, Wing et al. demonstrated reduced striatal dopamine transmission and impaired olfactory function in RBD comorbid with MDD. They suggested that the development of RBD symptoms in MDD might represent an early phase of neurodegeneration instead of an antidepressant-induced condition. However, it remains unknown whether subclinical RBD in MDD patients may represent an underlying neurodegeneration. Olfactory dysfunction, autonomic dysfunction, and findings of occipital hypometabolism and incident RWA provide the opportunity to suspect the prodromal DLB state. Because there is little information of psychiatric aspects of the prodromal DLB state, more research in middle-aged and older patients with psychiatric disorders is needed.

O.55

Insights from the National Alzheimer's Coordinating Center (NACC) for DLB Research

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The NACC was established in 1999 to receive data from NIA-funded Alzheimer's Disease Centers (ADC) and to make those data available to interested researchers and promote collaboration among the ADCs. "minimal" cross-sectional, retrospective data were first collected reflecting the cumulative enrollment at ADCs for the period of 1984 until September 2005. This included approximately 66,000 subjects of which nearly 11,000 had neuropathology data. These subjects included the entire cognitive spectrum and also a variety of underlying neurodegenerative and vascular brain diseases in addition to Alzheimer's disease. More importantly, in 2005 the NIA-ADC Clinical Task Force (J. C. Morris, Chair) formulated the "Uniform Data Set (UDS), a detailed, standardized clinical examination. The UDS was adopted by the ADCs as their principal data collection package. It is of unique value because these data are collected at each annual ADC visit, i.e., longitudinally, and maintained at NACC for research distribution. The UDS currently included some 33,000 subjects, about 3,800 of whom have also had neuropathological examination. From that series approximately 1200 have a primary clinical diagnosis of Lewy Body related diseases, and of those nearly 300 have neuropathology data. These represent only those clinical diagnoses considered to be "Primary", so certainly LBD may quite commonly co-occur in many other of the enrolled subjects, and that is an important area of discussion and research. Presently, a DLB clinical task force is formulating a DLB specific clinical data collection tool to more carefully characterize clinical DLB on ADC subjects. Those data may begin to be collected before the end of 2015. The combination of the standardized longitudinal clinical data and standardized neuropathological data collection make the UDS a deep research reservoir for thirsty investigators. Within the last year NACC has also begun to receive structural MRI images (a variety of sequences on about 2000 subjects); fluid biomarker measures are just beginning to be received, however. In addition, NACC has collaborated with the Alzheimer's Genetic Consortium (ADGC) and the National Cell Repository for Alzheimer's Disease (NCRAD) and NIAGADS to facilitate genome wide association studies and sequencing studies; much of those data are also available. DLB and associated disorders have been the principal subject of only about 30 published papers so far, but many more are awaiting researcher's keen and careful eye.

POSTERS - Biofluid Biomarkers

P.1

Alzheimer's disease CSF biomarkers as predictors of cognitive decline in Lewy body dementia

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Background: Co-morbid Alzheimer's disease (AD) pathology is common in Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB). In PD, low CSF Aβ42 markers predict long-term cognitive decline, but its role in DLB is less known. Objectives: To determine if AD CSF biomarkers (Aβ42, t-tau and p-tau) predict cognitive decline Lewy body dementia patients (DLB or PDD). Materials and Methods: From E-DLB, a large European multicenter study, we analyzed AD CSF biomarkers and serial MMSE (baseline, 1 and 2-year) when available, in 65 LBD patients (DLB=59, PDD=6) from three centers. Since DLB and PDD were similar in clinical and CSF features they were combined into a LBD group. 3 different local assays and cut-off values were used to analyze and dichotomize CSF biomarkers. We measured the association of repeated MMSE with a positive AD CSF profile (defined as pathological Aβ42 + pathological t-tau or p-tau) and with CSF biomarkers individually. In addition to Mann-Whitney and Student's t-test to compare longitudinal MMSE by AD CSF profile, linear regression analysis was performed adjusting for baseline MMSE. Results: LBD patients did not differ significantly in baseline clinical characteristics by AD CSF profile. The rate of cognitive decline from baseline to two-year follow-up was more rapid in the positive AD CSF profile group (n=11, mean decline 6.8) compared with the negative group (n=24, mean decline 1.9), but this did not reach statistical significance. Subjects with low CSF Aβ42 and high t-tau levels had a more rapid decline during two-years, but without statistical significance. Conclusions: AD CSF biomarkers were not significantly associated with cognitive decline measured by MMSE over 1-2 year in LBD, although there were indications that low Aβ 42 and high t-tau levels were associated with more rapid decline. Future prospective studies should include larger samples, central CSF analyses and longer follow-up.

P.2

Diagnostic value of cerebrospinal fluid biomarkers (Phospho-Tau, total-Tau, Aβ42 and Aβ40) in prodromal Alzheimer's disease and dementia with Lewy bodies

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Background: Dementia with Lewy bodies (DLB) symptoms are close to those of Alzheimer's disease (AD), and the differential diagnosis is difficult especially early in the disease. Unfortunately, Alzheimer's disease (AD) biomarkers in cerebrospinal fluid (CSF) and more particularly Aβ1-42 appear to be disrupted in dementia with Lewy bodies (DLB). However, the level of these biomarkers has never been studied in the prodromal stage of the disease. So we propose to compare these biomarkers between DLB and AD, with a particular focus on the prodromal stage. Methods: A total of 166 CSF samples were collected at the memory clinic of Strasbourg. They were obtained from prodromal DLB (pro-DLB), DLB dementia, prodromal AD (pro-AD), and AD dementia patients, and elderly controls. Patients were classified according to the criteria of McKeith (McKeith et al., 2005) and DSMV for DLB patients and the criteria of McKhann (McKhann et al., 2011) and Dubois (Dubois et al., 2007) for Alzheimer's patients. The results of lumbar puncture were not considered for the classification of patients. Phospho-Tau, total-Tau, Aβ42 and Aβ40 were measured in the CSF. Results: At the prodromal stage, contrary to AD patients, DLB patient's biomarkers levels in the CSF were not disrupted. At the demented stage of DLB, Aβ42 levels were reduced as well as Aβ40 levels, suggesting a decreased of amyloid burden in DLB dementia patients. So the Aβ42/Aβ40 ratio remained unchanged between the prodromal and demented stages, contrary to what was observed in AD. Conclusions: We have shown that at the prodromal stage the DLB patients had no pathological profile.So, CSF AD biomarkers are extremely useful for differentiating AD from DLB patients particularly at this stage when the clinical diagnosis is difficult. Thus, these results open up new perspectives on the interpretation of Alzheimer's biomarkers in Dementia with Lewy bodies.

P.3

Translational Lipidomics: Harmonizing LC-ESI-MS Targeted Lipidomic Methodologies in Clinical Study of Dementia with Lewy Bodies

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The emerging field of neurolipidomics seeks to understand how dynamic changes in membrane composition regulate brain cell function and how these changes can be used as biomarkers to predict disease outcome and track disease fate. Commonly conceptualized as undulating fields of identical molecules, neuronal membranes are, in fact, made up of hundreds of chemically and molecularly diverse lipid species. For the first time, significant technological advances in liquid chromatography (LC), electrospray ionization (ESI), and mass spectrometry (MS) are enabling membrane composition to be profiled comprehensively at the molecular level. Coupled with subcellular fractionation and careful consideration of extraction protocols that enrich for different phospholipid families, species that vary by only one double bond, a single methylene group, or carbon chain linkage can now be quantified directly in synaptic preparations. These advances are allowing for discovery of novel biomarkers of disease transition, progression, and fate and new mechanistic insight into the determinative roles of lipid metabolism in neurodegenerative disease. Yet, as with imaging biomarkers, accuracy and reproducibility are fundamentally dependent on how lipid biomarkers are measured. We seek to profile the changes in the circulating plasma and cerebrospinal fluid (CSF) sphingolipidome that, either alone or in combination with changes in a-synuclein, identify antecedent cognitive impairment in DLB patients. To do so, we present here data highlighting the challenges in harmonization of protocols, analyses, and lipid identification required for multi-centre replication and validation of biomarker results obtained through neurolipidomic investigations.

P.4

Using Targeted Lipidomics to Interrogate Blood-based Biomarkers

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Can circulating lipid biomarkers predict vulnerability (or resiliency) to devastating mental health disorders? Unbiased lipidomic approaches have identified changes in circulating lipidomes of neurodegenerative disease. Validation of lipid biomarker specificity, sensitivity, and reproducibility, however, depends not only on the quality of the patient cohorts but also upon the quality and rigor of sample preparation. It is well known that processing of serum and plasma during blood collection can alter metabolomic profiles. The impact of fluid processing on lipid profiles, however, has only begun to be examined. Conceptually, the clotting process, for example, can trigger artifactual accumulation of certain ceramides. Moreover, heparin can signal both cytokine release from leukocytes, activating multiple sphingolipid metabolic pathways, and potentiate platelet response to endogenous alkylacetylglycerophosphocholines (also known as platelet activating factors). Feedback is inevitable as platelet activating factors can, in turn, artificially increase ceramide production during fluid processing. To directly address this methodological issue, we present data comparing lipidomic profiles of the same patients derived from serum or plasma (collected and processed simultaneously), thus identifying differences in lipid composition at the molecular level caused solely by fluid processing.

P.5

Effect of an AD CSF Profile on Core Clinical Features of Dementia with Lewy bodies: Results From E-DLB

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Background: Concomitant Alzheimer's disease (AD) pathology is common in dementia with Lewy bodies (DLB). Neuropathological studies suggest that DLB patients with concomitant AD pathology had more pronounced cognitive dysfunction compared with pathologically pure AD or DLB while alive. However, few in vivo studies exist, so the influence of co-morbid AD pathology on clinical symptoms is not clear. In this study we investigated the effect of concomitant AD pathology, assessed by the presence of AD biomarkers in cerebrospinal fluid (CSF), on the core clinical features (parkinsonism, visual hallucinations and cognitive fluctuations) in a large DLB cohort. Methods: From a European multicenter DLB cohort (n=1086) we selected 155 probable DLB patients who had CSF and clinical data available. CSF Aβ42, tau and ptau-181 were analyzed locally by ELISA assays. An AD+ CSF profile was defined as tau/Aβ42 ratio >0.52 (Duits et al., 2014). Based on this profile, the patients were divided into AD+ and AD- groups. Between-group cross-sectional analyses for clinical variables (age, sex, education, disease duration, parkinsonism, visual hallucinations, cognitive fluctuations and MMSE score) were performed. Results: An AD+ CSF profile was present in 44% (n=69) of patients. Patients in the AD+ group were older (73 versus 68 years, p=0.001), more likely female (36% versus 18%, OR=2.652; 95%CI=1.16-6.57; p=0.01), and had more visual hallucinations (65% versus 43%, OR=2.39; 95%CI=1.20-4.72; p=0.01). Controlling for age and sex, visual hallucinations remained significantly associated with an AD+ CSF profile (OR=2.09; 95%CI=1.02-4.28; p=0.04). No significant between-group differences were found for education, disease duration, MMSE score, parkinsonism or cognitive fluctuations. Conclusion: results from this large European multicenter DLB cohort showed that biomarker evidence for co-morbid AD pathology is associated with more frequent visual hallucinations. These results suggest that co-morbid AD pathology have a broad impact on non-motor features in DLB.

CLINICAL – Cognitive, Neuropsychiatric, Motor, Sleep and Autonomic

P.6

Visual Hallucinations and Rate Of Cognitive Decline in DLB. A Longitudinal Multicenter Cohort Study (E-DLB)

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Background: Visual hallucinations (VH) are one of the core features of dementia with Lewy bodies (DLB). In Alzheimer's and Parkinson's disease, VH predict a more rapid cognitive decline, but few studies have explored the predictive power of VH in DLB. Objective To test the hypothesis that VH are associated with a more rapid cognitive decline in DLB Methods: From a large international multicenter study, E-DLB, retrospective information on VH and cognitive test scores (Mini-Mental State Examination-MMSE) were available for 942 DLB patients, who were diagnosed using the 2005-criteria. The procedure for assessing VH varied among centres, but for each patient this question was actively explored. Annual follow-up including MMSE was available for 544 (year 1), 392 (year 2), and 110 (year 3) patients. In addition to bivariate analyses, linear regression analyses was performed adjusting for potential confounders including baseline MMSE score. Results: Patients with VH (n=612, 65%) had slightly longer disease duration and were more commonly female than those without VH (N=330), but the groups did not differ regarding age, education or UPDRS motor score. There were no significant differences between those with and without VH regarding MMSE score at baseline (20,2 vs 20.9), or regarding decline during the three years in the bivariate analyses, although there was a numerically more rapid decline in the VH group at year 2 and year 3. Conclusions: Our findings do not indicate an association between VH and the rate of cognitive decline in DLB. Prospective design with harmonized procedures, inclusion at time of diagnosis, and longer follow-up time are needed to better describe clinical predictors of cognitive decline in DLB.

P.7

Central and Systemic inflammation in Dementia with Lewy Bodies and Alzheimer's disease

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Background: The clinical features and neuropathology of Dementia with Lewy Bodies (DLB) overlaps with Alzheimer's disease (AD). There is growing evidence supporting a role for inflammation in the aetiology and progression of AD but currently there is little evidence in DLB. We propose that central and systemic inflammatory processes are altered in DLB compared to AD and controls, and that these changes are significantly associated with the neuropathological and clinical features of the disease. Methods: Clinical study: 120 participants (40 DLB, 40 AD and 40 controls) are being recruited to take part in an observational cross-sectional study. Participants will be assessed for cognitive, mood, behavioural and motor symptoms. Serum cytokine markers will be analysed using ELISA. Flow cytometry will be used to obtain peripheral lymphocyte differential counts and stimulation studies performed to investigate immune cell responsiveness. Neuropathology study: Post-mortem human brain tissue from 60 cases (30 DLB and 30 controls) has been provided by Brain Banks. Cases were selected based on post-mortem neuropathology reports. Tissue is being immunostained for the pathological features of DLB (α-synuclein) and AD (amyloid-β and phosphorylated tau), and a broad range of microglial antibodies including Iba1, HLA-DR, Fcg receptors (CD64, CD32, CD16). Protein load is being quantified using ImageJ software. Results: Clinical study: Recruitment of participants is ongoing. Clinical data and blood samples are being collected for each participant. Neuropathology study: Preliminary data on 39 cases shows no significant difference in Iba1 load between the DLB and control groups. The remaining Iba1 slides are currently being analysed as well as α-synuclein, amyloid-β and phosphorylated tau immunostaining. Conclusions: A greater understanding of the role of inflammation in DLB will determine if pharmacological therapies based on established inflammatory changes in AD are likely to be viable in DLB, or if specific treatment approaches may be needed.

P.8

Clinical Characteristics Associated with Neuropathological Lewy Body Disease Subtypes Among Non-Demented Subjects in the Uniform Data Set

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Background: The National Alzheimer's Coordinating Center's Uniform Data Set (UDS) and Neuropathology Data Set were used to assess whether demographic, clinical, and Alzheimer's disease neuropathological characteristics were associated with neuropathical Lewy body disease (LBD) subtypes. Methods: Our sample included 87 non-demented subjects with brainstem predominant (bpLBD; n=28), limbic (limLBD; n=36), or neocortical LBD (neoLBD; n=23) at autopsy. The following characteristics from the last visit were compared by LBD subtype using unadjusted linear and logistic regression: age, sex, education, ≥1 APOE e4 allele, heart rate (HR), systolic and diastolic blood pressure (SBP; DBP), body mass index (BMI), cognitive status, Parkinson's disease (PD) diagnosis, Clinical Dementia Rating sum of boxes (CDR-SB), Unified Parkinson's Disease Rating Scale (UPDRS), rapid eye movement sleep behavior disorder (RBD), Geriatric Depression Scale (GDS), visual hallucinations, and Alzheimer's disease neuropathology (ADNP). Adjusted linear and logistic regression models, controlling for age, sex, ADNP, APOE e4 and time between the last visit and death, were run to examine whether LBD subtypes differed by GDS score, PD diagnosis, CDR-SB score, UPDRS motor score, HR, SBP, DBP, or BMI. Results: Compared to bpLBD, those with neoLBD were more often male, less often had normal cognition, were more often depressed, and had worse CDR-SB and UPDRS motor scores; and those with limLBD less often had normal cognition and were more likely to have worse CDR-SB scores. Compared to bpLBD, limLBD was associated with worse CDR-SB scores (OR: 0.86, p < 0.001); and neoLBD was associated with worse CDR-SB scores (OR: 0.62, p=0.004), worse UPDRS motor scores (OR: 8.09; p=0.02), and higher DBP (OR: 5.44, p=0.04). Conclusion: Among autopsy subjects who were not demented before death, those with neoLBD were significantly more likely than those with bpLBD to be male, have worse UPDRS scores, and have higher DBP, associations not seen when comparing limLBD and bpLBD.

P.9

MMSE and MoCA Performance in Parkinson's Disease and Dementia with Lewy Bodies: A Multicenter 12 Month Follow-Up Study

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Background: A brief and accurate instrument is needed to test cognitive impairment in Lewy body disorders, but there is no consensus on which one is the most suitable in everyday clinical practice. In particular, little is known about the sensitivity of the two most common global scales, the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) to measure cognitive decline over time. Methods: Baseline (n=265) and one-year follow-up (n=153) scores on MMSE and MoCA were available for patients with Parkinson's disease (PD) with (N=197) and without (N=40) dementia, and dementia with Lewy bodies (DLB) (N=28) from an international consortium, E-DLB. Percentage of relative standard deviation (RSD%) at baseline for each scale as measure of inter-individual variance and percentage rate of change in MMSE and MoCA scores over time were compared. Results: RSD% for the MoCA (21%) was significantly greater than that for the MMSE (13%) (p< 0.03) in the whole group. This difference was significant in PD without dementia (11% vs. 5% p< 0.01), but not in PDD (30% vs. 19% p=0.37) and DLB (15% vs.14% p=0.78). In contrast, the percentage rate of change during one-year follow-up did not differ significantly between the two tests either in all patients [-2.43% (5.05) for MMSE and -2.40% (5.88) for MoCA, p=0.9], or in any subgroup (PD, PDD; DLB). Conclusion: The MoCA appears to be a more sensitive instrument to measure cognition cross-sectionally in PD without dementia. MMSE and MoCA might be similarly sensitive cross-sectionally in LBD with dementia and appear equally sensitive to cognitive decline over time across the full spectrum of LBD.

P.10

Subjective Daytime Hypersomnia is Greater in Mild Dementia with Lewy Bodies Compared to Mild Alzheimer's Dementia and Behavioral Variant Frontotemporal Dementia

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Background: Excessive daytime somnolence commonly occurs in dementia with Lewy bodies (DLB) but may also occur in Alzheimer's dementia (AD) or behavioral variant frontotemporal dementia (bvFTD). We sought to determine whether excessive daytime sleepiness is an early feature of DLB compared to AD and bvFTD. Methods: The Mayo Alzheimer's Disease Research Center database was queried to identify all patients who a) met published criteria for AD, DLB or bvFTD, b) had mild dementia based on a Clinical Dementia Rating (CDR) score =1, and c) had the Epworth Sleepiness Scale (ESS) completed by an informant (an ESS score ≥10 is considered abnormally sleepy). We compared demographics, mean ESS scores and the frequency of an ESS score ≥10 between the three groups. Results: Data on 159 subjects (111 AD, 31 DLB and 17 bvFTD) were analyzed. AD patients were more frequently female (p < 0.01), and the bvFTD patients were younger (p < 0.01), than the other two groups. There was no difference in education between the three groups. DLB patients had higher ESS scores compared to the other two groups (DLB mean 13.7 ± 4.6, AD mean 8.8 ± 5.2, bvFTD mean 9.6 ± 7.9, p < 0.01). An ESS score ≥10, indicating abnormal sleepiness, was significantly more frequent in the DLB group compared to the AD and bvFTD groups (DLB: 81%, AD: 45%, bvFTD: 44%, p < 0.01). Conclusions: In a group of patients with mild dementia, the frequency and severity of informant report of excessive daytime somnolence is significantly greater in DLB compared to AD and bvFTD. This suggests that informant report of excessive daytime somnolence in the mild stages of a dementia may help to distinguish DLB from AD and bvFTD early in the disease.

P.11

Quantitative EEG Patterns as Supportive Diagnostic Tool in Early DLB: A Validation Study from a European Multicenter Cohort

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Background: Quantitative EEG (QEEG) has been demonstrated to be able to distinguish DLB from AD patients (predictive value 100%) in a single cohort study (Bonanni et al,Brain2008;131:690-705). Whilst EEG in AD is characterized in posterior derivations by alpha dominant frequency (DF)>8Hz, prevalent (frequency prevalence, FP) in >55% of the EEG epochs and DF variability (DFV) Aim: To validate the aforementioned QEEG method in independent cohorts of DLB vs. AD patients. Method: We analyzed, blind, with automated software, EEG traces of 55 DLB and 60 AD with MMSE>20, collected from 5 European Centers (results from EEGs from more patients will be presented at the meeting). Age (mean±SD) was 74±6 in DLB and 78±7 in AD groups, MMSE was 24.4±3.2 and 22.8±2.0, respectively. EEGs from 19 scalp derivations (international 10-20 system) were acquired as 30min continuous signals and epoched in off-setting as series of 2seconds-long epochs. 90 epochs/patient were processed by Fast Fourier Transform on each epoch (frequency resolution of 0.5Hz). Results: Age was lower (ANOVA, $p < 0.01$), MMSE was higher ($p < 0.01$) in DLB vs. AD patients. Despite age/MMSE reflecting a milder disease stage in DLB, EEG specific abnormalities were found only in DLB. DLB and AD groups differed for DF($p < 0.01$), DFV(p=0.03), FP pre-alpha($p < 0.001$) and FP alpha($p < 0.001$). DLB patients presented with DF < 8Hz (DF mean±SE=7.1±0.2), FP pre-alpha>40% of epochs (52.1±3.0), FP alpha < 32%(25.4±3.4). DFV was 1.0±0.1. AD patients displayed alpha DF (8.4±0.2), DFV=0.8±0.1, FP pre-alpha=23.2±3.2, FP alpha=56.7±4.2. The highest sensitivity and specificity (70-80%) were found for DF and DFV. FP alpha and pre-alpha showed a sensitivity of 63-69% and specificity 72-81%. Conclusions: We confirm the validity of QEEG analysis as supportive diagnostic tool in early disease DLB patients.

P.13

RBD and Neuropsychological Performances in Patients with MCI and Dementia.

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Background: REM sleep behavior disorder (RBD) is associated with impaired visuospatial functions. The main goal of this study was to determine if patients with cognitive impairment and RBD differ from patients without RBD in neuropsychological performances. Methods: This cross-sectional study compared neuropsychological performances in a cohort of 246 subjects from Western Norway. Probable RBD was diagnosed with the Mayo Sleep Questionnaire. Cognitive functions were evaluated with the MMSE, CVLT-II, VOSP Cube and Silhouettes, Boston naming test, Golden Stroop test, Verbal fluency and Trail Making Test A and B. Separate logistics regression analyses for each neurocognitive variable were performed, adjusted for age, education and total MMSE. Results: Among 246 patients 47 (19,1%) were diagnosed with probable RBD. 27 (57,4%) of the RBD patients had been diagnosed with DLB. Groups with and without RBD did not differ in age, education, and dementia severity or dementia medications, but there were more males in the RBD group. The RBD group scored higher on the VOSP Silhouettes, CVLT-II delayed recall, and on MMSE orientation. The RBD group had significant lower scores on Stroop Word and Stroop Colour. Lower scores on the Stroop Word (p=.003) and Stroop Colour tests (p=.034) were associated with RBD after adjusting for age, MMSE total score, dementia medication and education in a logistic regression model. Conclusions: In contrary to other studies we did not find any significant differences in visuospatial neurocognitive tests between patients with and without RBD. There were no differences in other domains such as: verbal memory, executive functions or attention if adjusted. Subjects with RBD performed worse both on Stroop Word and Stroop Colour suggesting, slower reading and/or motor speech, which to our knowledge has not been reported earlier.

P.15

The Development of an Evidence-Based Lewy Body Dementia Practical Management Toolkit: Results from the DIAMOND-Lewy Study

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Background: Lewy body dementia (LBD) includes dementia with Lewy bodies and Parkinson's disease with dementia. LBD affects approximately 160,000 people in the UK and the prevalence is expected to increase in the coming years. Clinically, LBD remains under-detected. The aim of the 'Improving the diagnosis and management of neurodegenerative dementia of Lewy body type in the National Health Service' (DIAMOND-Lewy) study, which comprises multiple work packages, is to improve patient management and clinical outcome through the development and assessment of an evidence-based practical management toolkit for clinicians. This work package (Work Package 3) describes the development of the LBD management toolkit for routine clinical use. Methods: A three-round Delphi survey process was used. Expert LBD panel members were asked to indicate whether they agreed or disagreed with a series of evidence-based statements, based on the findings of a systematic review prepared as part of the work package, within a practical management toolkit. The level of agreement, expressed as a percentage, was derived from their responses. Statements with agreement levels of 85% or higher were retained in the final guidelines. Statements with agreement levels of results. Following Round 3, a total of 161 statements were retained in the final guidelines. Conclusions: Based on the input of expert panel members, PPI and systematic evidence, this management toolkit has the potential to greatly improve the clinical management and care of LBD patients in the NHS. The subsequent work package (Work Package 4) will test the feasibility and effectiveness of the management toolkit in a pilot study within old age psychiatry and Parkinson's disease clinical services.

P.16

Depressive Symptoms Are Associated with Daytime Sleepiness and Subjective Sleep Quality in Dementia with Lewy Bodies

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Background: Sleep disturbances are extremely common in individuals with DLB, and they frequently experience subjectively-poor sleep quality and excessive daytime sleepiness. Depression, which is also common in DLB patients, is a potential risk factor for sleep disruption, although this relationship has not previously been studied. The aim of this cross-sectional study was to investigate the association between depressive symptoms, subjective sleep quality and daytime sleepiness in DLB. Methods: DLB patients (n = 32), with the aid of a reliable informant, completed measures of subjective sleep quality (Pittsburgh Sleep Quality Index; PSQI), subjective sleepiness (Epworth Sleepiness Scale; ESS) and depressive symptoms (15-item Geriatric Depression Scale; GDS-15). Cognitive function, cognitive fluctuations and motor function were also assessed. The relationship between PSQI, ESS, and GDS-15 scores were analysed using Pearson correlations. Results: GDS-15 scores were significantly positively associated with ESS scores (r = .51, p < .01) and were also significantly positively associated with PSQI scores (r = .59, p < .001), indicating that more severe depressive symptoms were associated with excessive daytime sleepiness and poorer sleep quality. ESS and PSQI scores were not related to cognitive function, cognitive fluctuations or motor function. Conclusions: More severe depressive symptoms are associated with poorer subjective sleep quality and greater daytime sleepiness in DLB. Although the directionality of this relationship cannot be confirmed in the present study, these findings are potentially clinically relevant as daytime sleepiness or poor sleep quality in DLB should prompt further evaluation for depression. Future studies are necessary to determine the nature of these associations and whether, for example, the treatment of depressive symptoms can reduce excessive daytime sleepiness and improve sleep quality in DLB.

P.17

Understanding the Relationship Between Visual Hallucinations, Visuo-perceptual Function and Attention: A Pilot Study

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Background: In Lewy body diseases (LBD), complex visual hallucinations (CVH), visuo-perception (VP) and attention (ATTN) deficits are common and distressing symptoms. Despite a number of proposed models, our understanding of CVH is limited as we currently do not have good methods to objectively quantify the phenomenon whilst in state, nor do we know what aspects of VP and ATTN function are important in for their manifestation. This study aimed to explore what aspects of VP and ATTN correlate best with CVH in a LBD population, and how performance on these tasks correlated with performance on two illusion tasks which could be considered as surrogates for CVH. Methodology In this study, seven patients with Lewy body dementias (LBD) and twelve healthy aged-controls completed a series of neuropsychological measures, in addition to a battery of computerised ATTN and VP tasks. We also utilised two novel illusion tasks considered to be potential surrogates for CVH: the pareidolia task and the mirror gazing task. Results: We found significant VP and ATTN impairment in LBD patients, although these deficits did not correlate with typical CVH measures. In the pareidolia task, it was found that LBD patients see more illusory images in noise and this was associated with (a) greater VP impairment and (b) greater CVH frequency and intensity. Surprisingly, we found that a greater percentage of healthy controls than LBD patients reported perceptual changes within the mirror-gazing task. Conclusions: We believe that the pareidolia task may be an effective clinical tool in objectively measuring CVH in LBD, and findings using this task are suggestive implicate impairment in top-down processing in the manifestation of CVH. Furthermore, findings from the mirror-gazing task could be suggestive of impairment in bottom-up processing in LBD hallucinators.

P.18

REM Sleep Without Atonia in Psychiatric Patients: Clinical Relevance to Lewy Body Disease

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Background: The close association between REM sleep behavior disorder (RBD) and neurodegenerative disorders has been previously established. The relationship, however, between REM sleep without atonia (RWA), which is a hallmark of RBD on polysomnography (PSG), and Lewy body disease (LBD) remains unclear. RBD and psychiatric symptoms often precede the clinical diagnosis of Parkinson's disease (PD)/dementia with Lewy bodies (DLB). Moreover, RBD has been increasingly reported in patients with psychiatric disorders. In this study, the clinical features of psychiatric patients exhibiting RWA and its relevance to LBD were investigated. Methods: We retrospectively reviewed the clinical profiles of 55 consecutive patients who underwent PSG at a psychiatric ward at Nagoya University Hospital. They were 32 men and 23 women with a mean age of 47 ± 22 (range: 18–73) years. Results: We excluded 25 patients with sleep apnea syndrome and identified 12 patients who exhibited RWA. Of the12 patients exhibiting RWA, seven had no episode of dream-enactment behavior, which corresponds to subclinical RBD. Two young patients fulfilled the clinical criteria for narcolepsy. In contrast, the other mid-dle-aged and older psychiatric patients with a mean age of 65 years exhibited clinical characteristics of LBD. Seven of 10 patients fulfilled the clinical criteria for PD (n = 1), DLB (n = 4) and idiopathic RBD (n = 2). The remaining three patients had clinical diagnosis of major depressive disorder and exhibited no episode of dream-enactment behavior. They partially shared common prodromal symptoms and radiological findings with PD/DLB: three had isolated occipital hypoperfusion and one had mild dopamine transporter deficit. Conclusions: The presence of RWA may be indicative of the underlying pathophysiology of LBD, even when RBD symptom is absent. Because it remains unknown whether middle-aged and older psychiatric patients with subclinical RWA are presenting the prodromal state of PD/DLB, continued follow-up of the patients will be needed.

P.19

REM Sleep Without Atonia May Help Diagnose Lewy Body Disease in Patients with Somatic Symptom Disorder

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Background: Lewy body disease (LBD), including Parkinson's disease (PD) and dementia with Lewy bodies (DLB), is defined pathologically as degeneration in the central and peripheral nervous system associated with Lewy bodies. It is well known that somatic symptom disorder often antedate the clinical diagnosis of PD/DLB. It is crucial to make the initial diagnosis of LBD in patients with psychiatric symptoms, because administration of psychotropic drugs often causes or exacerbates extrapyramidal signs. Given the close association between REM sleep behavior disorder (RBD) and LBD, REM sleep without atonia (RWA) on polysomnography (PSG) may help us to suspect LBD in patients with somatic symptom disorder. Methods: We reviewed clinical profiles of five patients with initial diagnosis of somatic symptom disorder who exhibited RWA on PSG. They were 3 men and 2 women with a mean age of 68.4 (range: 55–78) years. The mean Mini-mental state examination score was 26 (range: 22-30). Polysomnographic recording and scoring were performed according to the American Academy of Sleep Medicine Manual. The optimal cutoff values for RWA establishing a clear definition of RBD accompanying abnormal dream-enactment behavior by the SINBAR group were used. Results: Only two patients had a clinical history of dream-enacting behavior and fulfilled the clinical criteria for RBD. The cutoff value in the mentalis was valid for a correct diagnosis of RBD in five patients: clinical conditions corresponded to subclinical RBD in the remaining three patients. Final clinical diagnoses were made as probable DLB in three patients, but two patients did not meet the clinical criteria of PD/DLB. Both patients exhibited constipation. Moreover, cardiac [^{123}I]-metaiodobenzylguanidine scintigraphy revealed mild increased washout rates. Conclusions: Continued follow-up of the patients will be needed to determine whether these patients with somatic symptom disorder are presenting the prodromal state of PD/DLB.

P.20

Sense of Presence in Dementia with Lewy Bodies

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Objective: To report the phenomenon of a sense of presence in dementia with Lewy bodies (DLB) and provide clinical and neuroimaging characteristics. Background: The sense of presence is a false perception that a being, usually person or animal, is present in the immediate vicinity. The sensing person denies "seeing, hearing, or feeling" the being but "knows" it is present. The sense of presence can be said to differ from a hallucination in that one or more of the five sensory modalities is not involved, from an illusion because a sensory stimulus is not misinterpreted and from a delusion because the person reports not just a belief, but an actual sensation, of a being in his presence. In the popular literature, a sense of presence can be linked to the concept of a "sixth sense." While the sense of presence is rarely described in the neurologic literature, our experience within a Behavioral Neurology outpatient clinic is that a sense of presence is not uncommonly seen in patients with Lewy body disease. Methods: Case report. Results: We report a patient who met criteria for probable DLB who experienced the sense of presence. He often felt that people were around him, sometimes over his shoulder or following him, and could provide detailed description of the people, however denied actually seeing the people. These sensations were transient and not bothersome. We incorporate the patient's clinical findings, as well as structural and functional neuroimaging, to formulate a hypothesis as to the pathophysiology of the sense of presence. Conclusion: The sense of presence can be associated with DLB and vivid imagery can be associated with the sense even if visual hallucinations are not present. This phenomenon may be underreported in part as physicians do not differentiate this phenomenon from a hallucination or other type of misperception.

P.21

Olfactory Function in Mild Cognitive Impairment and Dementia Associated with Underlying Alzheimer's Disease and Lewy Body Disease

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Background: Olfactory dysfunction is well established in both dementia with Lewy bodies (DLB) and Alzheimer's disease (AD) dementia (ADem). Limited literature exists regarding olfactory function in mild cognitive impairment (MCI) preceding the development of these dementia syndromes. We hypothesized that olfactory function was lower in ADem and DLB compared to their correlating MCI states. Methods: We analyzed the olfactory function of normal control, MCI and dementia participants in the Alzheimer's Disease Research Center at Mayo Clinic using the Brief Smell Identification Test (B-SIT; range 0-12, with maximum score=12). Total B-SIT scores were analyzed across groups and between individual groups using the Kruskal-Wallis and Wilcoxon rank-sum tests respectively. Results: Data were available for the following groups: normal controls (n=31), mild cognitive impairment +/- REM sleep behavior disorder presumed associated with underlying Lewy body disease (MCI-DLB) (n=22), amnestic MCI presumed due to underlying AD (MCI-AD) (n=32), clinically probable DLB (n=19), and ADem (n=31). The median score on the B-SIT for controls was 11 (Interquartile range [IQR]=10-12), for MCI-AD and AD, lower at 7.5 (IQR=7-10) and 7 (IQR=4-9); and for MCI-DLB and DLB, the lowest at 6 (IQR=4-9) and 3 (IQR=2-7), respectively. In group comparisons, median score of the controls was significantly higher than all other groups. Conclusion: These data show reduced olfactory function in MCI associated with presumed underlying Alzheimer's disease and Lewy body disease. Whether olfaction decreases over the transition from MCI to dementia, and whether this is more profound in the DLB spectrum, will require longitudinal analyses in MCI subjects.

P.22

Autonomic Dysfunctions in Dementia with Lewy Bodies: An Aid in Diagnosis

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Background: Dementia with Lewy bodies (DLB) is the second most common cause of neurodegenerative dementia after Alzheimer's disease (AD) in people aged over 65 years. The differential diagnostic of DLB from AD is sometimes difficult when patients have just mild or moderate cognitive impairment. We hypothesized that autonomic dysfunction could be an important symptom to differentiate DLB and AD. The aim of our study was to (1) investigate dysautonomia in patients with DLB, AD and healthy elderly subjects, and (2) develop a questionnaire about autonomic dysfunctions, to differentiate DLB and AD. Methods: Forty one patients withDLB, 25 patients with AD and 16 healthy elderly subjects are included in the study. We compared the following autonomic dysfunctions between the three groups: anosmia, taste disorders, dry mouth/eyes/nose, rhinorrhea, sialorrea, watering, photophobia, constipation, sexual disorders and orthostatic hypotension. Based on these results, we proposed a questionnaire to differentiate DLB and AD. The sensitivity and the specificity of the questionnaire were estimated by a Receiver Operating Characteristics (ROC) curve. Results: Patients with DLB had significantly more autonomic dysfunctions that AD patients and healthy elderly subjects, concerning anosmia, taste disorders, dry mouth, dry eyes, rhinorrhea, constipation and photophobia. The questionnaire had a sensitivity of 83,3% and a specificity of 82,4% to differentiate DLB and AD. Conclusions: This study confirmed the high frequency of autonomic dysfunctions in DLB, contrary to AD. Our 7 items questionnaire differentiated DLB and AD with a sensitivity and a specificity superior to 80%. Further investigations are needed to confirm these results.

P.23

Polysomnographic Assessment of Sleep Comorbidities in Drug-Naïve Narcolepsy-Spectrum Disorders—a Japanese Cross-Sectional Study

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This is a large cross-sectional study which aimed to investigate comorbidity rate, degree of sleep-related breathing disorder, polysomnigraphically diagnosible rapid eye movement sleep behavior disorder/rapid eye movement sleep without atonia and periodic limb movements during sleep in Japanese drug-naïve patients with narcolepsy-spectrum disorders. A total of 158 consecutive drug naïve patients with narcolepsy with cataplexy, 295 patients with narcolepsy without cataplexy and 395 patients with idiopathic hypersomnia without long sleep time were enrolled. From retrospectively analyzed data of nocturnal polysomnography and multiple sleep latency test, higher rates of periodic limb movements during sleep (>=15 h-1) (10.2%) and polysomnographically diagnosable rapid eye movement sleep behavior disorder (1.9%) were found in patients with narcolepsy with cataplexy. They had more severe periodic limb movements during sleep especially during rapid eye movement sleep and higher percentages of rapid eye movement sleep without atonia than the other two patient groups. In the present large sample study, Japanese drug naïve patients with narcolepsy with cataplexy showed the highest comorbidity rates of periodic limb movements during sleep, polysomnographically diagnosable rapid eye movement sleep behavior disorder and rapid eye movement sleep without atonia among those with the other narcolepsy-spectrum disorders; the rates were lower than those for Western patients.

P.24

Possible Implications of Mild Cognitive, Neuropsychiatric and Motor Features in REM Sleep Behavior Disorder

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Background: Despite the well-established association between REM sleep behavior disorder (RBD) and the synucleinopathies, data regarding features predictive of eventual phenoconversion to mild cognitive impairment (MCI), dementia with Lewy bodies (DLB) or Parkinson's disease (PD) is sparse. Methods: We analyzed the demographic, clinical, and neuropsychiatric features of participants in a longitudinal research program with RBD (n=21) who did not meet established criteria for MCI, PD or DLB. Frequency and severity of neuropsychiatric (NP) features based on the 12 item Neuropsychiatric Inventory-short form (NPI-Q) were reviewed, excluding the item on sleep disturbances in order to avoid circularity. Results: Eight-one percent (17/21) were male with a mean age of 65.7 years, mean UPDRS motor subtest score of 1.3, mean Short Test of Mental Status score of 36 and mean Mini-Mental State Examination score of 28.9. The majority 12/21 (57%) had ≥2 neuropsychiatric features, with irritability (48%), anxiety (33%), depression and agitation (each 29%) being most frequent. Five of the seven cases with subjective cognitive complaints but normal performance on neuropsychological testing had ≥ 3 NP features. Among the cases with UPDRS >0 (n=7), 2 with subjective cognitive complaints had ≥ 5 NP features while 3 of the 4 who did not have complaints had ≤ 3 features. Conclusion: These findings might suggest that cases with NP features and subjective cognitive complaints may be on the course of phenoconversion to MCI/ DLB, whereas those with UPDRS >0 and low NP burden but without any cognitive symptoms may develop PD. Careful longitudinal assessment of RBD patients using cognitive, neuropsychiatric and motor testing may provide insights into the subsequent phenoconversion of RBD to MCI/DLB or PD.

P.25

Clinical Diagnosis of Dementia with Lewy bodies in Routine Secondary Care clinical Services: Results from The DIAMOND-Lewy Study

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Introduction: The aim of the 'Improving the diagnosis and management of neurodegenerative dementia of Lewy body type in the United Kingdom National Health Service (NHS)' (DIAMOND-Lewy) programme, which comprises multiple work packages, is to improve patient management and clinical outcome through the development, and subsequent assessment, of an evidence-based LBD practical management toolkit for clinicians. It has been estimated that only around one in 3 cases of DLB are currently detected in routine secondary care, despite the existence of validated diagnostic criteria. This component of the programme (Work Package 1A) includes a baseline assessment of DLB diagnosis in memory and dementia services within the NHS. Methods: The research team screened consecutive consultations at eleven memory/dementia services at sites in two areas, North East and Eastern England, over an 18 month period from January 2013. All contacts - initial assessment, review, ad hoc and emergency consultations were included. Results: Data collection is ongoing and to date case notes of over 8,500 individual patients, of whom 50% had a diagnosis of dementia, have been reviewed. Patients with DLB comprised 4-5% of all dementia cases, but there was considerable variation between different services, with prevalence rates ranging between 2% and 8% for individual services. Conclusions: The prevalence of clinically diagnosed DLB in secondary care services remains lower than that observed in neuropathological studies and there is considerable variation in rates of diagnosis between individual services, despite the existence of validated diagnostic criteria. Reasons for this might include limited recognition of core and suggestive clinical features, difficulty in translating recent advances in DLB research into clinical practice, and possibly also real differences in prevalence of the disease. A brief assessment tool incorporating the range of DLB symptoms, such as scales for visual hallucinations and fluctuations, suitable for use in routine practice, may help address this.

P.26

Figure Copy and Recall: A New Twist on Distinguishing Alzheimer Disease and Lewy Body Dementia?

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Background: Alzheimer disease (AD) and Lewy Body Dementia (LBD) have distinctive cognitive profiles, with episodic memory being more affected in AD and LBD patients typically exhibiting more impairments in executive and visuospatial ability. However, these differences may not be so evident on general cognitive screening tests. A validated, extended version of the Mini-Mental State Examination (MMX, MMSE) adds 20 points for memory, executive, and visuospatial functioning. The MMX was designed to address ceiling effects in the MMSE by expanding the distribution of high-end scores. It also includes a 4-point scoring scheme for both copying and reproducing the intersecting-pentagons figure after a brief delay. Methods/Design: We examined MMSE and MMX performance in 94 AD and 72 LBD subjects consecutively evaluated in a university memory clinic. In particular, we compared the distributions of MMX scores across different MMSE scores, focusing on the upper range. We also hypothesized that pentagon copy and recall might selectively distinguish AD and LBD patients, based on more impaired recall and copy, respectively. Results: AD and LBD patients had similar mean MMSE (20.7 vs. 21.4) and MMX (30.7 vs. 31.7) scores, respectively. MMSE vs. MMX plots showed a comparable range of MMX scores for a given high-end MMSE score across both groups. Among AD patients, 4 (4.3%) scored higher on figure recall than on copy, whereas 19 (26.4%) of LBD patients scored higher on figure recall than on copy ($X2 = 16.7$, $p<0.05$). Conclusions: Total MMSE and MMX scores are highly correlated in both AD and LBD patients. At the individual level, the MMX score may increase sensitivity to more subtle cognitive deficits than are evident by the MMSE score per se. About 25% of LBD subjects reproduced the figure better from memory than by copy, suggesting a double dissociation that may help distinguish it from AD.

P.27

Rate of Decline in DLB: Results from a Large Longitudinal Multicentre Cohort Study

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Objective: Dementia with Lewy bodies (DLB) is the second most common neurodegenerative dementia in older people following Alzheimer's disease (AD). DLB remains under-recognized in clinical settings and relatively little is known about its clinical course. By using data collected from a new pan-European consortium on DLB, here we describe the progression of cognitive decline in DLB. Methods: Data from patients with a clinical diagnosis of DLB (n=322), Parkinson's disease with dementia (PDD; n=111)) and AD (n=[123]) with 2 year follow up were collected from 20 centers in 13 European countries and 1 US center. Baseline clinical data, demographics, cognitive (Mini-Mental State Examination [MMSE]) and motor assessment (Unified Parkinson's Disease Rating Scale III [UPDRS III]) were included, and up to 2-year follow-up MMSE scores were analyzed. Results: There was a significant decline in MMSE score for DLB patients from baseline (mean (SD) 21.6 (4.9)) to 2-year follow-up (17.9 (7.2)), a mean (SD)3.7 (6.4) point decline. There were no significant differences in the rate of decline were found between DLB, PDD, and AD at year 2. In the DLB group multivariate regression analysis showed that greater MMSE decline was predicted by lower MMSE at baseline (B=0.218, p). Conclusions: In the largest DLB cohort to date, a significant cognitive decline over two years was observed, and changes were similar to those seen in PDD and AD. In DLB, a more rapid rate of decline is predicted by more severe cognitive and motor symptoms at baseline. Larger prospective studies on longitudinal course and prognostic values of different clinical and biomarker characteristics in DLB are needed.

P.28

Case Series: Behavioral Dysregulation in Individuals Diagnosed with Logopenic Progressive Aphasia

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Background: Diagnostic criteria for logopenic variant primary progressive aphasia (lvPPA) include slow rate of verbal expression due to pauses for word retrieval or verbal formulation, anomia with benefit from cuing, relatively spared single word comprehension with increased difficulty with complex sentence comprehension, impaired sentence repetition, and absence of agrammatic output (Gorno-Tempini et al., 2011). We identified 15 patients from a cohort of 60 who met criteria for lvPPA and had predominant parietal hypometabolism on FDG-PET (Krishnan et al., in review). Four of these 15 patients had striking behavioral dyscontrol and are described here. Methods: Review of the neurological, neuroimaging, genetics, and neuropsychological data on all four patients with striking behavioral dyscontrol. Results: All four patients were male who demonstrated strikingly similar behavioral dysregulation including extreme suicidal and homicidal ideation. The behavioral changes occurred approximately 7.25 years from illness onset and required emergent pharmacological intervention or inpatient hospitalization. Mean age: 65.5 years, age at onset: 62 years, illness duration = 5.9 years. All patients were APOE e4 positive, 3/4 patients were PiB positive and three were diagnosed with REM sleep behavior disorder. Neuropsychological evaluation showed significant deficits in attention, memory, and visuospatial skills. Most strikingly, 3 patients could not complete Trails B. Pathology was available for one patient and was consistent with diffuse Lewy body disease with co-existing Alzheimer's disease pathology (Braak NFT stage VI). Conclusion: There exists a subset of lvPPA patients with predominant parietal dysfunction who exhibit striking behavioral dyscontrol, possibly due to Lewy body disease. Recognition of such patients is important as they require unique pharmacologic management.

P.29

Impact of Armodafinil Therapy on Neuropsychiatric Features in Dementia with Lewy Bodies

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Background: Common features of DLB are excessive daytime somnolence and neuropsychiatric features of visual hallucinations, agitation, apathy, delusions, depression, euphoria and anxiety. While wake-promoting agents have been shown to improve somnolence in this population, no data have been gathered on their effect on neuropsychiatric features. Design: We conducted a 12-week open label pilot study using armodafinil 250 mg taken orally to investigate its efficacy on daytime somnolence in patients with DLB as a primary endpoint. In this study, we report secondary efficacy endpoints related to neuropsychiatric morbidity. Caregivers completed an abbreviated measure of neuropsychiatric symptoms using the Neuropsychiatric Inventory (NPI) at baseline and after 1, 2, and 3 months of therapy. Last-Observation-Carried-Forward (LOCF) method was used to impute the few missing data. Results: Twenty subjects (16 male) median age 72 years completed all baseline assessments, of which 17 subjects completed the three month protocol. Overall neuropsychiatric morbidity improved after 1 month of armodafinil therapy (p=0.002), and subsequent total NPI scores also were improved from baseline but not statistically significant. Specific neuropsychiatric features of visual hallucinations (p=0.001) and agitation (p=0.016) improved after 1 month of armodafinil therapy. The most notable NPI measure was apathy, with sustained improvement from baseline to months 1 (p=0.032), 2 (p=0.005), and 3 (p=0.006) of armodafinil therapy. No significant changes were noted in measures of delusions, depression, euphoria, or anxiety. Conclusions: Armodafinil therapy in our study population resulted in significant improvement of overall neuropsychiatric morbidity, visual hallucinations, and agitation early in the course of treatment. There was sustained improvement of apathy throughout the course of treatment. Our pilot study findings suggest improvement on some neuropsychiatric features of DLB with armodafinil.

P.31

Sleep Electroencephalography as a Marker of Cognitive Decline in Parkinson's Disease

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Background: Several studies have reported electroencephalographic (EEG) abnormalities during wakefulness in Parkinson's disease (PD) patients with or without dementia. Recently, our group has shown that sleep spindle perturbations were associated to later development of dementia in PD. However, few studies investigated rapid eye movement (REM) sleep EEG in PD and none has examined whether REM sleep alterations are associated with cognitive decline in this population. This longitudinal study aimed to evaluate non-REM and REM sleep abnormalities in PD patients according to their cognitive status at follow-up (mean: 4.5 years). Methods: Sixty-eight non-demented PD patients and 44 healthy controls underwent a polysomnographic sleep recording and a neuropsychological assessment. Power spectral analyses were performed on non-REM and REM sleep standard frequency bands in frontal, central, temporal, parietal, and occipital derivations. A ratio of slow-to-fast frequencies (delta+theta/alpha+beta) was also calculated for REM sleep. Analyses of covariance were performed when a significant correlation was found between EEG measures and clinical variables (i.e., disease severity, mood) to evaluate possible confounding factors. Results: At follow-up, 18 PD patients developed dementia (PDD) and 50 PD patients remained dementia-free (PDnD). At baseline, PDD patients showed reduced non-REM sigma power compared to PDnD patients (parietal, occipital) and controls (parietal). Enhanced non-REM beta power was also found in PDD patients compared to controls. In REM sleep, PDD patients showed a higher slowing ratio in all cortical regions compared to both PDnD and control subjects. PDD patients did not differ from controls on the ratio. Conclusions: Non-REM and REM sleep EEG abnormalities at baseline are more markedly impaired in PD patients who developed dementia. This study is in line with recent findings on altered sleep spindle activity (sigma) in PD associated with cognitive decline, and also suggests that REM sleep EEG slowing may be an early marker of dementia in PD.

P.32

The Dementia with Lewy Body - Alzheimer's Disease Continuum: A Striatal [18F]Fluorodopa Positron Emission Tomography Pilot Study

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Background: Dementia with Lewy bodies (DLB) is the second neurodegenerative dementia in autopsy series. However DLB represents a small proportion of clinical diagnoses in community studies. Concomitant of Lewy and Alzheimer's disease (AD) pathology is the main cause of the poor sensitivity of DLB diagnosis. DLB syndrome is indeed at the end of a pathological spectrum spanning from AD with occasional Lewy pathology to 'pure' DLB. Since pathological changes in substantia nigra are relatively specific to Lewy pathology in the context of an incipient dementia, we postulated that the extent could estimate the Lewy pathology burden in the whole brain, and we studied the correlation between the amount and intensity of DLB features and dopaminergic nigrostriatal dysfunction. Methods: A clinical score (LEwy pathology Screening in COgnitive Disorders LESCOD) was constructed from a selection of 36 putative clinical features of Lewy pathology divided into 9 categories (genitourinary dysfunction, othostatic hypotension, olfactory dysfunction, REM sleep behavior disorder, Parkinsonism, fluctuations, visiospatial/attention deficits and illusions/hallucinations). Nine patients (ongoing recruitment) with possible or probable AD with low, average or high LESCOD scores underwent [18F]fluorodopa Positron Emission Tomography (PET): caudate and putamen striatal to occipital ratio of [18F]fluorodopa were measured. Results: There was a correlation between LESCOD score and [18F]fluorodopa uptake values in the putamen (r=-0.85, p < 0.01) and in the striatum as a whole (r=-0.75, p < 0.02). No significant correlation was observed in the caudate (r=-0.56, ns). Conclusion: While our results need to be confirmed in a larger scale, we introduce a method to estimate Lewy pathology burden in AD through [18F]fluorodopa PET quantification of nigrostriatal dysfunction. Our pilot study paves the way to new clinical criteria to diagnose the Lewy body variant of AD.

P.33

Phenotyping Mild Cognitive Impairment to Aid Synucleinopathy Prediction

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Background: Community-wide screening is not yet feasible to detect early cases of dementia and as such current approaches need to focus on enriched cohorts. One potential population is those older adults who seek advice regarding memory complaints. In fact, many of these people will have Mild Cognitive Impairment (MCI), which represents an "at risk" state for conditions such as Alzheimer's (AD) and Dementia with Lewy Bodies (DLB). In addition, recent work has highlighted that the presence of Rapid Eye Movement sleep behavior disorder (RBD) is a potential preclinical marker for DLB rather than AD. This study sought to explore the presence of RBD in people with memory concerns. Methods: One hundred and forty-three consecutive community-dwelling volunteers with memory complaints underwent a comprehensive neuropsychological assessment and completed the RBD Questionnaire and the Geriatric Depression Scale. Results: Of the 143 participants (68 male), 62 were rated as non-MCI whilst 81 fulfilled criteria for a diagnosis of MCI. The presence of RBD was self-reported in 34 (24%) participants and MCI was confirmed in 24 (71%) of these RBD positive patients. Those with RBD were significantly more likely to have non-amnestic MCI (62%) than controls (29%) or amnestic MCI subjects (9%) ($\chi2 = 0.005$). Finally, a higher level of depressive symptoms was observed in RBD positive cases compared to those not reporting this symptom ($p = 0.042$). Conclusions: Results from the present study suggest that MCI patients with RBD were more likely to exhibit non-amnestic MCI rather than an amnestic phenotype, which was also associated with depressive symptoms. Such a cognitive and psychiatric profile is in keeping with patients who are ultimately diagnosed with DLB and suggest that targeting such patients with additional biomarker testing (smell, colour vision and transcranial ultrasonography) may help predict DLB.

P.34

Quantitative Analysis of REM Sleep Without Atonia in Neurocognitive Syndromes

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Objective: We aimed to determine whether quantitative REM sleep without atonia (RSWA) analysis aided distinction between patients with the neurocognitive syndromes of Dementia with Lewy Bodies (DLB) with and without REM sleep behavior disorder (RBD), amnestic mild cognitive impairment (aMCI), Alzheimer's disease (AD), and Frontotemporal Dementia (FTD). Background: RBD/RSWA is frequent in patients with synucleinopathies, especially DLB. Braak et al. have suggested an ascending pattern of synuclein accumulation. We hypothesized that patients with DLB+RBD would have greater RSWA than DLB patients without RBD, and those with presumed tauopathy and amyloidopathy pathologies. Design/Methods: Patients who underwent polysomnography (PSG) between 2008-2012 were included if they: (1) met diagnostic criteria for aMCI, AD, FTD, or DLB, and (2) had ≥1 supportive FDG-PET, neuropsychology, CSF amyloid/tau, or DaT-scan. Four groups were identified: AD/aMCI (n = 8), FTD (n = 6), DLB without RBD (DLB;n = 5), and DLB+RBD (n = 9). RSWA was determined by both visual and automated scoring. Regression analyses were used to control for significant demographic differences between groups. Results: Age at PSG and cognitive symptom onset was older in the DLB and DLB+RBD than AD and FTD groups. DLB+RBD patients had significantly greater RSWA than those with AD, FTD, or DLB without RBD, by both automated scoring (p = 0.0021) and visual scoring (p-value(p-value ranged < 0.0001 to 0.0031 for different indices). Correlation was moderately positive (R2 = 0.52) between automated and visual RSWA scoring). Conclusions: The DLB+RBD group had significantly higher RSWA than DLB without RBD, AD/aMCI, and FTD groups, suggesting that the subset of patients having DLB+RBD may follow a Braak-type caudal-rostral neurodegenerative course, whereas DLB without RBD may instead follow a different topography of synuclein accumulation. Automated RSWA analysis is a time-efficient and accurate tool for distinguishing DLB+RBD patients.

P.35

Cluster Analysis of Sleep Disorders and Dementia with Lewy bodies Using a Multidimensional Clinical Database

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REM sleep behavior disorder (RBD) is one of the symptoms that may precede the clinical diagnosis of Dementia with Lewy bodies (DLB) and a number of sleep abnormalities have been identified in patients affected with DLB that span beyond RBD. A retrospective study was conducted utilizing the DLB database of the University of Utah Movement Disorders Division to examine the association of RBD and other sleep related events to a series of preclinical and clinical symptoms of DLB. The database consisted of review of the occurrence of 25 of the most common symptoms of DLB coded from review of full medical record. Logistic regressions were used to identify the association of individual symptoms with sleep abnormalities. We observed that among 74 patients, 87.84% reported sleep abnormalities and sleep abnormalities were associated with multiple other symptoms. We observed patients with sleep abnormalities were more likely of presenting with the following symptoms: 10.51 times more likely to present with anxiety (p-value = 0.007), 12.9651 times more likely to present with bradykinesia (p-value = 0.002), 12.41 times more likely to present with cognitive fluctuations (p-value = 0.005), 19.07 times more likely to present with hallucinations (p-value = 0.001), 17.84 times more likely to present with memory problems (p-value = 0.001), 14.36 times more likely to present with saccadic eye movements (p-value = 0.002), and 15.16 times more likely to present with tremor (p-value = 0.001). Our findings support the presence of different phenotypical difference in the DLB patients with sleep abnormalities. These associations can be used to help in understanding the risk of DLB patients with sleep abnormalities to develop other symptoms and will ultimately translate improving physician's ability to create better care plans, earlier detection of symptoms, and resulting in a higher quality of life for the patient.

P.36

Dementia with Lewy Bodies in American Indians: A Case Series

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Background: American Indians are underrepresented in dementia research. To date, only one case series of two subjects has addressed the presence of Dementia with Lewy Bodies (DLB) in this population. The DLB Consortium has since revised the diagnostic criteria of DLB to include emphasis on suggestive features that may be incorporated into the diagnosis of possible or probable DLB. The present case series updates our knowledge of DLB in American Indians utilizing the current diagnostic criteria. Methods/Design: This retrospective case series describes clinical presentations of DLB in American Indians. Cases were identified through a query of the University of Texas Southwestern Alzheimer's Disease Center (UTSW ADC) database. Patients were evaluated at the Choctaw Nation Health Care Center in Talihina, OK, a satellite center of the UTSW ADC. Evaluations included detailed history, neurological examination, psychometric testing and other behavioral measures. Results: We identified ten patients of at least 50% American Indian ancestry, including five that were 100% as determined by their Certificate of Degree of Indian Blood, who reported DLB symptoms. Eight met criteria for probable DLB, and two met criteria for possible DLB. One case of possible DLB had pathologically confirmed Lewy Body variant of Alzheimer's disease. Median reported age of symptom onset was 76 years (range 51 to 81), which was on average two years before first evaluation by physicians specialized in dementia. Frequencies of core features were 90% with parkinsonism, 50% with hallucinations, and 30% with cognitive fluctuations. The only suggestive feature, dream enactment behavior consistent with REM behavior disorder, was present in 30%. These patients presented with an average mini-mental state examination score of 16.9 and an average Clinical Dementia Rating global score of 1.6 with a sum of boxes of 8.3. Conclusion: These cases together represent the largest known series of American Indians characterized with DLB.

P.37

Increased Mortality in Dementia with Lewy Bodies Associated with Reduced Prescription Rates for Anti-Dementia Drugs: A Naturalistic Study of Unselected Cases within Secondary Care

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Introduction: Previous studies of DLB have been based on select research cohorts, so little is known about the naturalistic patterns, characteristics and outcomes of the disease in everyday clinical settings. We used anonymization of routine clinical records to investigate naturalistic disease patterns, characteristics and outcomes of Dementia with Lewy bodies (DLB) compared with Alzheimer's dementia (AD). Methods: Using the Clinical Records Interactive Search (CRIS) methodology we were able to anonymise all clinical records for subjects aged >60 in a Trust providing secondary mental health care in England over an 8 year period. Using text searching followed by expert clinical review, we identified all cases of DLB diagnosed over this period, and a matched group of AD subjects (random 10% sample of all cases) for comparison. Results: 251 DLB cases and 222 AD cases were identified during the eight year period (2005-2012). DLB affected males and females equally and there was an approximately eight fold increase in DLB diagnoses across the study period. There was a significantly higher mortality rate for the DLB group compared with the AD group (38% vs 20%; p < 0.001), though no differences in age, cognitive function, or time from presentation to diagnosis between the two groups. Those prescribed anti-dementia drugs had a significantly lower mortality than those not on medication. Conclusion: In this naturalistic cohort we found an equal sex prevalence for DLB. Mortality in the DLB group was almost double that of the AD group. The reason for the higher mortality in this study was unclear, but the finding that mortality in DLB was associated with a reduced rate of anti-dementia drug prescription requires further study. CRIS methodology is a very powerful tool for the analysis of unselected cases in secondary care services.

P.38

Effect of Nelotanserin on Objective Sleep Parameters in a Phase 2 Study in Patients with Insomnia

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Background: Nelotanserin is a potent and highly selective 5-HT2a inverse agonist. Effects on sleep parameters in a Phase 2 study in patients with primary insomnia were evaluated to confirm CNS penetration and assess target engagement across doses. Methods: A randomized, double-blind, placebo controlled, three-way cross-over study in patients with primary insomnia was conducted. Patients received nelotanserin doses of 10mg and 40mg, or placebo at bedtime. Treatment duration was 7 days with a washout period of 7-9 days between treatments. Objective sleep parameters were assessed by polysomnography (PSG). Results: Nelotanserin produced statistically significant improvements in parameters of sleep maintenance and sleep consolidation. P-values reported below are pair-wise comparisons of nelotanserin to placebo.

	Wake after sleep onset (mins)	Number of arousals	Number of awakenings	Wake during sleep (mins)
Median Change from Screening - Modified Intent-to-Treat Population				
Placebo (n = 157)	-46.0	2.5	-1.5	-38.5
10 mg (n = 158)	-54.3 $p = 0.013$	-4.5 $p < 0.001$	-2.3 $p < 0.001$	-48.5 $p < 0.001$
40 mg (n = 158)	-49.8 $p = 0.199$	-7.0 $p < 0.001$	-2.3 $p < 0.001$	-45.8 $p < 0.001$

Conclusion: Nelotanserin produced statistically significant effects on objective sleep parameters with doses as low as 10 mg daily. These data indicate that nelotanserin reaches the target receptors in the CNS at clinically relevant doses, and supports its development in patients with Dementia with Lewy Bodies, a disorder commonly associated with serious sleep disturbances.

P.39

A Comparison of the Cognitive and Clinical Profiles of Prodromal Lewy Body Dementia and Prodromal Alzheimer's Disease

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Background: The clinical and neuropsychological profile of Lewy body dementia (LBD) is different to that of Alzheimer's disease (AD). Less is known about the cognitive profile and clinical features at the prodromal stage of mild cognitive impairment (MCI). Objective: To compare the clinical and neuropsychological profile of prodromal AD and LBD. Methods: Retrospective data from 415 MCI patients seen in the Neurocognitive Clinic between 1995 and 2015 were examined. All patients had a comprehensive assessment including history, neurocognitive testing (Cambridge Cognitive Examination-Revised, MMSE, Logical Memory Test, Trail Making Tests, word recall, letter fluency, naming) and physical examination including UPDRS score. RBD was assessed using the Mayo Sleep Questionnaire. Mann-Whitney tests were performed to determine whether there were differences on continuous test variables between MCI-LBD and MCI-AD groups. Chi-square and Fisher's exact tests were used to examine clinical features and gender. Results: Of the 415 patients seen, 21 (5%) patients converted to LBD and 115 (28%) converted to AD over a mean of 2.8 years. Patients in the MCI-LBD group performed significantly worse on Trail-Making Test, Letter Fluency and language expression. The MCI-AD group performed significantly worse on episodic memory tests. MCI-LBD patients also had significantly higher UPDRS score and were more likely to have visual hallucinations and RBD. There was a higher proportion of males in the MCI-LBD group. Conclusions: This preliminary analysis broadly confirms previous research showing that even at the MCI stage, there are clear differences in clinical features and cognitive profile between patients that will further progress to LBD or AD.

P.40

A Qualitative Analysis of Hallucinations in Dementia with Lewy Bodies

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Objective: To acquire qualitative information about hallucinations as one of the primary features of dementia with Lewy Bodies (DLB) through a new multidimensional questionnaire. Background: A key feature of (DLB) is hallucinations. McShane et al. implied that people who have Lewy Body pathology and have hallucinations have a more sever and rapid cognitive decline. There are some identifiable risk factors for experiencing hallucinations in DLB. First, medications can be notorious for causing hallucinations, particularly dopamine agonists. Other risk factors for DLB and hallucinations include lack of quality sleep (perhaps through life), vision impairment (differential of Charles Bonnet syndrome), anxiety and depression. The current study intends to identify other factors such as diet, mood, time of day, stress, as well as general fatigue. The current study also seeks to understand how this phenomenon affects the individual's life by asking self-report questions such as "Do [hallucinations] affect your daily life or your relationships with others?" Design/Methods: 2-part questionnaire administered to people affected by DLB. The first section of the questionnaire contains 25 questions directed towards the individual's observations and experiences with hallucinations. The next section contains seven questions and is designed for a third party who has observed the symptoms of the individual's DLB. Results: Preliminary results (14 responses from DLB patients after identifying and approaching 59 for a 24% response rate) reveal an intriguing variance of subjective interpretation/experience of hallucinations. For example, one individual adapted to the hallucinations with apathy, indifference, and minimization. Another constantly communicated with their spouse in order to better understand and cope with the symptom. Their adaptation was more akin to understanding and managing. Conclusion: This multidimensional questionnaire would be desirable for clinicians to obtain qualitative information from patients with hallucinations.

P.41

Dopamine Deficiency and Progression of Cognition in Dementia with Lewy Bodies

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Background: The nigrostriatal pathway is involved in motor, but also in cognitive (executive) functioning. In the diagnostic work-up of patients with a clinical diagnosis of dementia with Lewy bodies (DLB), the integrity of nigrostriatal neurons is commonly assessed by imaging the dopamine transporter (DAT) with [123I]FP-CIT SPECT. The aim of this study was to explore if the progression of cognition deficits is related to striatal dopaminergic deficiency in DLB. Methods: From a longitudinal dementia study in western Norway (n=266), 35 patients with probable DLB underwent [123I]FP-CIT SPECT brain imaging, 8 of these had normal scan results. Images were analyzed visually as well as semi-quantitatively by calculating a striatal binding ratio (SBR). Patient's cognitive functioning was assessed by mini-mental state examination (MMSE) with follow-up (FU) of five years. A linear mixed model (LMM) analysis was performed to assess the longitudinal development of MMSE during follow-up with [123I]FP-CIT SPECT results as predictor while including age, gender and education. Results: The LMM showed a significance interaction effect between follow-up time and [123I]FP-CIT SPECT results on MMSE decline using visual assessment (t=3.6 and p=0.004 at 3rd follow-up year). Patients with a normal visually evaluated [123I]FP-CIT SPECT scan or higher SBRs at baseline showed a more rapid progression of MMSE scores. When using three classes of SBRs (low, medium, high), the estimated mean MMSE was 24.2 in the low SBR class and 23.9 in the high class at baseline, while in the 3rd year of follow-up the MMSE declined in the low SBR class to 18.3 and in the high class to 11.8. The DLB patients with an abnormal scan (n=27) have numerically higher MMSE scores than the group with normal scans (n=8). Conclusion: More cognitive decline in patients with a normal [123I]FP-CIT SPECT scan at baseline may exist suggesting involvement of other pathologies.

P.42

An Analysis of Prognostic Counseling of Patients with Idiopathic REM Sleep Behavior Disorder

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Background: Prognostic counselling of patients with REM sleep behavior disorder (RBD) for phenoconversion to overt synucleinopathies including dementia with Lewy Bodies and Parkinson disease has not to our knowledge been previously analyzed. This topic is controversial given lack of disease-modifying interventions and uncertainty associated with prognosis. Objective: To analyze RBD patient and physician characteristics associated with the likelihood of prognostic counselling provided, as documented in the medical record. Methods: We conducted a retrospective chart review of 138 polysomnography-confirmed RBD patients diagnosed at Mayo Clinic between 2012-2015. We reviewed physician and patient demographics, initial complaint, and information discussed concerning phenoconversion risk between physician and patient as noted in the chart transcripts. Results: 65 (47.1%) of the 138 patient records reflected documentation concerning prognosis. Mean age of patients was 63.9 ± 13.5 years, and 100 (72.5%) were men. RBD was a secondary finding to the initial complaint in 87 (63%) of cases. Patients who reported dream enactment behavior, discussed RBD with their physician before polysomnography, and whose RBD was the primary initial complaint were significantly more likely to receive a prognosis concerning phenoconversion (all p < 0.05). Patients older than 60 years were more likely to receive a prognosis than younger individuals (p = 0.03). Compared to other sleep subspecialists, there was a trend toward greater prognostic documentation for sleep neurologists (p = 0.057), of whom men were significantly more likely to document disclosure than women (p = 0.0025). Conclusion: Several physician and patient specific factors appear to be significantlyassociated with the likelihood of prognostic documentation. Future surveys to assess physicians' thinking and patients' understanding and preferences are needed to determine whether physician behavior is appropriate and the reasons behind the identified differences in approach.

P.43

Delusions of Infidelity in Lewy Body Dementia

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Background: Lewy body dementia (DLB) is a common neurodegenerative condition. The core features of this disorder are Parkinsonism and perceptual disturbances; of which visual hallucinations are often the most commonly reported. Objective: To investigate the frequency of delusions in patients with Lewy body dementia. Methods: Retrospective cross-sectional survey of DLB patients in a community-based geriatric consultative service. We reviewed the clinical reports, including cognitive and behavioral assessment, and laboratory records of all patients with Lewy body dementia (DLB) seen in the Outpatient Geriatric Clinic from January 2013 – June 2015. We also examined some demographic data including age, gender, educational level and marital status. Results: We reviewed eleven patients who had been diagnosed with Lewy body dementia. Eight of these (66.67%) were males and 3 (33.33%) were females. The ages of patients ranged from 73 – 86 years. All the male and two of the female patients were married. Delusions and visual hallucinations were present in all 11 patients. Delusions of infidelity were the most commonly reported perceptual disturbance. It was present in 6 of the 8 male patients (75%). This was the most distressing behavior identified by the primary caregivers, who in all cases was the female spouse. Delusion of infidelity was not identified in the 3 female patients. Conclusions: Delusion of infidelity contributes to caregiving demands. Educating caregivers about this and other forms of perceptual impairments is imperative in the management of DLB.

P.44

Comparison of Performance on Montreal Cognitive Assessment in Patients with Dementia with Lewy Body Disease vs Alzheimer's Dementia

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Background: It is difficult to differentiate dementia with Lewy bodies (DLB) from Alzheimer's dementia (AD) in the early stage. Previous studies suggested that DLB patients performed worse on executive function, attention and visual spatial skills, but better in delayed recall when compared with AD patients in detailed neuropsychological assessments. Montreal cognitive assessment (MoCA) is a simple test which gained popularity in initial assessment of the patients with dementia. We assessed if MoCA can differ between these two groups. Methods: The data for two groups of patients who came for initial evaluation at our memory were collected for this cross sectional study. They had been diagnosed as probable DLB (n= 71) and AD (n= 57), respectively, according to the clinical criteria of the consortium on DLB, National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorder Association. Results: The mean age at initial visit was 71.8+/- 10 for AD patients and 73.2+/- 7.3 for DLB patients. The disease duration was 3.1+/- 1.7 for AD and 3.5+/-2.3 for DLB patients. We performed ind. t-Test to compare the cognitive domains of MoCA in 2 groups: AD patients performed significantly better than DLB patients on the visuospatial/executive tasks (p-value 0.009 effect size: 0.465) . However, the DLB patients out-performed the AD patients on delayed recall (p-value < 0.001 Effect size 0.609). There was no significant difference in other domain of testing. Interestingly, When we split up clock drawing from trail test and cube drawing, Visuospatial score is no longer significant, but executive and clock numbers are significantly worse in DLB patients compared to AD (p-value 0.001 and 0.002 respectively). Conclusion: The results of the present study show that the pattern of cognitive dysfunction in MOCA testing, in terms of executive functions and delayed recall differ between patients with DLB and patients with AD.

P.45

Differences Between Patients with Prodromal Dementia with Lewy Bodies and Prodromal Alzheimer's Disease with Memory Complaints as Presenting Symptom

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Introduction: Both DLB (Dementia with Lewy Bodies) and AD (Alzheimer's Disease) can present with memory complaints. It is difficult to differentiate between these diseases in the absence of other core criteria. In this study we tried to identify differences between patients who presented with memory complaints and were later diagnosed with DLB or AD. Methods: This is a retrospective study in which 56 patients, who presented with memory complaints, were included. Patients visited the memory clinic of the Erasmus Medical Center Rotterdam, The Netherlands, between 2008 and 2015. 25 patients were later diagnosed with probable DLB (mean: 18 months, min-max: 2-68 months) and 31 patients with AD (mean: 8 months, min-max: 2-43 months). Neuropsychological assessments and hippocampal volumes at first visit were compared with the use of analysis of covariance. Results: Patients with prodromal DLB scored significantly better on orientation in time and on the Visual Association Test, and significantly worse on Category and Letter Fluency than patients with prodromal AD. No other significant differences on neuropsychological tests were found. No differences were seen in hippocampal volumes between the groups. Discussion: Typical differences between DLB and AD on executive functioning, visuospatial ability or attention were not found. Smaller hippocampal volumes in AD in comparison to DLB were neither found. This might be due to the prodromal stage of the diseases or to the subgroup of DLB patients with memory complaints as first presentation. This study shows that differentiating between patients with prodromal DLB or prodromal AD, who present with memory complaints, is difficult. More research to identify better markers for differentiating between the prodromal stages of these diseases is necessary.

P.46

Sleep Onset REM with Prolonged Sleep Latency in Progressive Supranuclear Palsy But Not Corticobasal Syndrome

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Background: Few studies have investigated the sleep in Progressive supranuclear palsy (PSP), a 4 repeat (4r)-tauopathy. This disease may be particularly affected by sleep disruption as early neurodegenerative processes start in the brainstem, within areas associated with sleep/wake regulation. We hypothesized that PSP have poorer overnight sleep and are sleepier during the day compared to controls and Corticobasal syndrome (CBS), another 4R-tauopathy.
Methods/Design: PSP (n=17; 11 men; mean age: 69.8 ± 5.8 years), CBS (n=6; 4 men; mean age: 66.5 ± 9.4 years) and clinically healthy controls (n=12; 6 men; mean age: 72.7 ± 3.9 years) were studied at UCSF with overnight polysomnography and a multiple sleep latency test (MSLT) the next day. Results: Periodic limb movements were increased in PSP (60%, Con: 18% and CBS: 0%). PSP had increased time to sleep onset ($p < 0.01$), less total sleep time ($p < 0.01$) and increased wake during the night ($p < 0.05$) compared to controls. Strikingly, REM sleep was decreased in PSP compared to both controls ($p < 0.01$) and CBS ($p < 0.05$). Further, PSP took longer to enter REM sleep during the night compared to controls ($p < 0.05$). During the MSLT, PSP took longer to fall asleep as compared to both controls ($p < 0.001$) and CBS ($p < 0.05$). However, of the PSP that fell asleep during the nap trials, 33% had sleep onset REM episodes. Conclusions: Sleep disorders were increased in PSP, including increased insomnia-like features. In contrast to our hypotheses, PSP did not appear sleepier on the MSLT as compared to controls or CBS. The observed sleep onset REM during an MSLT with prolonged sleep latencies are both unexpected and novel. Our findings suggest, that regulatory mechanisms of sleep/waking as well as REM sleep are disrupted in PSP, and that these disruptions are specific to PSP and do not generalize across 4R-tauopathies.

P.47

Multidimensional Open-Access Clinical Database for DLB Diagnosis

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Objective: To establish a multidimensional database and evaluate the presentation of the symptoms most relevant to Dementia with Lewy Bodies (DLB). Methods: Office visit records were reviewed for 74 DLB patients with established care at the University of Utah Movement Disorders Clinic over a 12-month period. Twenty-five symptoms were coded for presence, severity, and progression using a REDCap database software platform. A total of 132,825 symptoms were coded. Two independent raters coded 11,891 symptoms resulting in a concurrence rate of 98.31% (1.10% symptom presence discrepancies, 0.27% severity discrepancies, and 0.31% progression discrepancies). Basic demographic information, medication history, and lifetime diagnosis code assignments were recorded. Results: We observed the co-occurrence of multiple symptoms. Statistically significant associations were observed when more than 12 other symptoms were clustered for the following symptoms: anxiety, balance impairment, bradykinesia, cognitive fluctuations, constipation, depression, fatigue, frequent falls, hallucinations, memory impairment, motor impairment, pain, rigidity, sleep abnormalities, and tremors. All symptoms were present in over 60% of cases whereas balance impairment, bradykinesia, fatigue, frequent falls, memory impairment, pain, rigidity, and sleep abnormalities were present in over 90% of cases. The spectrum of the reported symptoms was discussed during 68.45% of first office visits, excluding discussion of anosmia, apathy, erectile dysfunction, perspiration reduction which were seldom reviewed despite symptom presence: anosmia (24.53% discussed, 66.67% present), apathy (9.43% discussed, 70% present), erectile dysfunction (13.52% discussed, 88.89% present), and perspiration reduction (5.67% discussed, 60.00% present). Lack of discussion of anosmia, apathy, erectile dysfunction, and perspiration reduction may be attributable to priority given to symptoms most disruptive to the patient's life and/or the patient or clinician not associating the symptoms to DLB. Low evaluation rates for the select symptoms paired with high prevalence rates, suggests addressing these symptoms may provide clinicians increased evidence for diagnostic and treatment decisions.

POSTERS - GENETICS

P.48

APOE and TOMM40 Association with Lewy Body Disease and Other Dementias

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Background: APOE ε4 carrier status is a strong risk factor for Alzheimer's disease (AD) and a risk factor for cognitive impairment across the Lewy body disease spectrum (LBD). AD GWAS have identified SNPs within both APOE and TOMM40. Objective: Since many APOE ε4 non-carriers develop AD, the objective was to examine the association between TOMM40 SNPs and dementia subtypes in APOE e4 non-carriers (ε3/ε3). Methods/Design: Seven categories were tested for an association between dementia and SNPs within the TOMM40 gene, rs2075650 and rs59007384 as well as SNPs that define APOE ε2, ε3, and ε4 (rs429358, rs7412): 1) High-levels of AD pathology and no LBD (AD; n=253). 2) High-levels of both AD and LBD pathology (LBD-AD; n=252). 3) LBD and no or low levels of AD (DLB; n=99). 4) Parkinson disease (PD) dementia with high-levels of AD pathology (PDD-AD; n=25). 5) PD dementia with LBD and no or low levels of AD pathology (PDD; n=47). 6) PD without dementia and with no or low levels of AD pathology (PD; n=27). 7) Clinically diagnosed PD with and without dementia (cPD; n=1193). All categories were compared to controls with no or low level of AD pathology and no LBD (controls; n=278). Results: There was an association between APOE ε4 and TOMM40 SNPs and AD, LBD-AD, pDLB and PD. Within the APOE ε4 non-carriers there was an association between TOMM40 rs2075650 and disease for the AD, LBD-AD and marginally with pDLB groups, but not PDD-AD, PDD or PD, and not cPD, compared to controls. Conclusions: Within the APOE e4 non-carriers the association remained between the TOMM40 SNP and AD, LBD-AD, and pDLB, but not PD, suggesting that multiple SNPs at the TOMM40/APOE locus may play a role in the pathophysiology of both AD and LBD, but not PD.

P.49

Direct Genotyping of the APOE E2, E3 and E4 Haplotypes in a Large International Cohort of Neuropathologically Diagnosed Dementia with Lewy Bodies Cases

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In order to better understand the clinical and neuropathological similarities between dementia with Lewy bodies (DLB), Alzheimer's and Parkinson's diseases (AD and PD, respectively) we have recently performed an association of 54 genomic regions previously implicated in AD or PD in a large cohort of DLB cases and controls.[1] The results showed that the APOE locus presents the strongest genetic association with DLB, confirming previous findings[2] (top hit: rs769449, p=7.09x10-35, OR=2.7)1. However, due to the use of a genome-wide genotyping platform to perform these associations it was not possible to establish conclusively that the association at this locus represented an association with the APOE-E4 allele, even though this is expected given the high linkage disequilibrium between the variants (R2=0.8; D'=1 in the 1000 Genomes population between the top hit rs769449 and the rs429358 of the APOE-E4 haplotype). In this way, we have directly genotyped both SNPs contributing to the APOE- E2/E3/E4 haplotype (rs429358 and rs7412) in most of the same samples (n=773), using a previously described PCR-RFLP method.[3] The results from this study will allow us to unequivocally establish if the association peak observed at the chromosome 19q13.2 region is being driven by the APOE-E4 allele. Refs. 1. Bras J, Guerreiro R, Darwent L, et al. Genetic analysis implicates APOE, SNCA and suggests lysosomal dysfunction in the etiology of dementia with Lewy bodies. Hum Mol Genet. 2014;23:6139-6146. 2. Tsuang D, Leverenz JB, Lopez OL, et al. APOE epsilon4 increases risk for dementia in pure synucleinopathies. JAMA Neurol. 2013;70:223-228. 3. Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. Journal of lipid research. 1990;31:545-548.

P.50

C9ORF72 in a Large International Cohort of Neuropathologically diagnosed Dementia with Lewy Bodies Cases

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In 2011 a large intronic hexanucleotide expansion in C9ORF72 was shown to be the genetic cause of 9p21-linked frontotemporal dementia and amyotrophic lateral sclerosis cases[1,2]. Since then this expansion has been shown to be the most common genetic cause of familial ALS, FTD and ALS-FTD, as well as contributing to sporadic forms of these diseases. C9ORF72 expansions have also been seen associated with other clinical phenotypes including primary lateral sclerosis, progressive muscular atrophy, corticobasal syndrome and Huntington-like disorders[3]. Additionally, and more relevant to this study, the presence of C9ORF72 expansions has been identified in non-motor phenotypes including Alzheimer's disease[4] and Dementia with Lewy bodies (DLB)[5]. The identification of two DLB cases with expansions was done by screening 102 consecutive patients who fulfilled criteria for 'probable DLB' exhibiting at least two cardinal features (fluctuating cognition, recurrent visual hallucinations and parkinsonism, or one cardinal feature together with rapid eye movement sleep disorder). However, given the atypical clinical presentation of both DLB patients, the possibility of both being rare examples of a phenotype of FTD that mimics DLB was proposed[6]. In this way, the role of C9ORF72 expansions in DLB remains unclear. To address this issue we are currently determining the presence of pathogenic C9ORF72 expansions in a large cohort of neuropathologically confirmed DLB cases (n=650). DNA was extracted from brain tissue using standard procedures and we are using a fluorescent repeat-primed polymerase chain reaction assay to detect abnormal hexanucleotide (GGGGCC) repeat expansions (>30 repeats) within the C9ORF72 gene following the protocol previously described[1]. results from this study will conclusively resolve the role of C9ORF72 expansions in the etiology of DLB. References 1. Neuron. 2011;72(2):257-268. 2. Neuron. 2011;72(2):245-256. 3. Am J Hum Genet. 2013;92(3):345-353. 4. N Engl J Med. 2012;366(3):283-284. 5. Psychosis, J Neurol Neurosurg Psychiatry. 2012;83(10):1031-1032. 6. Cognitive and behavioral neurology. 2008;21(3):157-163.

P.51

MAPT Haplotype H1G is Associated with Increased Risk of dementia with Lewy Bodies

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Background: Dementia with Lewy bodies (DLB) is among the most common forms of dementia in the elderly, yet little is known about the underlying genetic risks. The microtubule associated protein tau (MAPT) gene has been associated with several tauopathies and synucleinopathies and specifically, the 900Kb MAPT haplotype H1 is associated with increased risk of disease. Recently, Bras et al. examined the role of MAPT in DLB, and although the association did not reach genomewide significance, the odds ratio of 0.78 is very similar to what has been observed previously for the protective H2 haplotype in other synucleinopathies. Methods: We were interested in understanding the role of MAPT haplotypic variation in determining risk of DLB. In order to assess diversity at the locus, we genotyped six MAPT haplotype tagging SNPs: rs1467967, rs242557, rs3785883, rs2471738, rs8070723, and rs7521 and screened a total of 431 patients with clinical DLB, 347 pathologically confirmed high-likelihood DLB/Lewy body disease (LBD) patients, as well as 1049 healthy controls. Separately for the clinical DLB and high-likelihood DLB LBD patient groups, haplotype frequencies were compared to controls using score tests of association with adjustments for age and gender. Results: Our analysis showed that a relatively rare MAPT haplotype, H1G, was associated with increased risk in clinical DLB compared to healthy controls (3.3% vs. 1.0%, OR=3.30, p=0.0017). This association was replicated in our high-likelihood DLB LBD series (2.6% vs. 1.0%, OR=2.26, p=0.035). Conclusion: These results support a role for H1G in disease risk, however, the exact functional variant at the locus is still unknown and additional studies are warranted to fully explain the genetic risk of DLB at the MAPT locus.

P.52

Rare MAPT Mutant p.A152T Increases the Risk of Dementia with Lewy Bodies

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Background:The microtubule associated protein tau gene (MAPT) variant c.454G>A (rs143624519; p.A152T) has been shown to increase risk of frontotemporal dementia spectrum disorders and Alzheimer's disease. Given that the MAPT locus is also a well-known risk factor for several synucleinopathies and additionally, a recent study by Bras et al. suggested a potential risk for dementia with Lewy bodies (DLB), we wished to assess the role of MAPT p.A152T with respect to risk of DLB. Methods: We therefore screened 442 patients with clinical dementia with Lewy bodies (DLB), 351 pathologically-confirmed high-likelihood DLB/Lewy body disease (LBD) patients and 1679 healthy controls collected at Mayo Clinic and evaluated the association between p.A152T and disease risk through a case-control study. Results: We detected 6 carriers of the mutant p.A152T in our DLB series, 3 in our LBD series and 4 in our control series. These observations result in a significant association of p.152T with clinical DLB (minor allele frequency (MAF): 0.68%, OR: 5.76, 95% CI: 1.62-20.51, p=0.007). The variant was also more common in the high-likelihood DLB LBD group compared to controls (MAF: 0.43% vs 0.12%, OR: 3.61, 95% CI: 0.80-16.20) but this was not significant (p=0.09). Conclusion: Taken together, our findings show that MAPT p.A152T is a rare low penetrance variant that increases risk of DLB. Considering the rare frequency of the variant, additional studies using greater sample size will be needed to further define the precise role of variant p.A152T in the etiology of DLB.

P.53

First GWAS in Lewy Body Dementia: APOE, APOC1, TOMM40 and PVRL2 Associated with DLB in Norway

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Introduction: No genome wide association study (GWAS) has yet been reported in Lewy Body Dementia (DLB). Previous genetic studies have found APOE, GBA, SCARB2 and SCNA to be associated with DLB in both clinically diagnosed and neuropathologically confirmed cases and so far none of the new Alzheimer's disease risk genes have been associated with DLB. Methods: We analyzed 201 cases diagnosed with possible DLB (n=28) or probable DLB (n= 173) and 1011 healthy controls from the Norwegian DemGene-consortium genotyped with the Illumina Omni Express Chip and performed standard quality control and analysis. We selected a p-value < 5 e-08. Results: The strongest associated loci correspond to: APOE, PVRL2, TOMM40 and APOC1. Further analyses are ongoing and the results will be presented at the meeting. Conclusion: We present the first GWAS in DLB confirming known associated risk genes from Alzheimer's disease. APOC1, TOMM40 and PVRL2 have not been previously associated with DLB. We suggest that these findings should be confirmed in independent samples, and suggest establishing a larger DLB consortium to reveal the genetic underpinnings in DLB.

P.54

E-DLB Genetics: Existing European Lewy Body Dementia Cohort Studies United in New Consortium

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Introduction: A joint effort to harmonize different clinical and biomarker protocols across Europe in multi-center cohort-studies in Lewy-body dementia (DLB) was finalized end June 2015 by a DLB work group for the EU joint programme in Neurodegenerative Disease Research (JPND). Compared to in AD and PD very few new risk genes have been identified in DLB applying next generation sequencing (NGS). The main challenge at present is collecting big enough DLB cohorts to have adequate power in bio statistical analyses. Aims: Identify available longitudinal DLB cohorts and develop methods for data pooling of DNA and clinical and biomarker data. Methods: Building on one national Norwegian dementia genetics consortium (DemGene) and an ongoing JPND funded project: Pre-clinical genotype-phenotype predictors of Alzheimer's disease and other dementias (APGeM) one of the work packages in E-DLB focused on identifying existing DLB cohorts with available DNA to initiate NGS studies including a well powered GWAS in DLB. Results: By now 5 new cohorts collecting DNA from persons diagnosed with DLB are available for data pooling in a new E-DLB genetics consortium. In total DNA from more than 630 persons diagnosed with DLB was made available for genotyping. Conclusions: A new European JPND funded DLB effort, E-DLB, the Norwegian DemGene and the European APGeM consortia have united ongoing DLB cohort studies and increased sample size making Next Generation Sequencing more feasible in DLB and new cohorts are welcome to join the E-DLB genetics consortium.

P.55

The Heritability of Lewy Body Dementia

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Background: Lewy body dementia (LBD) is a common form of dementia in the elderly population affecting approximately 1.4 million people in the United States. The pathogenesis of LBD is poorly understood. Similar to other adult-onset neurodegenerative diseases, a small proportion of familial cases have been described suggesting the existence of a genetic predisposition. To investigate the role of common genetic variants in the LBD pathogenesis, we performed a heritability analysis. Methods: We used Genome-Wide Complex Trait Analysis (GCTA) to estimate the heritability of LBD due to common variants in 158 pathologically confirmed, Caucasian LBD cases and 998 controls. Results: The heritability of LBD due to common variants was estimated to be 29%, which is comparable to the heritability of Parkinson disease. Conclusion: This is the first study that estimates the heritability of LBD due to common variants. Our results support the hypothesis that common genetic risk factors play a role in the pathogenesis of this devastating neurodegenerative disease. Additional studies investigating the role of heritability in non-Caucasian populations and exploring the role of rare variants are required for a complete resolution of the heritability in LBD.

P.56

Probing the Link Between Glucocerebrosidase Mutations and Synucleinopathies

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Background: Mutations in the lysosomal enzyme Glucocerebrosidase (GBA) have been associated with increased risk of developing both Dementia with Lewy bodies (DLB) and Parkinson's disease (PD) even in heterozygots. The link between GBA mutations and the clinical phenotype of DLB and PD, specifically in the cognitive domain has not been explored. Methods: A cohort of Ashkenazi Jewish PD patients (n=1517) and DLB patients (n=27 – recruitment ongoing) were included. Subjects were genotyped and undertook detailed neurocognitive and neurological assessments. Results: We found very high GBA mutation carrier rates among DLB patients (43%) and PD patients (20%), compared with the 6% GBA carrier rate among healthy Ashkenazi Jews. We found that both DLB and PD patients who carry mutations in the GBA gene have a lower age of onset than non-carriers (65.1 vs 70.6 in DLB group and 54.3 vs 62.2 in PD group) with severe GBA mutation carriers having a lower age of onset than mild mutation carriers. Rates of REM sleep behavior disorder were higher among the mutation carriers in both the DLB and PD groups. Among the DLB patients, GBA mutation carriers had higher rates of visual hallucinations (80% vs 60%). DLB patients with GBA mutations had lower scores on MoCA (18 vs 24) and more severe motor parkinsonism. Among PD patients, performance on cognitive testing was affected by GBA mutation type in a graded fashion with severe mutation carriers performing worst, then mild mutation carriers followed by non- carriers. Discussion: These findings indicate that patients with PD and DLB who carry GBA mutations present with a markedly different clinical phenotype in comparison to those who do not carry such mutations. Additionally, the specific mutation type (mild vs severe) appears to affect the severity of the disease.These findings strongly support a central role for GBA mutations in the pathogenesis and clinical phenotype of both these diseases.

P.57

Next Generation Sequencing of Alzheimer's and Parkinson's Disease Genes in Neuropathological Confirmed DLB, PDD and AD Cases

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Background: Next-generation sequencing (NGS) has been useful in gene discovery for complex genetic disorders. We sought to use a NGS-based comprehensive panel to identify pathogenic variants in a large sample of autopsied subjects with dementia. Methods: Subjects were classified as having neuropathologically confirmed Alzheimer's disease (AD; n=117), Lewy body dementia with Alzheimer's disease (LBD-AD; n=102), pure dementia with Lewy bodies (pDLB; n=53), and Parkinson's disease dementia (PDD; n=24). For each individual, we screened the entire coding region of 27 causative genes for PD and neurodegenerative dementias as follows: sample libraries were constructed and enriched for the genes of interest using xGEN custom probes. Using Illumina technology, >100X mean sequence coverage was generated for each sample; the resulting sequences were aligned to the human genome reference (hg19). We excluded those variants that did not meet standard quality values, those with >1% minor allele frequency in the Exome Aggregation Consortium (ExAC) database and those classified as low impact by SnpEff prediction tools. Results: Thirteen potentially pathogenic variant changes were identified, each in a different subject, including 3 high-impact changes (e.g., stop-gained, frameshift mutations) and 10 moderate-impact changes (e.g., missense mutations, in-frame deletions). Two of the three high-impact variants and 7 of the 10 moderate-impact variants were previously reported but with very low frequencies in ExAC (< 0.0001). Ten of the 13 variants were found in subjects with LBD. Interestingly, three LBD-AD and one PDD subject habored novel moderate-impact variants located in a gene previously implicated for PD, EIF4G1. Conclusions: Using a custom genetic sequencing panel, we identified potentially pathogenic variant changes in ~6% (10 out of 179) of subjects with LB pathology. Our findings suggest that NGS methods are likely to uncover meaningful genetic changes and should be incorporated in future studies of LBD.

POSTERS - Molecular Biology and Models

P.58

Analysis of Primary Visual Cortex in Dementia with Lewy Bodies Indicates GABAergic Involvement Associated with Recurrent Complex Visual Hallucinations.

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Background: A frequent finding in DLB is the presence of recurrent complex visual hallucinations (RCVH), along with the presence of glucose hypometabolism on imaging of the primary visual cortex. Design: We comprehensively analysed the primary visual cortex in post-mortem tissue taken from DLB patients to determine its role in the generation of RCVH. Results: Pathological investigation showed a paucity of alpha-synuclein pathology or neurofibrillary tangles and stereological analysis of neurones showed no change in density or volume in the primary visual cortex in DLB. However, although GAD65/67 immunohistochemistry showed no reduction in interneurone number, microarray analysis demonstrated an altered neuropeptide profile and changes in GABAergic markers in the primary visual cortex in DLB, suggesting that GABAergic neurones were structurally intact but functionally abnormal. These findings were supported by a significant loss of post synaptic GABA markers, such as gephyrin, GABARAP and Kif5A, along with decreased synaptophysin, suggesting altered synaptic activity. Postsynaptic glutamatergic neuronal signalling was also affected, with a reduction in vesicular glutamate transporter protein expression and PSD-95 expression. Conclusions: These changes support the concept of decreased inhibitory neurone activity and enhanced glutamatergic neuronal excitability within the primary visual cortex in DLB. It may be possible to reduce RCVH in DLB through targeting GABA neurones using selective GABAergic modulation or similar approaches using glutamatergic modification.

P.59

Modeling the Link Between Glucocerebrosidase Deficiency and Parkinsonism in Mice Reveals an Effect of GBA Haploinsufficiency

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Gaucher disease (GD) results from deficient lysosomal glucocerebrosidase (GCase). Mutations in glucocerebrosidase (GBA1) are a common risk factor for both dementia with Lewy bodies (DLB) and Parkinson disease (PD). In vivo mouse models of GD and PD were used to explore the association between these disorders. Transgenic mice hemizygous (hemi) or homozygous (homo) for human mutant A53T alpha-synuclein (α-syn) were crossed with heterozygous null gba mice (wt/ΔMGC), resulting in animals overexpressing mutant α-syn with a null gba allele (wt/ΔMGC//α-syn) as well as wt/wt, wt/α-syn and wt/ΔMGC mice. All were followed for 2 1/2 years, and monitored for weight changes and neurological symptoms. In wt/ΔMGC//α-syn mice, weight loss occurred first, followed by back arching, impaired axial rotation and limb paralysis. Mice were then euthanized along with their respective controls. Survival analysis studying 84 mice showed that wt/ΔMGC//α-syn hemi- and homo mice exhibit symptoms 9.76 weeks and 4.04 weeks earlier than α-syn hemi- and homo controls, respectively (p-value 0.023, 0.0030) and had a faster progression (p-value <0.0001). In 17 mice, quantification of α-syn aggregates in the pons indicated no significant differences between wt/ΔMGC//α-syn and α-syn mice. GCase activity and protein levels were comparable in wt/ΔMGC and wt/ΔMGC//α-syn mice. Similarly, α-syn levels did not differ between wt/ΔMGC//α-syn and α-syn mice. A whole transcriptome array performed on brain from mice with the different genotypes identified several candidate modifier genes, validated by real-time PCR. Interestingly, H2-T10 (3.37*10-12: fold change=6.98) was up-regulated in only wt/ΔMGC//α-syn mice, suggesting its potential role in the earlier and more severe phenotype observed. Preliminary ultrastructural and immunostaining studies of striatum, substantia nigra and midbrain show enhanced microglial activation and astrogliosis in wt/ΔMGC//α-syn mice. These data suggest that haploinsufficiency of GCase coupled with α-syn overexpression impacts disease onset and severity, and may be related to acute brain inflammation.

POSTERS - Neuroimaging

P.60

Cortical Sulci Modifications at the Prodromal Stage of Dementia with Lewy Bodies

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Introduction: The description of pro-DLB remains in its infancy although a prodromal phase of DLB has now been demarcated in DSM-V as mild neurocognitive disorder of Lewy body disease and preliminary descriptions of pro-DLB criteria have recently been described. We recently demonstrated the existence of insula atrophy at the early stage of DLB. The aim of this study is to describe cortical sulci modifications in prodromal DLB. Methods: We used four groups: 45 prodromal DLB (pro-DLB), 13 demented DLB (DLB-d), 13 prodromal AD (pro-AD) and 20 healthy elderly controls (HC). T1-weighted scans were processed using Morphologist 2012, a toolbox of BrainVISA (http://brainvisa.info). For each subject, 125 sulci were automatically extracted. For each sulcus, the average distance between the two walls of the pial surface was computed. This distance provides an estimation of the local atrophy leading the fold to open up. For each sulcus, after removal of age and sex effects using a linear model, Wilcoxon rank tests were used to compare groups. P-values are reported using the sulcus atlas of brainVISA, with FDR correction. Results: Pro-DLB patients had opening sulci in the left anterior insula and the right frontal lobe. Patients with d-DLB had opening sulci in frontal lobes including right anterior cingulate, left temporal lobe, left anterior insula and right occipital lobe. Differences between pro-DLB and pro-AD were in the medial temporal lobes. Conclusion: Pro-DLB patients have clear modifications of sulci in insula and right frontal lobe, and then larger modifications at the stage of dementia. Further studies are now needed to understand the involved underlying mechanisms.

P.61

Patterns of Amyloid Deposition in Dementia with Lewy bodies, Alzheimer's Disease and Healthy Controls

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Background: The pathological hallmarks of dementia with Lewy bodies (DLB) are Lewy bodies and Lewy neurites. Many cases of DLB also display amyloid-beta deposition, though it is unclear if this is clinically significant. Amyloid imaging ligands enable us to investigate this relationship in vivo. Methods: DLB (n=22), Alzheimer's disease (n=10) and control (n=15) volunteers had an amyloid PET scan using 18F-Florbetapir. Each subject also had a thorough clinical and neuropsychological assessment and, where possible, an MRI. Amyloid PET scans were visually rated as amyloid positive or negative. A region of interest analysis was performed to obtain semiquantitative measures of frontal, parietal, temporal, occipital, cingulate, striatal and mean cortical amyloid binding. Results: All AD cases were visually rated as amyloid positive, compared with 45% of DLB cases and 20% of controls. AD cases had significantly greater mean cortical amyloid deposition than DLB or controls. Deposition in DLB was intermediate between AD and controls. Relative binding (each region compared to overall cortical binding) was higher in the frontal cortex and lower in the occipital cortex in AD, leading to a greater frontal:occipital binding ratio in AD than DLB or controls (AD 1.15, DLB 1.05 (p=0.025 v. AD), Controls 1.02 (p=0.007 v. AD)). Amyloid deposition was correlated with hippocampal atrophy in the DLB group (R=-0.57; p=0.008), but not in AD (R=0.06; p=0.87) or controls (R=0.38; p=0.16). Amyloid positive and negative DLB cases will be compared for differences in clinical and neuropsychological profile. Conclusions: There is greater cortical deposition of amyloid in AD than DLB. The pattern of amyloid deposition seen in DLB is more similar to that seen in healthy controls than AD, but may have an association with structural brain atrophy.

P.62

Functional MRI Study of Attentional dysfunction in Lewy Body dementia and Alzheimer's Disease

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Background: Deficits in attention contribute to cognitive impairment in both Lewy body dementia and Alzheimer's disease. However, the underlying pathophysiological mechanisms are not clearly understood, and may differ between the two diseases. Methods: Using functional MRI, we investigated the three components of attention (alerting, orienting and executive/conflict function) using a modified Attention Network Test in 32 patients with Lewy body dementia (19 with dementia with Lewy bodies, and 13 Parkinson's disease with dementia patients) 23 with Alzheimer's disease, and 23 healthy controls. Results: Both Alzheimer's disease and Lewy body dementia patients were able to perform the task but had increased reaction times compared to controls. The functional MRI demonstrated a similar fronto-parieto-occipital network activation both during target presentation and preceding cues in all groups. Compared to controls, both Alzheimer's disease and Lewy body dementia patients had greater activation of this network for incongruent (executive/conflict) trials, accompanied by slower reaction times. In the default mode network, however, we saw diverging activity patterns in the Alzheimer's disease and Lewy body dementia groups. The Alzheimer's disease group had almost no deactivation during task. In contrast, patients with Lewy body dementia had an enhanced default mode network deactivation to all trials. Conclusions: We found evidence for similar frontoparietal hyperactivation but differing default mode network dysfunction in Alzheimer's disease and Lewy body dementia. Possibly the Alzheimer's disease group have a failure to switch from default mode to active task networks, whilst the Lewy body dementia group show heightened deactivation in an attempt to compensate for impaired attentional networks. This may have implications for future aetiologic evaluations as well as treatment of these domain specific cognitive symptoms.

P.63

Dopamine Transporter Imaging in Middle-Aged and Older Patients with Psychiatric Disorders

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Background: Lewy body disease (LBD), including Parkinson's disease (PD) and dementia with Lewy bodies (DLB), is defined pathologically as degeneration in the central and peripheral nervous system associated with Lewy bodies (LB). ^{123}I-N-fluoropropyl-2β-carboxymethoxy-3β-(4-iodophenyl)nortropane (^{123}I-FP-CIT) SPECT is used to detect the striatonigral dopaminergic denervation associated with LBs in patients with LBD. Although psychiatric symptoms often precede the clinical diagnosis of DLB by years or even decades, it remains unclear whether decreased striatal dopamine transporter (DAT) binding in psychiatric patients. Methods: We investigated clinical profiles of 16 patients with psychiatric disorder who underwent DAT scan. The specific binding ratio (SBR) was calculated as the quantitative evaluation for dopamine transporter deficit using DaTview analysis. They were 7 men and 9 women with a mean age of 71.9 (range: 55–85) years. The mean Mini-mental state examination score was 24.6 (range: 17-30). Results: The main psychiatric features at first visit to our psychiatric department were as follows: cognitive decline (n = 2), depression (n = 7), hypochondriasis (n = 4), and delusion (n = 3). Final clinical diagnosis was as follows: DLB (n = 11), Major depressive disorder (n = 4), and Somatic symptom disorder (n = 1). The mean SBR in DLB patients and in other psychiatric patients was 3.4 ± 1.2 (range: 1.2-4.9) and 4.2 ± 1.5 (range: 2.8-6.7), respectively. There was no significant difference in the mean SBR between them. The majority of the patients exhibited no asymmetry in dopamine transporter deficit. Conclusions: There was overlap in the SBR between psychiatric disorder and DLB, suggesting the pathological continuum between them. Because it remains unknown whether these psychiatric patients are presenting the prodromal state of PD/DLB, continued follow-up study of the patients will be needed.

P.64

Brain Connectivity Alterations May Predict Dementia in Parkinson's Disease

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Background: Dementia affects a high proportion of Parkinson's disease (PD) patients and poses a burden on caregivers and healthcare services. Only few longitudinal studies had identified EEG abnormalities that can predict PD patients at higher risk for dementia. An innovative approach to study brain dynamics is to measure brain signal variability, which considers what has generally been viewed as "noise" as part of the brain interactions. This study aims to prospectively follow a cohort of PD patients and identify cerebral anomalies in baseline resting state EEG that could predict the development of dementia. Methods/Design: We followed 62 dementia-free PD patients for a mean of 3 years. At baseline, all participants underwent waking resting state EEG and exhaustive neurological and neuropsychological assessments. Baseline resting state EEG of patients who developed dementia (N=18) was compared to those of patients who remained dementia-free (N=44) and of 37 healthy subjects. Multiscale entropy and phase locking value analyses were performed. Results: Partial least square statistical analysis revealed group differences that predicted which patients developed dementia. Patients who converted showed higher signal complexity and lower phase locking values in low frequencies than patients who remained dementia-free and controls. Conversely, both patient groups showed lower signal variability and higher phase locking values in high frequencies compared to controls, with the strongest effect in patients who developed dementia. Conclusions: These findings suggest that specific disruptions of brain communication can be measured before PD patients develop dementia. Our study providing a new potential marker to identify PD patients at highest risk of developing dementia and who could be the best candidates for neuroprotective trials for cognitive decline.

P.65

Relationships Between Gray Matter Atrophy Patterns, APOE Genotype, and Cognitive Impairment in Parkinson's Disease

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Background: Lewy body dementias including Parkinson's disease (PD) dementia are frequent, but their neurobiological mechanisms are not fully known. While the apolipoprotein E epsilon 4 (ApoEe4) genotype is associated with Alzheimer's disease (AD) risk and mesial temporal lobe atrophy on magnetic resonance imaging (MRI), less is known regarding its role in PD cognitive impairment. Our study aim was to investigate structural MRI brain changes, ApoEe4 genotype, and PD cognitive impairment. Methods: 96 PD subjects underwent clinical/cognitive evaluations, MRI scans (1.5T GE, T1-weighted sequences), and ApoE genotyping. PD subjects were classified as dementia (PDD), mild cognitive impairment (PD-MCI), or cognitively normal (PD-NC) using Movement Disorder Society criteria. Whole brain voxel-based morphometry analyses were conducted using SPM8. Regions of gray matter volume differences between groups were examined using t-tests and covariates, with a significance threshold of pa priori neuroanatomically-based cognitive systems from which volumes were extracted. Clinical/cognitive variables were compared with one-way ANOVAs. Binary logistic regressions were used to examine relationships between ApoEe4 allele and cognitive and imaging variables, adjusting for age and disease duration. Results: PDD subjects (n=23) were older and had longer disease durations than PD-MCI (n=44) and PD-NC (n=29) subjects. Presence of ApoEe4 allele did not differ significantly across PD cognitive groups (24.1% PD-NC, 31.8% PD-MCI, 34.8% PDD). Gray matter atrophy in all neuroanatomically-based cognitive systems was greatest in PDD subjects and least in PD-NCs. Atrophy in the dorsal-spatial system (superior/inferior parietal lobe, precuneus) best predicted the presence of ApoEe4 allele (p=0.032). Conclusion: Gray matter atrophy occurs in multiple neuroanatomical regions particularly frontal, temporal, and parietal areas and with PDD. Although ApoEe4 association with memory systems did not reach significance due to small cohort size, its relationship to parietal lobe atrophy may suggest a role in amyloid deposition or co-morbid neuropathologies.

P.66

Neurophysiological Biomarker for Differentiation of Lewy Body Dementias and Other Dementias

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Objective: Demonstrate the applicability and properties of a neurphysiologically based biomarker for differential diagnosis of AD and DLB. Methods: In a database, EEGs from 209 healthy (NRM), 22 individuals with DLB, 26 individuals with PDD, and 560 clinical subjects of other types than PDD and DLB, have been entered. Applying statistical pattern recognition (SPR) to a large set of EEG features classifiers contrasting clinical cohorts in a pairwise manner are developed. For each classifier, the SPR finds an optimal combination of the EEG features which separate the two groups under consideration. The accuracy, sensitivity, and specificity of each classifier are estimated using 10–fold cross validation. Results: The receiver operating characteristic (ROC) curves for the "NRM vs clinical" classifier system have the following qualities: area under curve (AUC) is 0.91(0.04), specificity (SPE) is 0.85(0.06), sensitivity (SEN) is 0.85(0.04), and the accuracy (ACC) is 0.85(0.05). The standard deviation is given in parentheses. For the "PDD/DLB vs other clinical types" classifier system the results are: AUC=0.92(0.01), SPE=0.84(0.05), SEN=0.88(0.03), and ACC=0.86(0.02). Applying the same methodology to the DLB and PDD groups showed no separation. Conclusion: We have introduced an EEG based neurophysiological biomarker for PDD and DLB combined into one group that shows good sensitivity and specificity and it is argued that this method can be a good addition to available methods. EEG is a standard method that is inexpensive and readily available and is therefore attractive for use in various settings.

P.67

The Pattern of Posterior Default Mode Network Failure Is Unique for Amyloid Status, Dementia with Lewy Bodies, and Alzheimer's Disease Dementia

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Background/Methods: The cascading failure model of Alzheimer's disease (AD) predicts an early failure of the posterior default mode network (pDMN) with "compensatory-like" increases in connectivity involving memory systems. However, we have previously noted pDMN failure in DLB subjects. We therefore used our novel task-free fMRI DMN subsystems analysis to compare the patterns of pDMN failure in PiB negative controls (CN-, n=60), PiB positive controls (CN+, n=11), DLB (n=31), and AD (n=78). Results: There was a significant effect of group on pDMN connectivity whether DLB groups were combined on PiB status [$F_{(3, 176)}=13.56$, $p < 0.001$] or not [$F_{(4, 175)}=10.12$, $p < 0.001$]. Pairwise comparison showed that AD had lower connectivity than CN-(μ=0.46 vs. μ=0.65, $p < 0.001$) and DLB (μ=0.55, p=0.01). The combined DLB group had lower connectivity relative to controls CN-(p=0.009). The DLB groups separated by PiB status also had lower connectivity relative to CN- (μ=0.54 [p=0.033] for DLB-, and μ=0.56 [p=0.05] for DLB+). CN+ subjects had lower pDMN connectivity (μ=0.54) relative to CN- (p=0.045). These results indicate that the pDMN is affected in all of these groups with AD potentially being the most affected group. However, when the entire pDMN connectivity maps for each group was compared to the CN- group, distinct patterns of increased connectivity emerged. CN+ subjects had higher connectivity in the posterior medial temporal lobe. DLB- subjects had higher connectivity in occipital, anterior cingulate, medial dorsal frontal and orbitofrontal regions. DLB+ subjects had higher connectivity in occipital-parietal, medial temporal (greatest in the amygdala), striatum, and medial/lateral dorsal frontal regions. AD subjects had higher connectivity mainly in the medial temporal lobe. Conclusion: The pattern of "compensatory-like" increases in connectivity after pDMN failure is unique for CN+, DLB-, DLB+, and AD. This may indicate the pattern of brain compensation for pDMN failure drives clinicopathologic trajectories. However, they may also be a consequence of them.

P.68

Pattern of AV-1451 Uptake in DLB and Its Association with Amyloid Deposition on PET

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Objective: Neurofibrillary tangle (NFT)-tau pathology is commonly seen in patients with probable dementia with Lewy bodies (DLB). The extent and distribution of NFT-tau pathology and the association of NFT-tau deposition with amyloid deposition in probable DLB is unclear. Our objective was to determine the pattern of AV-1451 uptake in patients with probable DLB, and its relationship with amyloid deposition on PET. Methods: We recruited probable DLB (n=6) patients from the Mayo Clinic ADRC, who underwent MRI, AV-1451 and C11-Pittsburgh compound B (PiB) PET examinations at baseline. An age and sex matched cohort of Alzheimer's disease (AD) (n=7) and cognitively normal (CN) subjects (n=16) who underwent similar multimodality imaging examinations were included. AV-1451 PET was normalized to the cerebellum and voxel-based analyses were performed on SPM. Regional gray matter (GM) AV-1451 uptake was measured by co-registering normalized PET images to MRI and segmenting GM regions using an in-house atlas. Results: Patients with AD dementia had significantly higher AV-1451 uptake than probable DLB throughout the whole brain particularly in the temporal lobes ($p < 0.05$; corrected with family-wise error). Patients with DLB had increased AV-1451 uptake in the inferior and middle occipital gyri compared to CN ($p < 0.001$; uncorrected). No association was found between the occipital AV-1451 uptake and global PiB PET uptake. Conclusions: In this small cohort of patients with probable DLB, AV-1451 uptake was most prominent in the occipital association cortex. Medial and lateral temporal lobe AV-1451 uptake was not significant, which distinguished probable DLB from AD dementia patients. Occipital association cortex is one of the earlier regions to be affected with diffuse Lewy body disease and is hypometabolic in probable DLB. The pattern of higher AV-1451 uptake in the occipital association cortex suggests that this region is involved with both LB and NFT-tau pathology independent of amyloid deposition in DLB.

P.69

Utility of ^{123}I-FP-CIT SPECT for Early Diagnosis of Dementia with Lewy Bodies: Correlation Between ^{123}I-FP-CIT SPECT Findings and Clinical Symptoms

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Objective: To evaluate the correlation between the objective scores of ^{123}I-ioflupane (FP-CIT) single photon emission computed tomography (SPECT) and the clinical symptoms in early stage of dementia with Lewy bodies (DLB), and to show the utility of ^{123}I-FP-CIT SPECT for early diagnosis of DLB. Methods: We compared the probable DLB group (PRB-DLB, n=18), the prodromal DLB group (PRD-DLB, n=25) and the probable Alzheimer's disease (AD) group. The PRD-DLB group was defined as the patients who have the prodromal symptoms related the Lewy body disease (LBD) such as REM sleep behavior disorder (RBD), olfactory dysfunction, autonomic dysfunction and depression, and shows the characteristic hypometabolism in the occipital lobe using 18F-fluorodeoxyglucose positron emission tomography. Specific binding ratio (SBR) was used for the objective assessment of ^{123}I-FP-CIT SPECT, and was compared between the three groups. Cognitive function (Mini-Mental State Examination, MMSE), motor symptoms (Unified Parkinson's Disease Rating Scores Part3, UPDRS3) and duration of LBD-related prodromal symptoms were compared between the two DLB groups, and the correlations between SBR scores and these clinical symptoms were examined. Results: Mean SBR scores of the PRD-DLB were significantly lower than those of the AD group, while they were significantly higher than those of the PRB–DLB group. In each of the two DLB groups, no correlation was found between SBR scores and MMSE scores. SBR scores of the PRB-DLB and total SBR scores of the two DLB groups showed negative correlations with UPDRS3 scores, whereas no correlation was found between SBR scores of the PRD-DLB group and UPDRS scores. Among LBD-related prodromal symptoms, duration of olfactory dysfunction or RBD episode showed negative correlation with SBR scores. Conclusion: ^{123}I-FP-CIT SPECT is useful for early diagnosis of DLB. In the early stage of DLB, long-term olfactory dysfunction and/ or RBD may indicate severer degeneration of the nigro-striatal dopaminergic pathway.

P.70

Baseline And Longitudinal Grey Matter Changes in Newly Diagnosed Parkinson's Disease: ICICLE-PD Study

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Background: Mild cognitive impairment in Parkinson's disease (PD-MCI) is associated with progression to dementia (PDD) in a majority of patients. Determining structural imaging biomarkers associated with prodromal PDD may allow for the earlier identification of those at risk, and allow for targeted disease modifying therapies. Methods: 105 non-demented subjects with newly diagnosed idiopathic Parkinson's disease (PD) and 37healthy matched controls had serial 3T structural MRI scans with clinical and neuropsychological assessments at baseline which were repeated after18 months. The MDS Task Force criteria were used to classify the PD subjects into PD-MCI (n=39) and PD with no cognitive impairment (PD-NC) (n=66). Freesurfer image processing software was used to measure cortical thickness and subcortical volumes at baseline and follow-up. We compared regional percentage change of cortical thinning and subcortical atrophy over 18 months. Results: At baseline, PD-MCI cases demonstrated widespread cortical thinning relative to controls and atrophy of the nucleus accumbens compared to both controls and PD-NC. Regional cortical thickness at baseline was correlated with global cognition in the combined PD cohort. Over 18 months, PD-MCI demonstrated more severe cortical thinning in frontal and temporo-parietal cortices, including hippocampal atrophy, relative to PD-NC and healthy controls, while PD-NC showed more severe frontal cortical thinning compared to healthy controls. At baseline, PD-NC converters showed bilateral temporal cortex thinning relative to the PD-NC stable subjects. Conclusions: Although loss of both cortical and subcortical volume occurs in non-demented PD, our longitudinal analyses revealed that PD-MCI shows more extensive atrophy and greater percentage of cortical thinning comparing to PD-NC. In particular, an extension of cortical thinning in the temporo-parietal regions in addition to frontal atrophy could be a biomarker in therapeutic studies of PD-MCI for progression towards dementia.

P.71

Orthostatic Hypotension, Cerebral Perfusion, and Visuospatial-Executive Deficits in Lewy Body Disorders: A Proof of Concept Study Using pCASL MRI

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Background: Orthostatic hypotension and cognitive impairment are two non-motor attributes of Lewy body spectrum disorders that significantly impact independence. Objective: This proof-of-concept study examined cerebral blood flow (perfusion) as a mediator of orthostatic hypotension and cognition. Methods: In fifteen patients with Lewy body disorders, we estimated regional perfusion using pseudo-continuous arterial spin labeling MRI, and quantified orthostatic hypotension from the change in systolic blood pressure between supine and standing positions. Executive, visuospatial, attention, memory, and language domains were characterized by neuropsychological tests. A matching sample of non-demented adults with cerebral small vessel disease was obtained to contrast perfusion patterns associated with comorbid vascular pathology. Results: Compared to the vascular group, patients with Lewy body disorders exhibited lower normalized perfusion to temporal and occipital lobes than to frontal and parietal lobes ($q < 0.05$). A greater orthostatic drop in systolic blood pressure was associated with lower perfusion in occipito-parietal regions in these patients (uncorrected $p < 0.005$; cluster size ≥ 20 voxels). Although orthostatic hypotension and supine hypertension were strongly correlated ($r=-0.79$, $p < 0.001$), the association of perfusion with supine blood pressure was somewhat distinct from that observed with the orthostatic change in pressure. Specifically, supine hypertension was associated with high perfusion to anterior and middle cerebral artery territories, as well as with low perfusion to posterior regions. In the orthostatic hypotension-defined regions, perfusion was directly related to performance on visuospatial and attention tasks ($p < 0.05$). Conclusion: These findings provide new insight into the associations between orthostatic hypotension, regional perfusion, and cognition in Lewy body disorders.

P.72

Comparative value of [(123)I]-FP-CIT SPECT [(123)I] and [(123)I] MIBG Myocardial Scintigraphy in Distinguishing between Dementia with Lewy Bodies and Other Types of Dementia

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Background: Decreased ^{123}I-FP-CIT uptake in the basal ganglia and reduction in cardiac (^{123})I-metaiodobenzylguanidine (MIBG) uptake are characteristic features of dementia with Lewy bodies (DLB), both supporting its correct identification in clinical practice. The aim of this multicentre study was to compare the diagnostic value of FP-CIT SPECT and MIBG myocardial scintigraphy in differentiating DLB from other types of dementia. Methods/Design: Our analyses included 23 patients with a clinical diagnosis of DLB (probable DLB, n=19; possible DLB, n=4) and 22 patients with non-DLB dementia (AD, n=12; bvFTD, n=9; PSP, n=1), who were referred to five Italian centres especially skilled in early detection of atypical dementias. All patients underwent FP-CIT SPECT and MIBG myocardial scintigraphy within few weeks of clinical diagnosis. All diagnoses at each centre were agreed upon by the local clinician and an independent expert (PT) without having access to FP-CIT SPECT and MIBG myocardial scintigraphy findings. Basal ganglia and myocardial images were visually classified as either normal or abnormal by two independent nuclear physicians who were blinded to the patients' clinical data. Results: The DLB and non-DLB groups were comparable for sex (females: 43% vs 41%, p=0.86), age at onset (68±6 vs 70±8, p=0.25), and age (72±5 vs 73±8 years, p=0.80) and global severity of dementia (MMSE, 21±4 vs 22±5, p=0.60) at first visit. Overall, sensitivity and specificity to DLB were respectively 91% and 100% for MIBG myocardial scintigraphy, and 87% and 73% for FP-CIT SPECT. Lower specificity of basal ganglia compared to myocardial imaging was due to decreased FP-CIT uptake in six non-DLB patients (AD, n=1; PSP, n=1; bvFTD, n=1, bvFTD with parkinsonism, n=3) who had normal MIBG myocardial uptake. Conclusion: MIBG myocardial scintigraphy appears to be more specific than FP-CIT SPECT for excluding non-DLB dementias, especially when parkinsonism is the only "core feature" exhibited by the patient.

P.73

Dementia with Lewy bodies Shows Higher Small-Worldness in Functional Brain Networks Compared to Healthy Controls

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Introduction. Previous research agrees that Alzheimer's disease (AD) is a disconnection disease where the most important functional and structural neuronal pathways are attacked by the disease, disconnecting brain regions and decreasing the brain's small-worldness (SW) –a network property that reflects efficient communication among neuronal groups. However there is a lack of comparable data in dementia with Lewy bodies (DLB). Methods. We analysed functional magnetic resonance images (fMRIs) from 19 patients diagnosed with DLB, 18 with AD and 17 healthy controls (HCs) using network measures (http://www.brain-connectivity-toolbox.net/). Functional images were parcellated into 112 seeded regions according to the Harvard-Oxford atlas for time-series extraction. Connectivity matrices were estimated as the absolute value of the Pearson correlation matrices, and then binarised using a range of equal edge sparsities (3.6-39.3%) as network threshold for all participants in the study. Results. In comparison to HCs, AD patients showed lower SW, supporting the current consensus of inefficient connectivity. However, SW in DLB was greater when compared to both HCs and AD (DLB>HCs>AD, p-value < 0.05 corrected for multiple sparsities).SW is commonly associated with efficient communication within the brain's functional network. However, in DLB a high SW is associated with an isolation of the brain's modular systems, i.e. disconnections between modules and relative preservation of within module functional connections. Additionally, network global efficiency was positively correlated with cognitive impairment in our DLB participants (MMSE: R=0.7, p-value=0.001 and CAMCOG: R=0.5, p-value. < 0.035. Conclusions. The current consensus in the study of functional networks is to associate a decrease in the brain's SW with brain disease, and this is currently the norm in AD. However, in DLB it appears that the brain's SW is altered by different mechanisms, causing it to increase and this might be related to the known cholinergic deficits and impairments in attention in DLB. These findings warrant further investigation.

P.74

Dementia with Lewy Bodies and Parkinson's Disease Dementia Show No differences in Resting State Functional MRI

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Introduction: Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) are differentiated by the one-year rule between the onset Parkinsonism relative to the onset of dementia. Both lie on the Lewy body disease spectrum and pathologically appear similar. Previous neuroimaging studies have reported however metabolic and structural differences between PDD and DLB. In this study we sought to clarify, for the first time, if there were differences in the resting state functional MRI (fMRI). Methods: We studied resting state fMRI from patients diagnosed with DLB (n=18) and PDD (n=12), and for comparison with included age-matched healthy controls (HC, n=17). Patients groups were matched for attention (p-value=0.52) and executive (p-value=0.67) functions, frequency and severity of complex visual hallucinations (VHs, p-value=0.23) and also by the level of cognitive impairments (MMSE: p-value=0.51 and CAMCOG: p-value=0.94). Seed analysis was implemented in 12 brain regions within three resting state network related to memory, attention and motor control: default mode network (DMN), fronto-parietal network (FPN), and sensory-motor network (MN). Groups were compared (unpaired t-tests) while controlling for age and sex confounds using FSL-randomise and multiple comparison correction. Results: When comparing patient groups against HCs, the PDD group showed broader differences for the supplementary motor area (MN) seed than the DLB group. For the parietal seeds (FPN), DLB patients showed broader differences than PDDs when both groups were compared against HCs. Equivalent impaired connectivity was found for seeds within the DMN (precuneus cortex) between patients and HCs. Finally, when comparing DLB against PDD, no functional differences were found for any of the 12 seeds studied. Conclusions: Previous investigations have reported structural differences between DLB and PDD, however both conditions did not show any significant functional difference. Our results support the notion that PDD and DLB are more similar than they are different.

P.75

Shape and Volume Abnormalities in Subcortical Structures Involved in Cortico-Subcortical Circuitry in Rapid Eye Movement Sleep Behavior Disorder

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Background: Idiopathic rapid eye movement sleep behavior disorder (iRBD) is considered a risk factor for the development of synucleinopathies. Abnormalities have already been reported in subcortical structures involved in cortico-subcortical circuitry. However, no study has yet investigated shape and volume abnormalities in these structures in iRBD patients.
Methods/Design: T1-weighted images were acquired in 41 patients with polysomnography-confirmed iRBD and 41 healthy controls matched for age and sex using 3T MRI. Subcortical structures (i.e., putamen, caudate nucleus, pallidum, and thalamus) were investigated for global volume and shape, respectively using structure-based volumetric analysis and vertex-based shape analysis. Vertex-based shape analysis allows for quantification of surface differences and overcomes some limitations of voxel-based quantification. Also, voxel-based morphometry (VBM) was used to investigate local gray matter volume changes. Generalized linear modeling was performed using permutation-based non-parametric testing (using 10,000 permutations). Results: Structure-based volumetric analysis showed reduced global volume of the right putamen and left pallidum. Shape analysis identified 3 clusters of abnormal shape in the left putamen and 1 cluster in the left pallidum. VBM revealed volume reductions in the frontal cortex (i.e., ventromedial and anterior cingulate cortices, motor and somatosensory cortices, and dorsolateral cortex), the basal ganglia, and the insular cortex. Correlation analyses revealed a negative relationship between UPDRS-III score on the left side and volume of the left putamen (r=-0.33). Linear discriminant analysis also revealed that shape abnormalities presented with better discriminative power than volume abnormalities. Conclusions: Patients with iRBD present with global volume and shape abnormalities in the putamen and pallidum, along with reductions of gray matter local volume in the frontal and insular lobes. Although structure-based volumetric and shape analyses converge on showing abnormalities in the left pallidum, both techniques seem complementary in showing abnormalities in the putamina. Volume abnormalities were associated with clinical variables such as motor symptoms.

P.76

Functional Connectivity of the Anterior Insula in Dementia with Lewy Bodies

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Introduction: The anterior insula (AI) is a brain structure involved in detection of salient stimuli across multiple modalities. Atrophy and hypoperfusion of the AI have been reported in dementia with Lewy bodies (DLB) in contrast to healthy elderly controls and patients with Alzheimer's disease. Under a network-model perspective, we aimed in this study to investigate AI relationships with other brain areas in both DLB and prodromal DLB based on functional connectivity MRI. Material and Methods: 41 prodromal (mild cognitive impairment) DLB patients, 14 DLB patients and 20 healthy elderly controls underwent a 6 minutes resting-state MRI sequence. Left and right AI were used as two separate regions of interest in a seed-based functional connectivity approach in which their time-course served as references to compute voxel-wise correlation maps. These maps were compared across groups by a voxel-wise ANOVA at $p < 0.001$. Results: DLB patients showed a decreased connectivity between left AI and bilateral prefrontal cortex, anterior cingulate cortex, left inferior parietal lobule, right middle temporal gyrus and bilateral visual association areas with respect to healthy controls. Dysconnectivity with right AI occurred in large part of the occipital cortex, and in precuneus, pre- and post-central central gyrus, bilateral prefrontal cortex and anterior cingulate cortex. The only dysconnectivity observed in prodromal DLB occurred between left AI and left prefrontal cortex and left parietal lobule ; right AI and right superior temporal sulcus and left orbitofrontal area. Discussion: Functional connectivity of AI in DLB differed from elderly controls. The pattern of frontal dysconnectivity closely matches the salience network, which is implicated together with AI in detection of exteroceptive and interoceptive salient stimuli, and in attentional, emotional, motor and autonomic adaptative response. Together with a large occipital dysconnectivity, our results suggest a deficit in salience processing and particularly of visual information.

P.77

Gray Matter Atrophy in Prodromal and Non-prodromal Dementia with Lewy Bodies and Alzheimer's Disease: A VBM-DARTEL Study

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Introduction: Structural brain imaging studies have reported loss of gray matter (GM) in non-prodromal dementia with Lewy bodies (DLB) compared to elderly healthy controls. To focus on an earlier stage of the disease in a differential diagnostic perspective, we aimed to describe patterns of atrophy in prodromal and non-prodromal DLB, and to assess for differences with Alzheimer's disease (AD). Material and Methods: 41 prodromal (mild cognitive impairment) DLB patients, 15 DLB patients, 14 prodromal AD, 21 AD patients, and 21 healthy elderly controls underwent a T1 3D MPRAGE MRI sequence. VBM-DARTEL analysis was conducted using SPM8 and included "new segmentation" into GM, spatial normalisation, modulation, and smoothing. Groups were compared using a voxel-wise ANOVA corrected for age, gender and total intracranial volume. Significant effects were identified with a statistical threshold of $p < 0.05$. Results: Prodromal DLB patients showed less GM in left insula, right rostral temporal lobe and median superior frontal gyrus relative to healthy controls. Prodromal AD did not differ neither from healthy controls nor from prodromal DLB. Non-prodromal DLB had more extended GM atrophy, with bilateral insula and frontal gyrus, right temporal pole, as well as cerebellum. AD was characterized by hippocampal, temporal, and temporo-occipital atrophy. DLB differed from AD with less GM in right insula and rolandic operculum, bilateral superior and middle frontal gyrus. The opposite contrast did not show any differences. Discussion: Gray matter volume was reduced in DLB as early as the prodromal stage, particularly in insula, rostral temporal lobe and frontal lobe. Our results supplement previous reports by describing these early abnormalities and supports the role of insula in DLB. The patterns of atrophy strongly differ between DLB and AD but not at the prodromal stage, limiting its perspective in early diagnosis.

P.78

Cerebral Infarcts and White Matter Hyperintensities in Probable Dementia with Lewy Bodies and Alzheimer's Disease Dementia.

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Background: Cerebrovascular disease is a risk factor for cognitive decline among elderly and contributes to cognitive impairment in patients with Alzheimer's disease dementia (AD); however, little is known about its impact on dementia with Lewy Bodies (DLB). We assessed frequency and distribution of infarcts and white matter hyperintensity load (WMH) in a cohort of DLB and AD patients. Methods: Patients with probable DLB (n=81) with a mean age of 72 years and patients with AD (n=240) with a mean age of 75 years were consecutively recruited to the Mayo Clinic Alzheimer's Disease Research Center. Two groups of cognitively normal controls (CN), age and sex matched to DLB (n=82) and AD (n=240) respectively, were recruited from the population-based Mayo Clinic Study on Aging. Each subject underwent 3T-MRI examination. FLAIR scans were assessed for the presence of cortical, subcortical and infratentorial infarcts. WMH were quantified using a semi-automated algorithm. Fisher's exact test and ANOVA were used to compare the clinical groups. Results: No differences were found in the proportion of cortical, subcortical or infratentorial infarcts among DLB and the matched CN group. On the contrary, AD patients had a higher frequency of cortical (p=0.01) and infratentorial (p=0.02) infarcts, but not subcortical infarcts, compared to the matched CN group. WMH volumes were significantly higher both in DLB and in AD compared to their matched CN groups (p < 0.001). WMH load was greater in women than in men in both AD (p=0.006) and DLB (p=0.04) groups after adjusting by age. Conclusions: Our results suggest that cerebrovascular disease may contribute to the cognitive impairment in patients diagnosed with both DLB and AD. However, unlike AD, DLB is characterized by a similar frequency of infarcts compared to CN. Both patients with DLB and those with AD have increased WMH load, which is greater in women than men.

P.79

Aβ Deposition Is Associated with Regional GM Atrophy Rates in Probable Dementia with Lewy Bodies

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Background: More than 50% of patients with Dementia with Lewy Bodies (DLB) have Amyloid-beta (Aβ) deposition as measured with C11-Pittsburgh-compound-B (PiB) binding on PET. The association of Aβ deposition with the changes in brain structure in patients with DLB is unknown. We investigated the longitudinal rates of GM atrophy and their association with baseline Aβ deposition in a cohort of clinically diagnosed DLB. Methods: Patients with Probable DLB (n=19), who were consecutively recruited to the Mayo Clinic AD Research Center, underwent PiB-PET and MRI examinations at baseline. Follow-up MRI were performed after a mean(SD) follow-up period of 2.5(1.2) years. Regional GM loss was determined on 3D high resolution T1 with the Tensor Based Morphometry-Symmetric Normalization. Linear regression was performed between baseline PiB standard unit value ratio (SUVR) and longitudinal change in regional GM volumes from an in-house modified anatomic labeling atlas adjusting for age at baseline. Results: DLB patients had a mean(SD) PiB SUVR of 1.53(0.36). Greater PiB SUVR was associated with greater GM loss in the amygdala (p=0.005), hippocampus (p=0.04), posterior cingulate cortex (p=0.03), occipital cortex (p=0.03), the caudate (p=0.006) and putamen (p < 0.001) nuclei after adjusting for age. Conclusions: In clinically diagnosed patients with probable DLB, Aβ deposition is associated with increased rates of GM atrophy in the limbic and paralimbic cortex as well the occipital lobe and corpus striatum. We previously showed that autopsy-confirmed DLB patients have increased GM atrophy rates in the limbic and paralimbic cortices only if they have additional AD-related pathology, particularly neurofibrillary tangle pathology. Current data suggest that presence of Aβ deposition is associated with the evolution of neurodegeneration potentially due to AD-related pathology in these regions. In addition, increased rates of atrophy in the occipital lobe and corpus striatum may suggest a potential interaction of Aβ deposition with LB disease.

P.80

Quantitative Regional Atrophy Changes as a Potential Phenotypical and prognostic Biomarker in Dementia with Lewy Bodies

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Background: A number of neuroimaging tecniques have been used to diagnose DLB; recently, quantitative regional atrophy mapping has been proposed to distinguish between the different types of dementia. However, only few neuroimaging studies explored the different clinical phenotypes of DLB. Objective: we conducted a study to explore the difference in quantitative regional atrophy and phenotypical difference in a series of clinically confirmed DLB cases. Methods: We identified 22 cases with a possible diagnosis of DLB of the clinical database of Center for Alzheimer's Care, Imaging & Research of University of Utah. In addition, we reviewed the medical records identifying the main clinical symptoms and divided our cases in three phenotypical subgroups: parkinsonism, hallucinations, and cognitive fluctuations. We segmented gray matter in structural brain images using SPM12 software, and then we compared regional gray matter density to a mixed clinical sample of 500 patients. Results: Among the 22 DLB cases there were 14 males and 8 females; 13 were assigned to the parkinsonism predominant group, 8 to the hallucinations predominant group, and 1 to the cognitive fluctuations group. The overall median age at diagnosis of DLB was 71 years (range: 62-84). We observed that DLB cases have a more specific pattern of atrophy involving the lateral orbitofrontal cortex and the temporo-occipital cortex. The hallucinations predominant group had a much more severe degree of atrophy when compared with parkinsonism predominant group. When we compared hallucinations predominant and parkinsonism predominant groups with age-matched controls, we observed a more severe atrophy in the hallucinations group but has the same spatial distribution across the groups. Conclusions: Quantitative regional atrophy changes may be a potential phenotypical and prognostic biomarker to differentiate the different phenotypes in DLB.

P.81

Whole-brain Patterns of 1H-Proton Magnetic Resonance Spectroscopy in Dementia with Lewy Bodies and Alzheimer's Disease

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Background: 1H-Proton MR spectroscopy (MRS) has demonstrated metabolic changes in neurodegenerative disorders such as Alzheimer's disease (AD) and dementia with Lewy bodies (DLB), but their pattern and relationship to clinical symptoms is unclear. Methods: In this study, we have acquired and analysed novel whole-brain 3T MRS data for subjects with DLB (N = 35), AD (N = 36), and similarly aged control participants (N = 35), who also underwent a detailed clinical and neuropsychological assessment. MRS spectral analysis was performed to quantify key brain metabolites followed by whole-brain image and statistical analysis using SPM. Results: Compared with controls, both DLB and AD subjects showed a significant decrease in most brain metabolites, with N-acetylaspartate to creatine (NAA/Cr), choline to creatine (Cho/Cr) and myo-Inositol to creatine (mI/Cr) levels reduced in posterior cingulate, thalamus, frontotemporal areas and basal ganglia. Glutamate and glutamine to creatine (Glx/Cr) level was more widely decreased in DLB (posterior cingulate, hippocampus, temporal regions and caudate) than in AD (only in posterior cingulate). DLB was also associated with increased levels of Cho/Cr, NAA/Cr and mI/Cr in occipital regions. Changes in metabolism in the brain were correlated with cognitive and non-cognitive symptoms in the DLB but not the AD group. Conclusions: Using whole-brain MRS, we have found a general reduction of metabolism in both DLB and AD, though with some occipital increases in DLB. In addition, decreases of Glx/Cr level were more widespread in DLB than in AD. The different patterns between the two diseases may have important implications for DLB in terms of improving diagnosis, better understanding disease specific neurobiology and targeting therapeutics.

P.82

Imaging in Prodromal Dementia with Lewy Bodies

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In recent years increasing attention has been paid to early diagnosis and relatedly to mild cognitive impairment (MCI) and the diagnosis of prodromal dementia. To date most of the discussion has focused on Alzheimer's disease (AD) with little focus on the pre-dementia stage of cognitive decline which culminates in Dementia with Lewy bodies (DLB). Proposals for early AD and MCI-AD have been published and these have included the use of imaging biomarkers. It is likely that such biomarkers will be important in identifying and defining prodromal DLB (pDLB). Accurate identification of pDLB involves both the exclusion of other major causes of early cognitive impairment, in older people these are predominantly the pathologies of AD and vascular cognitive impairment, and the inclusion of evidence of the synucleinopathy and associated neurochemical changes characteristic of DLB. Potential imaging biomarkers may therefore be divided into two types, negative and positive. Negative biomarkers include: MRI hippocampal atrophy and extensive white matter hyperintensities and infarcts; cerebral amyloid on PET-amyloid; hypometabolism in temporo-parietal and posterior cingulate areas on PET-FDG. Positive imaging biomarkers include MIBG scans showing cardiac denervation and FP-CIT evidence of dopaminergic deficits. This presentation will contain two main elements. First a review of the evidence for potential imaging biomarkers for pDLB, drawing on research from early DLB, PDD and AD. Second FP-CIT data will be presented from the ongoing Newcastle LewyPro study, which is a longitudinal study of pDLB. Although imaging evidence can provide positive and negative evidence supporting pDLB, since changes in early disease are necessarily more minor then multimodal imaging may be required for high sensitivity and specificity.

P.83

Evolution of Clinical Features in Possible DLB Depending on ^{123}I-FP-CIT SPECT Result

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Introduction: The diagnosis of possible dementia with Lewy bodies (DLB) is, by definition, uncertain. To make a diagnosis of possible DLB, patients only need to have one core or one suggestive feature in addition to dementia. We hypothesised that core and suggestive features would vary in their ability to predict an abnormal dopamine transporter scan and a follow-up diagnosis of probable DLB. The objective of the study was to assess the evolution of core and suggestive features over time according to the scan result and final diagnosis. Method: 187 patients with possible DLB (dementia plus one core or one suggestive feature) were randomized to have imaging or to follow-up without imaging. DLB features were compared at baseline and at 6-months follow-up according to imaging result and follow-up diagnosis. Results: For the whole cohort, the baseline frequency of Parkinsonism was 30%, fluctuations 29%, visual hallucinations 24% and REM sleep Behavior Disorder 17%. Parkinsonism at baseline was more prevalent in patients with abnormal imaging and a follow-up diagnosis of probable DLB and was the only feature that increased over the 6-months follow-up. There was relatively little evolution of the rest of the DLB features regardless of the final clinical diagnosis or the imaging result. Conclusion: In patients with possible DLB, apart from Parkinsonism, there was no difference in the evolution of DLB clinical symptoms over 6 months between cases with normal and abnormal imaging. Only Parkinsonism and dopamine transporter imaging helped to differentiate DLB from non-DLB dementia.

P.84

Utilization of DaTscan for Lewy Body Dementia - Practical Issues of a Specialty Clinic

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As there are no reliable diagnostic tools and FDA-approved medicine, neurologists find it is a very challenging task to diagnose and treat patients with dementia with Lewy bodies (DLB).The neuropathological hallmarks of DLB are quite diverse; they can be classified into pure cortical diffuse Lewy body disorder, brain-stem predominant Lewy body disorder (Parkinson's disease), and mixed-dementia (Lewy-body variant of Alzheimer's disease). In practice, clinicians usually use the published criteria of DLB to diagnose patients without any biomarker for underlying Lewy bodies. Often the diangosis of DLB can not be made with confidence. DaTscan, avaible in the US since 2011, has played a supportive role in diagnosing DLB. In this observational study, we review subjects with suspected diagnosis of DLB and their DaTscan results. From January 1st 2011 to June 30th 2015, we collected 10 patients who had done DaTscan and reviewed the clinical features, treatment outcomes and prognosis. results are reported here. First, with a positive DaTscan, severity of visual hallucinations can predict the outcomes of dopaminergic treatment. When the DLB patient presented simple visual hallucinations occasionally with mild Parkinsonism (bradykinesia and tremor at rest), they responded well to dopaminergic treatment without worsening hallucinations. The cognitive function of these patients usually did not decline. The long-term prognosis in terms of quality of life was better in the first year of treatment. By contrast, In DLB patients who presented complex visual hallucinations daily, the dopaminergic treatments usually worsened not only their psychotic symptoms but also cognitive function. A positive DaTscan result can not guarantee good outcomes of the treatment in this group. The quality of life was progressively worse in one year. Secondly, regarding treatment with cholinesterase inhibitors, a positive DaTscan result seemingly can predict that the DLB patient would tolerate cholinergic enhancement drugs. Thirdly, few DLB patients had a negative DaTscan result. The dopaminergic treatment was not recommended.

P.85

The First Multicenter study of ^{123}I-Meta-Iodobenzylguanidine Myocardial Scintigraphy for the Diagnosis of Dementia with Lewy Bodies

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Background: Meta-iodobenzylguanidine (MIBG) is a physiological analogue of norepinephrine. ^{123}I-MIBG myocardial scintigraphy has been used as a noninvasive tool for estimating myocardial sympathetic nerve damage. Degeneration of the cardiac sympathetic nerves is a neuropathological feature of Lewy body diseases. Multiple single center studies, including ours, reported very high sensitivity and specificity of ^{123}I-MIBG myocardial scintigraphy for the differential diagnosis of dementia with Lewy bodies (DLB) from Alzheimer's disease (AD) and other dementias. Methods: To establish the diagnostic value, we performed a multicenter study in 10 Japanese sites with 133 patients with clinical diagnoses of probable (n = 61) or possible (n = 26) DLB or probable AD (n = 46) established by a consensus panel. Three readers, unaware of the clinical diagnosis, classified the images as either normal or abnormal by visual inspection. All the institutions used standard acquisition conditions, and cross-calibration of heart-to-mediatinum (H/M) ratios among the institutions was performed with the phantom studies . The H/M ratios were calculated using an automated region-of-interest based system. Results: Using the H/M ratio, the sensitivity was 68.9% and the specificity was 89.1% to differentiate probable DLB from probable AD in both early and delayed images. By visual assessment, the sensitivity and specificity were 68.9% and 87.0%, respectively. In a subpopulation of patients with mild dementia (MMSE ≥ 22, n = 47), the sensitivity and specificity were 77.4% and 93.8%, respectively, with the delayed H/M ratio. Conclusions: Our first multicenter study substantiated the high diagnostic accuracy of ^{123}I-MIBG myocardial scintigraphy, especially in patients with mild dementia, which was comparable to that of [123]I- FP-CIT SPECT multicenter study. Based on its high diagnostic specificity, it is recommended to upgrade the abnormal MIBG myocardial scintigraphy to one of the suggestive features of DLB in the consensus diagnostic criteria for DLB.

P.86

Initially Normal Rated [123]FP-CIT SPECT images in Patients with Probable Dementia with Lewy Bodies: Results of Repeated Imaging

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Objective :Low striatal dopamine transporter (DAT) binding uptake on single photon emission computed tomography (SPECT) imaging is a strong biomarker for the diagnosis of dementia with Lewy bodies (DLB). Little is known about patients meeting clinical criteria for probable DLB having a normal [123I]FP-CIT SPECT (DLB+S-). The aim of this study is to characterize DLB patients with normal [123I]FP-CIT SPECT compared to DLB-patients with abnormal scans at baseline, with clinical and SPECT follow up. Methods: Sixty-seven DLB-patients with [123I]FP-CIT SPECT scans were selected from the Amsterdam Dementia Cohort. Stability of diagnosis was based on yearly clinical follow-up visits. All [123I]FP-CIT SPECTs were evaluated independently by two nuclear medicine physicians and in the case of normal scans follow-up imaging was collected. We matched (1:2) DLB+S- patients for age and disease duration to DLB+S+ patients and compared clinical characteristics. Results: Seven of the 67 (10.4%) [123I]FP-CIT SPECTs were reported normal. Of these, 43% presented with extrapyramidal signs (vs 71% of DLB+S+ patients), 86% with hallucinations (vs 43%), and 100% with REM sleep behavior disorder (RBD) (vs 60%), at baseline. Baseline MMSE scores were comparable, but after one year the DLB+S- group seemed to perform better (median 20 vs 25). In 5/7 DLB+S- patients, a second [123I]FP-CIT SPECT was performed during follow-up (9-38 months) and these scans were all reported abnormal. Discussion: This study is first to describe a subset of DLB patients with initial normal [123I]FP-CIT SPECTs, which turned abnormal during disease progression. We hypothesize that DLB+S- cases could represent a subtype of DLB with possibly a different severity or spread of alpha-synuclein pathology. For clinical practice, if an alternative diagnosis is not imminent in a DLB+S- patient, repeating [123I]FP-CIT SPECT should be considered.

POSTERS – NEUROPATHOLOGY

P.87

Dissecting Hippocampal Lewy Pathology in Dementia with Lewy Bodies

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Background: Despite considerable effort, the anatomic and neuropathologic correlates of cognitive impairment in Dementia with Lewy Bodies (DLB) remain unclear. While some studies have implicated alpha-synuclein-containing Lewy bodies in the neocortex, others have pointed to potential contributions of alpha-synuclein pathology in the hippocampus. Methods/Design: We systematically examined hippocampal Lewy pathology and its distribution in hippocampal subfields in 95 clinically and neuropathologically characterized cases from the brain bank of the UCSD Shiley-Marcos Alzheimer's Disease Research Center (ADRC). Results: We found that alpha-synuclein pathology in our DLB cases was predominant in two hippocampal subregions: the CA2 subfield and the entorhinal cortex (EC). While alpha-synuclein pathology in the CA2 subfield mainly consisted of Lewy neurites and punctate alpha-synuclein profiles resembling presynaptic staining, perikaryal Lewy bodies were much more abundant in the EC. Lewy neurites in CA2 centered within a small subregion just distal to the mossy fiber projections from the dentate gyrus. Since CA2 is thought to receive inputs from the EC, our data suggests involvement of the EC-to-CA2 circuitry in the pathogenesis of DLB. This hypothesis is supported by clinicopathological correlations showing that the extent of EC Lewy pathology is significantly correlated with learning on trials 1-5 of the California Verbal Learning Test (CVLT) (r=-.239; p=.023), a standardized verbal memory test impaired in DLB. After controlling for test-death interval this relationship held, and a significant correlation between trials 1-5 learning and extent of CA1 Lewy pathology emerged (r=-.249; p=.031). CA1 Lewy pathology burden also significantly correlated with immediate recall (r=-.249; p=.031) and delayed recall (r=-.290; p=.012) on the Visual Reproduction Test in this setting, and with score on the Dementia Rating Scale (DRS) (r=.265; p=.021). Conclusions: Thus, Lewy pathology in the CA1 subfield, despite being less than in the CA2 subfield and the EC, may contribute importantly to dementia in patients with DLB.

P.88

Mixed Alzheimer's and Lewy Body Disease

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Background: Mixed pathology is frequently seen in brains of demented and non-demented elderly at post mortem examination. Mixed dementia on the other hand is less frequent and neuropathologically should only be diagnosed if criteria for more than one full blown disease are met. In cases that were neuropathologically diagnosed as mixed Alzheimer's and neocortical Lewy body disease (mixed AD/LBD) but clinically presented either as AD or LBD, the latter including dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) the amount of hyperphosphorylated microtubule associated tau (HP-т), amyloid-β protein (Aβ) and α-synuclein (α-syn) was measured. Methods: The study group consisted of 28 cases (mean age, 76.11 SE: ±1.29 yrs; m:f 17:11) of which 19 were neuropathologically diagnosed as mixed AD/LBD. Clinically, 8 mixed AD/LBD cases were diagnosed as AD (cAD), 8 as DLB (cDLB), and 3 as PDD (cPDD). In addition we investigated cases that were both clinically and neuropathologically diagnosed as either AD (pure AD; n=5) or DLB/neocortical LBD (pure DLB; n=4). Sections from neocortical, limbic and subcortical areas were stained with antibodies against HP-т, Aβ, and α-syn. Results: cAD cases had higher HP-т loads than both cDLB and cPDD and the distribution of HP-т in cAD was similar to the one observed in pure AD while cDLB showed comparatively less hippocampal HP-т load. cPDD cases showed lower HP-т and Aβ loads and higher α-syn loads. Conclusions: Here, we show that in neuropathologically mixed AD/LBD cases both the amount and the topographical distribution of pathological protein aggregates differed between distinct clinical phenotypes and our findings suggest that in cAD severe α-syn pathology may have been triggered by AD pathology.

P.89

Autopsied Dementia with Lewy Bodies Cases at the National Brain and Tissue Resource for Parkinson's Disease and Related Disorders (NBTR-PD) and Arizona Alzheimer's Disease Core Center (AZADCC)

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Background: The NBTR-PD and AZADCC are funded by the US NINDS & NIA, respectively; both are served by the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and the Brain and Body Donation Program (BBDP). The mission is to perform longitudinal standardized clinical assessments, conduct rapid autopsies with comprehensive neuropathological examinations and provide high-quality brain & body tissue to researchers. Methods/Design: BBDP brain-only autopsies began in 1987, AZSAND clinicopathological operations in 1996, neuropathologist examinations in 1997, AZADCC in 2001, whole-body autopsies in 2005 and NBTR-PD in 2011. Results: Of 1266 autopsies with a neuropathologist examination, 120 meet 2005 DLB Consortium intermediate or high diagnostic criteria. Median age is 82, 57% are male, 56% are ApoE-E4 carriers, median postmortem interval is 3.0 hours. 84% of DLB cases meet NIA-Reagan AD intermediate or high neuropathological criteria. Other major concurrent brain disease is common, including vascular dementia (12), hippocampal sclerosis (7), progressive supranuclear palsy (1), corticobasal degeneration (1), Huntington's disease (1), Pick's disease (1) and glioblastoma (1). One or more infarcts are present in 46%. As reported by others (Nelson et al, J Neurol 2010 257: 359–366), only a small percentage of cases (27%) were clinically suspected, while of those that received a clinical diagnosis of DLB or Lewy body disorder, 85% were confirmed neuropathologically. Available clinical data includes MMSE (n=95), UPDRS (46), sleep questionnaire (42) and smell test (28). More than 110 cases have frozen brain tissue as well as postmortem CSF and blood serum. 47 had whole body autopsy with both fixed and frozen tissue available. Conclusions: DLB researchers are invited to request tissue and/or data. Information, as well as custom assistance with requests, is available at www.brainandbodydonationprogram.org.

P.90

Cognitive and Behavioral Features in Multiple System Atrophy with Lewy Body-Like Inclusions

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Background: Lewy body (LB)-like inclusions occur to a variable degree in cases of multiple system atrophy (MSA) and when present, this type of neocortical α-synuclein inclusion is associated with cognitive impairment. Objective: To evaluate the cognitive and behavioral features in patients with neuropathologically confirmed MSA with LB-like inclusions. Methods: Neuropathological review in 35 autopsy-proved MSA patients MSA included α-synuclein immunohistochemistry in sections of brainstem, cerebellum, basal ganglia, thalamus, medial temporal structures, and neocortex. Cognitive impairment was based on subjective complaint and objective testing using short test of mental status (STMS), Montreal Cognitive Assessment and formal neuropsychometric testing. The clinical record was reviewed for cognitive features, hallucinations, behavioral dyscontrol, and sleep disorders. Results: Of the 35 MSA patients, 11 (31%) had cognitive impairment. In those 11 patients, the most common deficits on the STMS were in calculation (n=10, 91%), attention (n=6, 55%), and construction (n=3, 27%). Neuropathological examination revealed that the majority (n=28, 80%) had at least some LB-like cytoplasmic inclusions. These were isolated findings restricted to brainstem and/or limbic regions in most cases (n=19), however 9 patients (26%) showed step-wise progression of this pathology (brainstem to limbic to neocortex) with neocortical involvement in 5. Of those 5 patients, 4 had cognitive impairment while the other had hallucinations and behavioral dyscontrol. Dream enactment behavior was present in 4 patients (80%) with neocortical LB-like inclusions, compared to 10 patients (33%) without inclusions (p = 0.13). Overall median survival was significantly longer in MSA patients with LB-like inclusions (9.7 years, interquartile range 7.2-14.8) compared to those without inclusions (6.3 years, interquartile range 4.6-8.0; p = 0.043). Conclusions: Our data suggest that 1) cognitive impairment and hallucinations in MSA may be related to underlying LB-like pathology and 2) longer disease course may predispose to development of neocortical LB-like cytoplasmic inclusions in MSA.

P.91

Alpha-Synuclein Burden Predicts Duration of Illness in Dementia with Lewy Bodies (DLB)

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Background: A shorter duration of illness in DLB has been attributed to concomitant Alzheimer pathology, but prior studies relied on Lewy body counts and did not include Lewy neurites. We used quantitative image analysis that includes neuritic pathology to determine the contribution of α-synuclein, tau and amyloid-β burden to duration of illness. Methods: DLB patients (n=49) were followed at Mayo Clinic Florida and underwent autopsy. Quantitative image analyses of α-synuclein (LB509), tau (PHF-1) and amyloid-β (4G8) burden was perfsormed in five neocortical regions and three limbic regions. Percentage burden was calculated by pixel count algorithms for 4G8 and LB509, and by a color deconvolution algorithm for PHF-1. A multiple linear regression analysis examined the contribution of pathology to duration of illness, and a commonality analysis examined the unique and shared variance between predictors. Results: Patients were predominantly male (82% male), mean illness duration was 7.2 ± 3 years and 92% harbored 3 or 4 core DLB clinical features. Pathologically, 15 patients had transitional Lewy body disease (TLBD), and 34 had diffuse Lewy body disease (DLBD), of which 27 and 22 were considered high- and intermediate-likelihood DLB, with Consortium for DLB Criteria. Greater density of each pathology was associated with shorter illness duration ($p < 0.05$). The regression model was significant ($R2 = 0.25$, $p < 0.004$), and revealed that α‑synuclein predicted duration of illness ($p=0.03$) over and above that of tau ($p=0.6$) and amyloid-β ($p=0.22$). 20% of the variance was explained uniquely by α-synuclein and by α-synuclein's shared variance with tau and amyloid-β. Separate analyses of the DLBD group showed the same pattern. Conclusions: A shorter duration of illness in DLB is associated with greater α-synuclein burden, both uniquely and in synergy with AD pathology. These results reveal the important contribution of overall α-synuclein burden (including Lewy neurites) when assessing clinical-pathologic relationships.

P.92

Differential Contribution of α-Synuclein, Tau and Amyloid-β to Rate of Decline in MMSE and DRS

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Background: Mini Mental State Examination (MMSE) and Dementia Rating Scale (DRS) are commonly administered to monitor change in dementia severity over time. We examined the degree to which α-synuclein, tau and amyloid-β explains the annualized rate of change for the MMSE and DRS in dementia with Lewy bodies (DLB). Methods: Clinically probable DLB patients (n=35) with baseline Global Deterioration Scale scores < 6 were longitudinally followed until autopsy at Mayo Clinic Florida. Quantitative image analysis of α-synuclein (LB509), tau (PHF-1) and amyloid-β (4G8) was undertaken in cortical, limbic and hippocampal regions. Separate hierarchical multiple regression analyses were performed for MMSE and DRS annualized rate of change with mean total percentage density of α-synuclein, tau or amyloid-β as independent variables. Results: Mean years of follow-up was 3.7 ± 2, estimated onset age of cognitive impairment was 67 ± 8 years, education was 15 ± 3 years, and duration of illness was 7.6 ± 2 years. 91% had three or four core clinical DLB features (visual hallucinations, REM sleep behavior disorder, fluctuations , parkinsonism) during life. Baseline MMSE was 25 ± 3, and DRS was 125 ± 10. For the MMSE model ($R^2 =0.39$), tau and amyloid-β explained the annualized rate of change over and abovethat explained by α-synuclein (change $R^2= 0.30$, $p < 0.05$). For the DRS model ($R^2 =0.31$), α-synuclein and amyloid-β accounted for the annualized rate of change over and above tau (change $R^2= 0.29$, $p < 0.05$). Conclusions: A faster rate of MMSE decline was associated with greater tau and amyloid burden, while a faster rate of DRS decline was associated with greater α-synuclein and amyloid-β burden. When assessing rates of cognitive change, cognitive screens of dementia may be differentially sensitive to the contributions by α-synuclein, tau and amyloid-β in DLB.

P.93

Anosmia in Dementia with Lewy bodies: A Retrospective Analyses Exploring Cluster of Prediagnostic Symptoms

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Background: The clinical phenotype of dementia with Lewy Bodies (DLB) is heterogeneous, and often the disease is misdiagnosed as other dementias or movement disorders such as Parkinson disease (PD). Anosmia is a symptom commonly associated with Lewy body pathologies and can be present many years prior to diagnosis of alphasynucleinopathies. However, a number of studies have reported that self-report of anosmia is unreliable and that the use of objective olfactory testing should be used in determining loss of sense of smell. Methods: We performed a retrospective review of medical records of patients seen at the University of Utah Department of Neurology. The presence of twenty-five symptoms, including anosmia, was recorded into an online database. We identified 74 cases with DLB; only patients who were coded with a probable diagnosis of DLB were included. We analyzed the dataset to identify the cluster of symptoms associated with anosmia in DLB. Results: Of the 74 patients reviewed, 15 (20.27%) patients reported the presence of anosmia. Anosmia was not statistically associated with age or sex. A logistic regression analysis found that anosmia was nearly statistically associated with myoclonus ($p = .061$, odds ratio = 3.34). Anosmia was not statistically associated with any other motor or cognitive symptoms of DLB. Conclusion: Our results suggest that anosmia is prevalent in the phenotype of Lewy body disorders such as DLB. However, anosmia does not appear to significantly associated with any motor or cognitive symptoms. Our study further supports the need to use objective tests along with other diagnostics in order to improve and provide for more accurate diagnosis of Lewy body pathologies.

P.94

Neuropathological Influences on the Clinical Phenotype of Lewy Body Dementias

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Background: There is heterogeneity in the onset of dementia and degree of co-morbid Alzheimer's disease (AD) neuropathology across synucleinopathies. The objectives of this study were to examine the relationship between AD neuropathology and the clinical expression of dementia in a large multi-center cohort of autopsy-confirmed Lewy body dementias (i.e. Parkinson's disease dementia, PDD and Dementia with Lewy bodies, DLB). Methods/Design: Patients selected had a clinical diagnosis of PDD (n=96) or DLB (n=77) with autopsy-confirmation of synucleinopathy (SYN, i.e. brainstem, limbic or neocortical stage) with (SYN+AD) or without (SYN-AD) a secondary diagnosis of AD (Braak>III and CERAD>B). We examined demographics and the burden of tau, senile plaque and alpha-synuclein neuropathology on an ordinal scale in five cortical regions between pathologically- and clinically-defined groups. Results: SYN+AD had an older age at disease onset (ADO) (71.1+7.8years), shorter motor-dementia interval (MDI) (2.1+6.4years) and shorter disease-duration (DD) (8.8+5.1years) than SYN-AD (ADO 62.2+11.5,MDI9.3+11.7,DD13.6+7.3;p < 0.001). SYN+AD pathology was found in 75% of clinical DLB (56/75) cases and only 36% of PDD+AD (34/94;p< 0.001). DLB also had higher burden of cortical alpha-synuclein pathology than PDD (p < 0.001). Clinically, DLB cases had an older ADO (72.1+9.0) and shorter DD (6.6+2.5) than PDD (ADO63.2+10.2,DD14.4+6.8;p < 0.001). Subgroup analyses comparing DLB+AD to PDD+AD and DLB-AD to PDD-AD found both DLB+AD and DLB-AD had an older ADO and shorter DD compared with PDD+AD and PDD-AD, respectively (p < 0.001). In contrast, comparison of DLB+AD and DLB-AD finds similar demographics (p>0.1). Conclusions: PDD and DLB exist on a spectrum of synucleinopathies and co-morbid AD neuropathology may influence clinical phenotype. The clinical diagnosis of DLB may have prognostic utility, as co-morbid AD does not fully explain the differences in clinical expression of PDD and DLB.

P.95

Transitional Lewy Body Disease with Minimum Alzheimer Pathology May Not Represent Probable DLB: Two Autopsied Cases Reports

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Objectives: The diagnostic criteria for dementia with Lewy bodies (DLB) mentioned the correlation of distribution for Lewy pathology and degree of Alzheimer pathology as a likelihood of the DLB clinical syndrome.The cases of limbic type of Lewy body disease (LBD) with mild Alzheimer pathology (neurofibrillary tangle Braak stage 0-II), would tend to classify as high-likelihood category. However, previous studies indicated that the prevalence of probable DLB is not frequent in this category. In this study, we reported 2 autopsy cases with the pathological category without observed any core features of diagnostic criteria. Cases: Case 1: A 78-year-old Japanese man. At the age of 77, he became hypochondriacal and paranoid following the death of his wife. Because he became violent and threatened others, he was admitted to a psychiatric hospital. Sixteen days after admission, he died of acute pneumonia. Case 2: A 75-year-old Japanese man. At the age of 71, he developed delirium when he was treated with a steroid for ANCA-associated vasculitis. His abnormal behavior continued, and neuroleptic sensitivity, autonomic symptoms and psychiatric symptoms were observed. Neither of the patients exhibited visual hallucinations and parkinsonism in their clinical courses. Both patients had transitional LBD with concurrent neurofibrillary tangle (NFT) Braak stage II, which thought to be high-likelihood DLB pathology. The nigral degenerations were less observed in these cases, being confirmed the absence of parkinsonism. Conclusions: In the pathological category of transitional LBD with Braak NFT stage 0-II, other clinical conditions, such as Parkinson's disease dementia, rather than probable DLB may be common. Further clinicopathological study will be needed.

P.96

Neuroinflammation in Lewy Body Dementia

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Evidence of neuroinflammation as a key factor in the pathogenesis of neurodegenerative conditions is accumulating. However, whether inflammation has a protective or damaging role remains unclear. In light of studies in Alzheimer's disease and Parkinson's disease which have provided much of the evidence for inflammatory pathology in neurodegeneration, we reviewed the literature for evidence of inflammation in dementia with Lewy bodies and Parkinson's disease dementia. Neuroinflammation has been confirmed in vivo using PET imaging, with microglial activation seen in Parkinson's disease dementia and recently in dementia with Lewy bodies. Levels of activation in Parkinson's disease and Parkinson's disease dementia suggest chronic inflammation, but there is also evidence of an association with a decline in cognitive ability and neuronal function. Microglia are known to be activated by a range of conformations of alpha-synuclein, the key component of Lewy bodies. Constituents of both the innate and adaptive immune systems are associated with this interaction, suggesting alpha-synuclein can trigger a broad inflammatory response. Evidence of neuroinflammation in Lewy body dementia is further supported by pathological and biomarker studies. Though genetic and epidemiological studies support a role for inflammation in Parkinson's disease, evidence in Lewy body dementia is limited, with few studies undertaken. Our review highlights the need for future studies to further establish the presence of inflammation in dementia with Lewy bodies including imaging, genetic and biomarker studies. There is also a need to identify whether the nature and extent of microglial activation in Lewy body dementia can be linked to structural change, progression of domain specific cognitive symptoms and peripheral inflammation. Answers to these questions will enable the evaluation of immunotherapies as potential therapeutic options for prevention or treatment of dementia with Lewy bodies and Parkinson's disease dementia.

P.97

Pathological α-Synuclein Distribution in Subjects with Coincident Alzheimer's and Lewy Body Pathology

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Background: Since Braak's original description of Lewy body pathology stages, several studies have described a significant number of cases that do not fit the porposed the staging system across cohorts. We explored if coincident pathologies might modify the pathology distribution. Methods: We analyzed the distribution of Lewy body (LB) related pathology (LRP) in cases from the Center for Neurodegenerative Disease and the Banner Sun Health Research Institute Brain and Body Donation Program to test if coincident Alzheimer's disease (AD) could modify the distribution of alpha-synuclein LRP). We included 308 subjects with AD and LRP pathologies (AD-LB), 147 Parkinson's disease (PD) and 75 PD with coincident AD (PD-AD) cases classified as: 1) brainstem, 2) amygdala and limbic predominant, 3) brainstem and limbic stage and 4) neocortical stage. Results: AD-LB limbic stage cases showed a lower burden of LRP in the brainstem and frontal cortex than PD cases. Conversely, AD-LB and PD-AD cases had a higher burden of LRP in posterior neocortical areas, especially occipital cortex. Overall, the AD-LB cases showed higher dopamine active transporter immunoreactivity in the putamen compared to the PD and PD-AD groups, and there was less substantia nigra neuron loss in the neocortical and limbic LRP stages. Finally, the AD-LB groups showed a lower burden of LRP in the spinal cord, vagus nerve, submandibular gland and esophagus. Conclusions: We propose that LRP follows the progression originally described by Braak in PD with an initial brainstem involvement, whereas in cases with coincident AD lacking motor impairments or a clinical DLB profile, LRP may spread initially from the olfactory bulb and amygdala to other areas. The presence of AD pathology may modulate the progression of LRP through mechanisms that remain to be elucidated, but could be linked to distinct strains of these pathologies.

P.98

Associations Between Hyperphosphorylated Tau, Full Length β-Amyloid and Pyroglutamylated Amyloid-β with α-Synuclein Phosphorylated at Serine-129

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Background: Pathologies characteristic of Alzheimer's disease (i.e. hyperphosphorylated tau (HP-T) and β amyloid (Aβ) plaques) often co-exist in patients with dementia with Lewy bodies and Parkinson's disease dementia in addition to lesions positive for α-synuclein. Recent studies have pointed to a synergistic relationship between these aggregations, which may have clinical implications. Pyroglutamylated amyloid-β (pE(3)-Aβ) and α-synuclein phosphorylated at serine-129 (pSer129 α-syn) are post-translational modifications of amyloid-β and α-synuclein respectively and research into their contribution to disease pathogenesis is gathering pace. This study aimed to elucidate associations between HP-T, pE(3)-Aβ and full length Aβ with pSer129 α-syn in DLB and PDD. Methods: The study consisted of 34 post-mortem brains (mean age, 76.21 SE:±0.97 yrs; m:f 20:14), 21 diagnosed as DLB and 13 as PDD. Fixed sections of frontal cortex, cingulate, thalamus and entorhinal cortex were stained for antibodies against HP-T, full length Aβ, pE(3)-Aβ and pSer129 α-syn and quantitative pathological burden was assessed using image analysis. Results: Preliminary analysis revealed pE(3)-Aβ correlated positively with pSer129 α-syn in the frontal cortex and cingulate in PDD cases, whilst full length Aβ correlated with pSer129 α-syn in the majority of regions in PDD and in the thalamus of DLB cases. HP-T positively correlated with pSer129 α-syn in entorhinal, frontal and cingulate in the combined cohort and in cingulate and entorhinal cortex in PDD cases. Discussion: This study supports previous data suggesting a synergistic relationship between Aβ and pSer129 α-syn and also introduces pE(3)-Aβ as a potential contributor, making it an interesting target for future study. In addition to Aβ, HP-T may also play a role in a putative synergistic relationship and further investigations are warranted to unravel the effects these pathologies have on each other and the clinical phenotype of DLB and PDD.

P.99

Investigating the Pathological Correlates of Motor Dysfunction in Dementia with Lewy Bodies and Parkinson's Disease Dementia

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Background: In addition to inclusions of α-synuclein (α-syn), dementia with lewy bodies (DLB) and Parkinson's disease (PDD) exhibit co-pathologies more frequently associated with Alzheimer's disease (i.e. hyperphosphorylated tau (HP-T) and β amyloid (Aβ) plaques). Deficits in motor control as a result of degeneration of the nigro-striatal pathway and motor circuitry are common to both disorders with the pathological correlate yet to be identified. This study investigated a putative association between individual and combined pathologies on α-synuclein burden, extrapyramidal motor features associated with DLB and PDD and differences in the distribution of lesions in relation to cortical and limbic pathology. Methods: The study consisted of 44 fixed post-mortem brains (mean age, 74.4 SE: ±0.84 yrs; m:f 31:13), 23 were DLB and 21 PDD. HP-T, Aβ and α-syn burden was quantified in substantia nigra, striatum, external globus pallidus, thalamus, cortical and limbic regions. Burden of all three individual pathology scores (IPS) were summated producing a combined pathology score (CPS) for each region. End stage motor dysfunction was measured by part III of the Unified Parkinson's Disease Rating Scale. Results: In PDD, HP-T load correlated with α-syn load in the striatum, thalamus and external globus pallidus, whilst CPS of HP-T and Aβ correlated with α-syn load in the striatum. In DLB, IPS of Aβ and a CPS of Aβ and α-syn correlated with UPDRS in the striatum and thalamus. Distribution of HP-T and Aβ loads were similar between disease groups however entorhinal α-syn load was affected least in PDD whilst had the second highest α-syn load in DLB. Discussion: This study supports growing evidence of a synergistic relationship between HP-T and α-syn, and whilst Aβ in combination with α-syn may be associated with UPDRS in DLB, the pathological correlate of motor dysfunction in DLB and PDD is yet to be elucidated.

POSTERS – Neuropsychology and Cognitive Neuroscience

P.100

Neuropsychological Profile in Early DLB: Comparison with Alzheimer's Disease

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Aim: The neurocognitive profile in early dementia with Lewy-bodies (DLB) may differ from the profile in early Alzheimer's disease, but few studies have been reported. Thus, in the present study, we investigate the neuropsychological profile in DLB as compared to AD. Material and Methods: From the baseline of a longitudinal cohort study including patients with mild dementia in western Norway, 77 patients with probable DLB and 113 patients with probable AD were included. A neuropsychological test battery consisting of the MMSE, Golden Stroop test, Boston naming test (BNT), California Verbal Learning test-II (CVLT), semantic verbal fluency, Trail-making test (TMT) A and B, the Silhouettes test from VOSP, were administered. Separate logistic regression analyses for each neurocognitive variable were performed, adjusted for age, sex and education, followed by a forward stepwise multivariate logistic regression including all variables.Results: The separate logistic regression analyses showed that for visuospatial functions, inability to perform the MMSE pentagon test predicted DLB (p=.007), but that VOSP silhouettes score was nonsignificant. Lower scores on attention and psychomotor speed (TMT-A, Stroop Word, Stroop Color) predicted DLB (p Stepwise logistic regression resulted in a model including Stroop Word, CVLT delayed recall and delayed recognition and ability to perform Trail-Making B, adjusted for age, sex and education. Sensitivity for predicting DLB was 77% and specificity was 83%. Conclusions: Low reading speed, inability to perform TMT-B and less impairment on delayed recall and recognition may be a clinically applicable approach for distinguishing early DLB from AD through neuropsychological tests.

P.101

Electrophysiological Correlates of Attentional Dysfunction in Dementia with Lewy Bodies

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Background: Dementia with Lewy bodies (DLB) is characterised by attentional impairments although the underlying aetiology is poorly understood. Using electrophysiological approaches, we investigated the extent to which attentional network efficiency was differentially affected in DLB patients (n=22) relative to Alzheimer's disease (AD) patients (n=24) and age-matched healthy controls (n=19) by using a modified version of the Attention Network Test (ANT). The ANT, a visual attention task, probes the efficiency of three anatomically defined attentional networks: alerting, orienting and executive-conflict. Methods: Participants completed the ANT whilst undergoing high-density electroencephalography (EEG) recordings (128 channels). Time-frequency wavelet analyses were conducted to investigate event-related spectral perturbations (ERSP), between 4-90Hz, in the 500ms after stimuli presentation. Attentional network ERSP was calculated by contrasting oscillatory reactivity following relevant stimuli, and repeated-measures (time x region) ANOVAs were conducted with a between-subject factor of group (controls, AD, DLB). Results: For the alerting network, the DLB group exhibited attenuated ERSP in the lower frequencies (< 30Hz); in the theta range (4-7Hz) the controls and AD group showed global synchronisation (across all regions), peaking at approximately 300ms, which was absent in the DLB group. Lack of DLB theta synchronisation between 250-450ms over the right parietal cortex associated with a higher total score on the Clinical Assessment of Fluctuation scale. ERSP associated with the orienting and executive networks was comparable across all groups, comprising intermittent synchronisation of reduced power relative to the alerting network, which was diffuse across the time and frequency domains in all regions. Conclusions: Attenuated global oscillatory reactivity in the DLB group specific to the alerting network is indicative of this fractionated aspect of attention, the ability to maintain an alert state, being differentially affected in DLB. Lack of theta reactivity in the right parietal region may be a potential contributor to the pathophysiology of cognitive fluctuations in DLB.

P.102

Cognitive Profile in Prodromal Dementia with Lewy Bodies

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Background: Cortical and subcortical cognitive impairments have been found in Dementia with Lewy Bodies (DLB). Roughly they comprise visuo-constructive and executive dysfunction, while memory would remain relatively spared. However, the cognitive profile of patients with prodromal DLB, remains poorly illustrated to date. Methods: We included 37 patients with prodromal DLB – DSM V – (age: 67.1 ± 8.6, 16 men, MMSE: 27.4 ± 1.6) and 29 healthy controls (HC; age: 68.8 ± 7.9, 15 men, MMSE: 29.0 ± 0.9). They were presented an extensive neuropsychological test battery assessing memory, executive functions, visuo-perceptive and -constructive abilities, language and social cognition. Results: Patients had lower scores on a visual recognition memory test (ps ≤ .021), and lower free (all ps ≤ .035), but not total, recall performances on a verbal episodic memory test than HC. Short term memory (p=.042) and working memory (p=.002) were also lower in patients. Assessment of executive functions showed no slowing, but overall lower performances in patients than in HC (all ps ≤ .049), while that of instrumental functions yielded mixt results. Indeed, patients had lower scores on language tests (ps ≤ .022) and apraxia for pantomime of tool use (p=.002) and imitation of meaningless gesture (p=.005), as well as weakened visuo-spatial abilities (p = .047). However, visuo-constructional and visuo-perceptual abilities did not differ between both groups. Finally, theory of mind abilities are lower in patients than in HC (p < .05), but their emotion recognition abilities are similar. Conclusion: This study presents the cognitive profile in prodromal DLB. In line with literature, our results show lower performances in patients than in HC on tests assessing executive functions. However, we found, from a prodromal stage of DLB, memory and social cognition deficits, as well as weakened visuo-spatial and praxic abilities, while visuo-constructional abilities are still unaffected.

P.103

Prospective Memory Impairment in Parkinson's Disease and Rapid Eye Movement Sleep Behavior Disorder

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Nearly a third of patients with Parkinson's disease (PD) and half of patients with REM sleep behavior disorder (RBD) are diagnosed with mild cognitive impairment (MCI). Their common profile of cognitive decline is usually characterized by executive and attention deficits. Previous neuropsychological studies on prospective memory (PM), defined as the ability to execute an intention at an appropriate moment in the future, have reported impairment in dementia-free PD. However, no study to date has investigated its integrity in RBD. The aim of this study was to compare PM performance in PD and RBD according to their MCI status.Seventy-eight participants were included: 15 PD, 44 polysomnography-confirmed idiopathic RBD patients (19 with MCI and 40 without MCI) and 19 healthy controls (HC). A computerized general knowledge task was developed to evaluate PM. Ten target words, varying in perceptual distinctiveness (salience), were embedded in the task. Instructions were to simultaneously answer questions and detect target words. Participants underwent neurological and neuropsychological assessments for MCI diagnosis. Repeated-measures ANOVA did not reveal a significant group X salience interaction. A significant main group effect was observed, F (2, 75) = 9.81, p < 0.05. Compared to HC, both PD/RBD patient groups showed significant difficulty detecting salient targets. PD/RBD with MCI also performed poorly when targets were more difficult to detect (non-salient condition), while performance observed among patients without MCI was comparable to that of HC. Once completed, only MCI patients had trouble remembering the target and/or the action to perform when detected. results suggest that target detection impairment in PD/RBD without MCI can potentially be attributed to altered executive and attention mechanisms. In contrast, MCI patients' poor performance on both detection conditions may additionally be due to forgetfulness. PM could therefore be a promising indicator to early cognitive dysfunction in PD/RBD.

P.104

Early Bottom-Up Visual Information Processing in Hallucinating Patients with Parkinson's Disease with Dementia: A Preliminary Visual Evoked Potential Study

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Background: A number of reports suggest that bottom-up visual processing is relatively intact in Parkinson's disease with dementia (PDD). However, previous studies have implicated bottom-up deficits in the aetiology of visual hallucinations (VH). The visual evoked potential (VEP) can be used as a marker of bottom-up visual information transfer, but the findings in PDD are mixed. Therefore, in this study we sought to characterise the VEP in PDD patients with a range of VH severity. Methods: PDD patients with a range of VH severity (n = 14), and age matched controls (n = 17) underwent electroencephalography, where a checkerboard pattern was used to elicit the VEP response. Occipital P100 component latencies and amplitudes were compared between groups using a one-way analysis of covariance test, controlling for age. The relationship between VEP latencies and amplitudes, and VH severity, was tested using Pearson correlations. Secondary correlations were performed between measures of medication (levodopa dose and number of medications) and disease duration. Results: There were no significant differences in P100 latency and amplitude between groups. However, VH severity was negatively associated with P100 latency ($p < .001$) but not amplitude. VH severity was also associated with greater disease duration ($p < .001$). Finally, as expected, disease duration was further associated with an increased levodopa dose ($p < .05$) and a higher number of PD medications ($p < .001$). Conclusions: The inverse relationship between VH severity and VEP P100 latency was unexpected but may reflect that an intact bottom-up system is a necessary prerequisite for the manifestation of visual hallucinations. Further studies examining the relevance of top-down function and its relationship with bottom-up processing are warranted to help understand the observed relationship between VEP P100 latency and VH severity.

P.105

Association of Boston Naming Test Error Types with Distribution of Lewy Bodies and Neurofibrillary Tangles

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Introduction: In dementia with Lewy bodies (DLB), the distribution of Lewy bodies may be limbic-brainstem predominant ("transitional DLB", TLBD) or cortico-limbic-brainstem ("diffuse DLB", DLBD). However, a subset of DLB patients has concomitant Alzheimer disease (AD) pathology. Clinically, DLB patients demonstrate worse attention and visuoperceptual/spatial functions compared to memory and naming, whereas AD patients demonstrate the opposite profile. We hypothesize that Boston Naming Test (BNT) item error types typically related with AD (semantic or circumlocutory) are associated with AD pathology in DLB. Methods: A prospective sample of clinically-diagnosed DLB patients from Mayo Clinic Rochester and Florida was classified at autopsy as TLBD (n=27) and DLBD (n=75), and Braak NFT stage was determined. Baseline cognitive assessment was obtained and BNT error types were coded into four categories: Perceptual, Phonemic, Semantic, or Circumlocutory. Results: At baseline, the TLBD and DLBD groups did not differ in age, education, MMSE, Global Deterioration Scale, and number or onset of core DLB features. TLBD and DLBD groups did not differ in baseline performance on the BNT, delayed recall on Auditory Verbal Learning Test (AVLT), Logical Memory-II, or performance on Block Design or Rey-Osterrieth Complex Figure copy. DLBD patients had more BNT circumlocutory errors than TLBD ($p < 0.05$). A higher Braak NFT stage also was associated with worse delayed recall on AVLT ($r= -0.25$, $p < 0.05$) and Logical Memory ($r= -0.30$, $p < 0.01$), BNT ($r= -0.32$, $p < 0.01$), and greater BNT circumlocutory errors ($r= 0.22$, $p < 0.05$). When classified jointly by Lewy body distribution and Braak NFT stages < 4 (low) and Braak NFT ≥ 4 (high), circumlocutory errors were greatest among DLBD patients with high Braak NFT stage ($p < 0.05$). Conclusions: BNT circumlocutory errors are more frequent in patients with both cortical Lewy bodies and high Braak NFT stage.

POSTERS – Non-Pharmacologic, Psychosocial, Education, Cognitive, Movement

P.106

Principles for Managing Lewy Body Dementia: Patient and Carer Perspectives from the DIAMOND-Lewy Study

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Background: The aim of the DIAMOND-Lewy programme is to improve the diagnosis and management of Lewy body (LBD) through a series of linked work packages. This includes the development, and subsequent assessment, of an evidence-based LBD practical management toolkit for clinicians through a systematic review and Delphi survey. To inform the development of the management toolkit, we also explored the views of patients and carers on the symptoms they found most troubling and their experiences of medical consultations for LBD. Methods/Design: Qualitative interviews with patients (n=13) and carers (n=18); and two workshops with patients (n=10) and carers (n=13). Interviews were recorded and transcribed; data from the workshops were recorded on flip charts. All data were analysed thematically. Results: Patients and carers highlighted the day to day challenges of living with LBD (e.g. aggression, sleep problems, apathy, falls and paranoia). Carers typically felt unprepared to manage these issues and often relied on trial and error. Many found it difficult to discuss their concerns in consultations partly because of the stigma associated with some symptoms, their desire to present themselves as being able to 'cope' and the interpersonal issues involved in joint consultations. Conclusions: There is a clear mismatch between the issues of most concern to patients and carers and the existing evidence base. A key issue for the research team is how to integrate the insights from qualitative data with evidence from RCTs in the management toolkit. We have addressed this by drawing on the qualitative data to develop management principles which highlight improved communication, agreeing priorities for management and enabling patients and carers to raise difficult issues in consultations for LBD.

P.107

The Effect of Exercise on Individuals with Dementia with Lewy Bodies: A Systematic Review

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Background: Dementia with Lewy Bodies (DLB) is estimated to be the second most prevalent dementia, affecting 1.3 million Americans. Physical function declines through Parkinsonism and sedentariness exacerbated by the cluster of motor, psychiatric and cognitive symptoms in DLB. Exercise may improve functional outcomes in Parkinson's disease (PD), as well as Alzheimer's disease (AD). However, due to the multi-domain DLB symptom cluster, vulnerable individuals are often excluded from exercise studies evaluating physical function in PD or cognitive function in dementia to avoid confounding results.The aim of this review was to evaluate existing literature reporting the effects of exercise or physical activity on physical, cognitive or psychological function in DLB. Methods: A high-sensitivity search was executed across 19 reputable databases. Peer-reviewed articles of any language and quality, published or unpublished, that analysed effects of isolated exercise or physical activity on participants with indicative DLB or PD dementia were evaluated. Results: The initial search retrieved 111,485 articles; 275 full articles were reviewed with 240 (87.2%) articles subsequently deemed ineligible due to exclusion of participants for comorbidities of either dementia or Parkinsonism. Five low-quality articles were deemed eligible (14 participants for exercise, 2 control). Interventions included motor, cueing, strength or aerobic exercise variants. Homogeneity of outcomes was low. Notably, improvements in habitual gait speed in one trial (n=9) and one case report (n=1) exceeded minimal clinical significance reported for AD cohorts (0.09m/s). Other outcomes evaluated in the majority of participants appeared to improve modestly after intervention. Conclusions: Scarce research exists for any outcome in DLB. This review confirms that high-quality exercise studies for PD as well as dementia cohorts consistently exclude DLB participants. Small, uncontrolled samples of participants analysed indicate exercise may improve physical function. Larger, more robust study designs are needed to explore exercise efficacy, feasibility and clinical relevance in DLB.

POSTERS – Patient and/or Care Partner Education

P.108

Strategies to Assist Care Partners Become Effective Members of Their DLB (Dementia with Lewy Bodies) Spouse's Health Care Team

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Background: Care partners of spouses with Dementia with Lewy Bodies DLB) face unique challenges and have special needs. While they and care partners of parents or other family members with DLB share some of the same issues, the unique relationship between spouses presents distinct concerns. DLB spousal care partners also have much in common with spouses who care for loved ones with other progressive terminal illnesses, but the characteristic symptoms of DLB pose a different set of problems. Among the many responsibilities of DLB spousal care partners is becoming an active member of their loved one's health care team to include developing a relationship with the primary physician whether that be a geriatrician, neurologist, psychiatrist, or other specialist. How is this the same as and different from the role of other types of care partners? The literature provides some guidance on how to become an effective member of one's own health care team, somewhat less about how to be an advocate for a loved one with an illness other than DLB, but little about how to assume the role of a member of the health care team for a spouse with DLB. Methods: Data sources include a review of professional and lay literature, content analysis of archived messages from an online DLB spouse support group, and a voluntary, anonymous online survey open to members of several online DLB support groups (DLB Caring Spouses, LBDA Forum, and several Facebook groups). Results: This project results in an electronic brochure suitable for printing that presents strategies to assist DLB spousal care partners develop working relationships with health care professionals; communicate effectively with doctors before, during, and after their spouse's visits; prepare for and follow up on visits; and be prepared for emergency room visits and hospitalizations.

P.109

The Role of Care Partners in Medications for their Loved Ones with Dementia with Lewy Bodies

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Background: One of the most common topics discussed in support groups for care partners of loved ones with Dementia with Lewy Bodies (DLB) is medications. DLB is a multi-system disease which makes treatment of its symptoms quite challenging. For example, medications used to treat one symptom may cause negative reactions with respect to other symptoms. At the far end of the continuum are drugs that can cause neuroleptic malignant syndrome (NMS) which can be fatal. Up to 50% of people with DLB who are treated with any antipsychotic medication may experience severe neuroleptic sensitivity. It is understandable that care partners are concerned about their loved ones' medications. Few care partners have training as a physician or pharmacist, so what are they to do? Their challenge is great because many physicians and pharmacists know too little about the medications used to treat people with DLB. Furthermore, most of their loved ones are unable to take an active role in assessing the relative merits and risks of medications. Methods: The author reviewed the professional and lay literature and compiled suggestions from reputable health resources, her personal experiences and observations, and ideas from care partners in a variety of online support groups (with no violation of confidentiality). Results: The synthesis of data from a variety of sources resulted in a list of guidelines for what care partners can do to be proactive in working with a loved one's health care team in managing medications and avoiding potentially Lewy-dangerous drugs. The document also includes a comprehensive list of questions to ask a doctor about a loved one's medications. It is not intended to substitute for the reader's frequent interaction with his/her loved one's health care providers on the topic of medications used to treat the symptoms of DLB and other conditions.

P.110

Empowering Dementia Caregivers Plan for the Challenges Ahead through Structured Dementia Education Programs

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As the number of individuals living with dementia increases, so does the number of caregivers. Better understanding how dementia affects the life of a person living with dementia provides caregivers the unique opportunity to plan for care. Hepburn, Tornatore, Center, and Ostwalt (2001) reported that increased knowledge of dementia challenges offers benefits to caregiver and patient outcomes. A structured form of dementia education to better understand those challenges is a foundational measure to improve the quality of life for both the individuals living with dementia and their caregivers (Family Caregiving Alliance, 2004). Dementia Dialogues is an evidence-informed dementia education program designed to educate caregivers, family members, and professionals working with individuals living with dementia. Since its inception in 2003, over 21,000 individuals who have a vested interest in cultivating their knowledge surrounding dementia have been trained in Dementia Dialogues. Based on post training evaluations of Dementia Dialogues, participants reported that they have a better understanding of dementia. Because of this understanding, participants believed that they could improve the lives of individuals living with dementia.ReferencesFamily Caregiving Alliance. (2004). Caregiver education and support programs: Best practice models. Retrieved from https://caregiver.org/sites/caregiver.org/files/pdfs/Education_Monograph_01-20-05.pdf.Hepburn, Tornatore, Center, and Ostwalt. (2001). Dementia family caregiver training: Affecting beliefs about caregiving and caregiver outcomes. Journal of the American Geriatrics Society (49)4, 450-457.

POSTERS – Treatment

P.111

Excessive Influence on the Cardiac Conduction System of Choline Esterase inhIbitors (ChEIs) in Patients with Dementia with Lewy Bodies (DLB)

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Background and Objective: Bradycardia is more frequently in patients with dementia with Lewy bodies (DLB) than in those with Alzheimer's disease (AD). Cardiac autonomic dysfunction is also known to occur in DLB patients. The adverse effect of choline esterase inhibitors (ChEIs) is bradycardia. To assess the influence of ChEIs resulting in bradycardia in DLB patients, we performed electrocardiography in patients with AD and DLB before and after the administration of a ChEI, then we compared the changes in their heart rate (HR). Patients and Methods: Eleven patients with DLB and 24 with AD were examined. All patients were not takeing drugs that influences the cardiac conduction system, nor medications for arrhythmia, or cardiac disease. All patients were treated with a ChEI. Electrocardiography was performed before and after the ChEI administration. The HR, PR time, QRS time, and QTc time were measured and the differences were computed between pre- and post-administration time points. Results: The mean decrease in HR after the ChEI administration was 12 ± 3/min and 3 ± 5.7/min in the DLB and AD groups, respectively. This indicated a statistically more significant decrease in HR in the DLB group than in the AD group ($p < 0.05$). Discussion: The ChEI induced significant decrease in HR in patients with DLB in this study may be due to both autonomic dysfunction and the hypersensitivity of the cardiac conduction system to ChEIs in these patients. When administering ChEIs to patients with DLB, to avoid the risk of bradycardia, electrocardiography should be performed not only before, but also periodically after, the ChEI administration to monitor changes in HR.

P.112

Effect of RVT-101 and Donepezil on Extracellular Neurotransmitters in the Medial Prefrontal Cortex and Dorsal Hippocampus of Conscious Rats

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Background: The 5-HT6 antagonist RVT-101 is undergoing evaluation as an adjunct to donepezil for the treatment of Alzheimer's disease. The neurochemical effects of this combination in forebrain structures of the rat were examined. Methods: Using in vivo dual probe microdialysis in rats, the effects of donepezil (0.3 and 1.0 mg/kg PO) and RVT-101 (0.3, 1.0 and 3 mg/kg PO) were examined alone and in combination for effects on extracellular levels of acetylcholine, dopamine, noradrenaline and serotonin in the medial prefrontal cortex (mPFC) and dorsal hippocampus (dHipp). Results: RVT-101 at ≥1 mg/kg significantly increased acetylcholine in both the dHipp and mPFC. Donepezil significantly increased acetylcholine in the dHipp at both doses and in the mPFC at 1 mg/kg. The acetylcholine increase induced by either drug alone was potentiated in the dHipp by co-administration of donepezil/RVT-101 at 0.3 mg/kg mg/kg and in the mPFC by co-administration of donepezil/RVT-101 at ≥0.3/0.3 mg/kg. RVT-101 and donepezil increased dopamine and noradrenaline in the mPFC, but these effects were not significantly potentiated when the drugs were co-administered. Neither drug alone, nor the combination, affected dopamine or noradrenaline levels in the dHipp or serotonin levels in the dHipp or mPFC. Estimated exposure (AUC0-t) in rats at 3 mg/kg is approximately one-fifth of the human exposure associated with the therapeutic 35mg daily dose, suggesting that neurochemical effects in humans may be greater than observed in this study. Conclusion: Co-administration of RVT-101 and donepezil results in significantly greater extracellular levels of acetylcholine in the rat dHipp and mPFC than is induced by either drug alone. These results support the therapeutic use of this drug combination.

P.113

Safety of Nelotanserin in a Randomized Placebo-Controlled Phase 2 Study

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Background: Nelotanserin is a highly potent and selective inverse agonist of the 5-HT2a receptor. Nelotanserin penetrates into the CNS and improves objective sleep parameters demonstrating target engagement. The safety of nelotanserin was explored in a Phase 2 study in patients with primary insomnia. Methods: This was a randomized, double-blind, placebo controlled, three-way cross-over study in patients with primary insomnia. Patients received nelotanserin doses of 10 mg and 40 mg, or placebo (PBO) at bedtime. Treatment duration was 7 days with a washout period of 7-9 days between treatments. Safety was evaluated by adverse event (AE) assessments, 12-lead ECGs, clinical laboratory results, cognitive function testing (Digit Span Test, Digit Symbol Copy Test, and Digit Symbol Coding Test), and physical exam. The safety population included subjects who received at least one dose of study drug. Results: Treatment emergent adverse events (TEAE) were similar between PBO (29.4%), 10 mg (32.1%), and 40 mg (25.9%). Eight subjects (3.5%) discontinued due to adverse events: four in the placebo arm, one in the 10 mg arm, and three in the 40 mg arm. The majority were due to increased CPK and associated with strenuous activity. The most common TEAEs considered related to study medication in ≥ 3% of subjects were somnolence (4.2-7.4%), fatigue (1.2-5.4%), and headache (1.2-3.0%). There were no notable differences between active and placebo groups and no relationship to dose. No SAEs or clinically significant changes in vital signs or ECGs were observed. No evidence of cognitive impairment, next day motor impairment or withdrawal effect was noted. Conclusion: Nelotanserin was generally well-tolerated, with a low discontinuation rate due to adverse events in this Phase 2 study in patients with primary insomnia. This safety profile supports further development for additional indications, including in patients with Dementia with Lewy Bodies.

P.114

Disease Modifying Therapy of Dementia with Lewy Bodies with Quaternary Ammonium Anti-Muscarinic/Cholinesterase Inhibitor

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Dementia with Lewy Bodies (DLB) is a rapidly progressing neurodegenerative disease with a characteristic profound reduction in CNS choline acetyltransferase . This case series suggests a sustained disease modifying effect from a level inhibition of cholinesterase that can only be achieved with concurrent peripheral muscarinic blockade. Patients were selected from those seen in a single geriatric consultation clinic after 2010. DLB was diagnosed by the Consensus criteria of the third report of the DLB consortium (2005) by a geriatrician, with concurring neurologist.. Patients received rivastigmine at doses greater that the upper limit of FDA approved dosing. Does greater than 12 mg oral, or 13.3 mg transdermal were paired with glycopyrrolate 1-2 mg orally twice daily. Concurrent use of carbidopa/levodopa, selegiline was permitted but use of dopamine receptor agonists, other acetyl-cholinesterase inhibitors or anti-muscarinic agents was not. Criteria for selection included treatment more than one year, the ability to perform a Mini Mental State Examination (MMSE) at the time of initiation and the availability of follow up data. The MMSE was performed in a standardized format .Function Assessment Stage (FAST) was determined by nurse and physician after an interview with patient and caregivers. MMSE values over time were compared to the published rate of decline of DLB. All patients had MMSE and functional improvement, with 8 of 9 having a sustained stabilization of MMSE score , 2 of whom have had stable MMSE for over 5 years. This study suggests that disease course modification of Dementia with Lewy Bodies is possible with the high level inhibition of cholinesterase achievable when rivastigmine is combined with glycopyrrolate. The implications for the treatment of neurodegenerative diseases associated with the abnormal accumulation of protein metabolites warrants further research.

P.115

Antipsychotic Use in Parkinson Disease Is Associated with Increased Mortality

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Objective: To determine if antipsychotic (AP) use in Parkinson disease (PD) is associated with increased mortality. Background: Over the disease course, 60% of PD patients experience psychosis, and 80% develop dementia. Use of APs in PD is common, with 50% of patients diagnosed with psychosis receiving treatment. AP use in patients with dementia in the general population is associated with increased mortality and morbidity, but it is not known if this risk extends to PD patients as well. Methods: In this retrospective, matched, case-control cohort study, Fiscal Year 1999-2010 national Veterans Affairs health system administrative data was used to examine the risk associated with AP use in a large cohort of idiopathic PD patients with stable recent health. We compared 180-day mortality rates in those patients initiating an AP with matched non-AP users (matched on age (+- 2.5 years),gender,race, index year, presence of dementia, time from dementia dx to index date (+- 180 days), time from PD dx to index date (+- 180 days), delirium, hospitalization, 3-category Charlson's Comorbidity Index, and new non-psych medications within 14 days of AP prescription). Cox regression models accounting for matching were run using both intent-to-treat (ITT) and exposure period only analyses. Results: 251 DLB cases and 222 AD cases were identified during the eight year period (2005-2012). DLB affected males and females equally and there was an approximately eight fold increase in DLB diagnoses across the study period. There was a significantly higher mortality rate for the DLB group compared with the AD group (38% vs 20%; p < 0.001), though no differences in age, cognitive function, or time from presentation to diagnosis between the two groups. Those prescribed anti-dementia drugs had a significantly lower mortality than those not on medication. Conclusions: AP use is associated with an increased mortality risk in PD patients, after adjusting for measurable confounders related to PD severity and comorbidity. This result highlights the need to use this medication class cautiously in this population. Future studies should examine causes of death in AP users to inform clinical care, as well as the role for non-pharmacologic strategies in managing psychosis in PD. In addition, new APs that do not increase mortality in patients with neurodegenerative diseases need to be developed.

P.116

Acute refractory Psychosis in a Patient with Dementia with Lewy Bodies: Report of a Successful Treatment with Electroconvulsive tHerapy

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Objective: To describe a patient with Dementia with Lewy Bodies (DLB) suffering from pharmaceutically intractable psychosis, deteriorating after starting antipsychotic therapy, successfully treated with electroconvulsive therapy (ECT). Methods: The patient was diagnosed with probable DLB based on the following criteria: progressive cognitive impairment, REM-sleep behaviour disorder, parkinsonism, psychotic symptoms and a $[^{123}I]$FP-CIT SPECT with bilateral decreased tracer uptake in the putamen. The psychotic symptoms worsened after starting treatment with risperidone and were refractory to treatment with clozapine, rivastigmine and lorazepam, leading to a life-threatening agitated state and respiratory insufficiency needing ICU admission . ECT was started after consent from his family. Results: ECT was administered three times per week without any complications. During the initial 6 treatments the hallucinations, delusions and motor agitation decreased gradually. After another 4 treatments also his cognitive impairment and parkinsonism improved. Medication was tapered and the patient was able to return home were he is relatively independent in daily acitvities. The striking improvement in his medical condition sustained during follow-up. At the last follow-up visit at 6 months, he reported no hallucinations, MMSE score was 24/30. Conclusion: Neuroleptic sensitivity is one of the hallmarks of DLB. Antipsychotic therapy can lead to a rapid deterioration with imposing psychosis. ECT may be an effective treatment for pharmaceutically intractable psychosis in DLB patients. Literature on ECT for treatment of psychosis in other neurodegenerative disorders indicates that ECT is safe in these patients.

LATE BREAKING - GENETICS

P.117

A Cluster of Structural Variants in Intron 4 of SNCA Gene Confers Risk for Lewy Body Pathology in Alzheimer's Disease and Affects SNCA Expression Profiles

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Genetic associations of the SNCA gene with several Lewy-body (LB) related disorders have been reported. However, the actual genetic variant(s) that underlie the observed associations remain largely elusive. Structural variants (SVs) are among the most polymorphic loci in the human genome, and it has been suggested that non-coding SVs are involved in gene regulation. However, studies about their possible role in complex human disorders are underrepresented. We recently showed that tagging-SNPs across the SNCA locus were significantly associated with increased risk for LB pathology in cases with AD-type of dementia. Building on these results, herein, we embarked on an effort to identify SVs within the SNCA locus, that contribute to the risk to develop LBV/AD. Using a bioinformatics algorithm to catalogue and score SVs in a region of SNCA-intron 4, followed by a deep phased-sequencing analysis, we identified four distinct haplotypes within a highly-polymorphic low-complexity CT-rich region. We then showed in an autopsy series of cases with LBV/AD compared with AD-only controls that a specific haplotype of this CT-rich region conferred risk to develop LBV/AD (p=0.0004). We further investigated the genetic association with biological functions. Expression analysis using temporal cortex samples demonstrated that the CT-rich site acts as an enhancer element, where the risk haplotype was significantly associated with elevated levels of SNCA-mRNA expression (p=0.02). We also detected significantly higher SNCA-mRNA levels in LBV/AD brains compared to AD controls (pSNCA that contributes to LB pathology in AD patients, possibly via cis-regulation of the gene expression. Experiments using iPSCs and genome-editing technologies to validate and modulate the regulatory effect of this CT-rich haplotype are underway.

AUTHOR INDEX