

## Original Article

# Alpha rhythm oscillations and MMSE scores are differently modified by transdermal or oral rivastigmine in patients with Alzheimer's disease

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**Abstract:** Background: Alzheimer's disease (AD) is the most common cause of dementia in older patients. Rivastigmine, a reversible cholinesterase inhibitor, has been shown to improve the clinical manifestations of AD by delaying the breakdown of acetylcholine (ACh) released into synaptic clefts. Moreover, there is evidence that ACh modulates EEG alpha frequency. Objectives: the objectives of this pilot study in patients with AD were to determine the effects of two formulations of RV (transdermal and oral) on Mini-Mental State Examination (MMSE) scores and on alpha frequency in particular the posterior dominant rhythm. Methods: twenty subjects with AD were randomly assigned to receive either RV transdermal patch (RV-TDP, n=10) or RV capsules (RV-CP, n=10) according to the standard recommended dosage regimen. All patients were driven to the maximum drug dosage. Diagnosis of AD was made according to NINCDS-ADRDA criteria and the Diagnostic and Statistical Manual of Mental Disorders IV. All patients underwent EEG recordings at the beginning and at the end of the 18-month study period using P3, P4, O1 and O2 electrodes each at high (10.5-13.0 Hz) and low (8.0-10.5 Hz) frequency. MMSE scores were determined at the start of the study and at three successive 6-month intervals (T0, T1, T2, and T3). Results: administration of RV-DP increases the spectral power of alpha waves in the posterior region and is associated with improved cognitive function as evidenced by significant changes in MMSE scores. Conclusion: RV-DP provides an effective and long-term management option in patients with AD.

**Keywords:** Alpha rhythm oscillations, MMSE scores, rivastigmine, Alzheimer's disease

## Introduction

Alzheimer's disease (AD) represents a serious public health issue affecting approximately 5.4 million individuals in the United States and is projected to affect up to 16 million by 2050 [1]. AD is a neurodegenerative disorder affecting major brain areas including the cortex and limbic system, and is characterized by progressive decline in memory with impairment of at least one other cognitive function. For a correct diagnosis, the disorder must not be limited to a period of delirium, must have been present for at least 6 months, and must not have any other alternative explanation. AD features ongoing deterioration of patients' function which results in substantial and long-lasting disability over the approximate 7 to 10 years from diagnosis to eventual death [2]. The clinical symptoms of AD usually appear in patients aged more than 60 years and the incidence of AD increases

with advancing age. The incidence of AD is high and, although slightly variable among different ethnic groups and populations, generally affects 3% of people aged 65-74 years, 19% of those aged 75-84 years, and 47% of those aged 85 years and over [3]. AD is the likely cause of approximately two-thirds of all cases of dementia [4, 5] and affects at least 15 million people worldwide [6, 7]. The economic costs associated with AD are progressively growing up. These costs include productivity loss from the workforce (patients and caregivers) and direct medical costs associated with the treatment and institutionalization of patients with AD [8]. As life expectancy increases, so the incidence of AD will continue to rise, with economic costs in the United States predicted to triple by the year [9].

Progressive neuronal loss, reduction in cholinergic function and consequent diffuse atrophy

and ventricular enlargement appear to be the key steps leading to the development of cognitive and/or behavioural symptoms as different brain regions are affected during the course of AD, and this may be preceded by hypoperfusion of the regions involved. This relationship is relatively well defined for the cognitive symptom domain of AD [10, 11]. The loss of cholinergic innervation to the cortex and hippocampus as a result of progressive neurodegeneration is related to declining cognitive function. The functionality of the cholinergic system is reduced further by a declining number of post-synaptic nicotinic receptors and a reduction in pre-synaptic muscarinic receptors in late-stage AD [12, 13]. The loss of 30-95% of cholinergic neurones correlates with a reduction in the levels of the biosynthetic enzyme for acetylcholine (ACh), choline acetyltransferase (ChAT) [14, 15].

Following release at the synapse, ACh is inactivated rapidly by the action of cholinesterases (ChEs). There are two types of ChE enzyme present in normal human brain. The predominant type, comprising 90% of the total ChE activity in cortex and hippocampus of healthy human brain, is acetylcholinesterase (AChE) and the remaining 10% is butyrylcholinesterase (BuChE) [16]. AChE is either membrane bound within cholinergic nerve terminals or is present in the synaptic space, whereas BuChE is associated with glial cells [17]. In the normal brain, the inactivation of synaptic ACh is well accepted to be performed mainly by the action of AChE with little contribution from BuChE [18]. Recently, however, sensitive histochemical techniques have identified more widespread distribution of BuChE in human hippocampal and temporal neocortical areas and an ability of BuChE to hydrolyse the ACh surrogate acetylthicholine in the presence of a specific inhibitor of AChE. Thus it has been proposed that BuChE may have a greater role in normal cholinergic transmission than previously surmised [19]. Furthermore, recent findings with AChE knockout mice suggest that under some circumstances, BuChE may play a constitutive (rather than just back-up) role in the hydrolysis of ACh in the normal brain, possessing an ability to substantially substitute for lost AChE [20]. In the brain of patients with AD, there is a progressive decline in levels of AChE over the course of the disease while levels of BuChE rise [16], possibly due to glial cell proliferation [21].

Both BuChE and AChE exist as a series of three globular forms, G1, G2 and G4, of which G1 and G4 predominate in the CNS [22, 23]. The G4 form of AChE is the most abundant form in the healthy human brain and most active in the breakdown of ACh, while the G1 form is present in smaller amounts and plays a lesser role in ACh degradation [24]. In the ageing and AD brain, however, levels of the G4 form decrease whilst those of the G1 form stay the same [23] or increase slightly [25]. Increase in levels of the G1 forms of both AChE and BuChE are most pronounced in those brain regions affected by AD pathology and the activity of these enzymes is positively correlated with increasing density and pathogenicity of amyloid protein in the AD brain [25, 26].

The change in the relative levels of AChE and BuChE may have implications for the pathological changes in AD and degradation of synaptic ACh. Recent studies have demonstrated that among ChE-positive neurones in the human amygdala, BuChE activity is more common than AChE activity, while in the hippocampus, AChE and BuChE are found to co-exist within the same neuronal elements [27]. ChE inhibition may, therefore, offer a route to enhancing endogenous levels of ACh in the AD brain. If cognitive deficits, as well as behavioral symptoms, arise from cholinergic deficiency or deficiencies in neurotransmitter systems modulated by the cholinergic system, the administration of a ChE inhibitor may offer symptomatic benefits [28-30].

Emerging data provide new insights into the way the cholinesterase inhibitors might be working in the brains of demented patients, and how individual agents may affect different brain regions. In addition to enhanced neurotransmission in cholinergic neurons, acetylcholinesterase (AChE)-positive neurons in thalamic nuclei project diffusely to the cortex, modulating cortical processing and responses to new and relevant stimuli, while butyrylcholinesterase (BuChE)-positive neurons are found in thalamic nuclei that project specifically to the frontal cortex, and may have roles in attention [31, 32]. Rivastigmine is the only commonly used cholinesterase inhibitor that inhibits both AChE and BuChE, and this may explain its effects on attention and memory. Importantly, beneficial effects on attention and memory may have a secondary impact on other key symptom

domains of AD, including cognitive performance and daily function. Oral and transdermal rivastigmine are currently approved for treating symptoms of mild-to-moderate Alzheimer's. Rivastigmine is a small, potent molecule that is both lipophilic and hydrophilic—properties that make it well suited to transdermal therapy. Winblad and colleagues [33] compared the efficacy and tolerability of the patch application versus capsules and placebos based on data from a large double-blinded randomized controlled trial on >1,100 patients with AD. Regarding the primary cognition outcomes, they demonstrated a similar efficacy of the patch compared to capsules, with superior tolerability in the former. Indeed it was associated with only about one third as many gastrointestinal side effects. No difference in other side effects was observed between the higher-dose patch and oral treatment. Because gastrointestinal side effects are the type most frequently reported in association with this agent, the transdermal delivery system appears to offer advantages in terms of tolerability. On the whole, rivastigmine transdermal patch formulation may offer tolerability, convenience and therapeutic advantages for this patient population. Moreover, by providing continuous delivery of drug with reduced fluctuation levels in the plasma, transdermal administration may improve tolerability and make optimal doses easier to achieve, with positive effects also on cognitive performance.

EEG studies have demonstrated peculiar changes of background alpha frequency oscillatory activity both in healthy people and in AD patients [34-49]. Animal as well as human studies have demonstrated that the cholinergic system has a modulatory influence on cortical brain rhythms. Cholinergic stimulation mainly results in a shift in the power spectrum towards faster frequencies, whereas interference with cholinergic function leads to an increase in slow wave activity [50-54]. Considering the presence of a cholinergic deficit in AD, this would suggest that a hypofunctional cholinergic system might be responsible for the observed slowing of background oscillatory activity in AD. Along this line of reasoning, it seems likely that treatment aimed at restoring cholinergic function would at least partly reverse the observed slowing of background activity in AD. In AD patients, treatment with

cholinesterase inhibitors is associated with a decrease of low frequency EEG activity [37, 38]. The action of cholinesterase inhibitors is aimed at increasing cholinergic brain activity by interfering with the function of the enzyme acetyl (and/or butyryl) cholinesterase, responsible for the breakdown of acetylcholine in the brain [55]. In a recent study on Parkinson disease associated to dementia (PDD), after treatment with rivastigmine, PDD patients demonstrated an increase in relative power in the alpha range in parieto-occipital [56].

The objectives of this pilot study in patients with AD were to determine the effects of two formulations of RV (transdermal and oral) on Mini-Mental State Examination (MMSE) scores and on alpha frequency in particular the posterior dominant alpha rhythm.

### Materials and methods

#### *Subjects*

Twenty subjects with AD were recruited from the Translational Outpatient Memory Clinic (TOMC) of the Scientific Institute for Research and Care (IRCCS) of Alzheimer's and psychiatric diseases Centro S. Giovanni di Dio-Fatebenefratelli' in Brescia, Italy. All experimental protocols had been approved by the local ethics committee. Informed consent was obtained from all participants or their caregivers, according to the Code of Ethics of the World Medical Association (Declaration of Helsinki). Twenty subjects with AD were randomly assigned to receive either RV transdermal patch (RV-TDP, n=10) or RV capsules (RV-CP, n=10) according to the standard recommended dosage regimen (4.6 to 9.6, and 6-12 mg for transdermal and oral formulation respectively).

#### *Diagnostic criteria*

Diagnosis of AD was made according to NINCDS-ADRDA criteria and the Diagnostic and Statistical Manual of Mental Disorders IV. Patients were rated with a series of standardized diagnostic and disease severity instruments, including the Mini-Mental State Examination (MMSE), the Clinical Dementia Rating Scale (CDRS), the Hachinski Ischemic Scale (HIS) and the Instrumental and Basic Activities of Daily Living (IADL, BADL) [57-60]. In addition, patients underwent diagnostic neuro-

**Table 1.** Socio-demographic characteristics and MMSE ANOVA results. Significant results are highlighted in bold

	RV-TDP	RV-CP	<i>p</i> value
Number	10	10	
Age	82.2±2.3	80.3±2.5	0.2
Education	5.4±1.7	4.9±2.1	0.1
MMSE T0	21.07±2.4	18.3±3.6	0.06
MMSE T6	22.1±2.5	18.1±5.3	<b>0.04</b>
MMSE T12	21.1±1.6	15.9±4.9	<b>0.006</b>
MMSE T18	21.2±3.1	13.6±5.06	<b>0.001</b>
MMSE T12-T0	RV-TDP vs RV CP Baseline Covaried		<b>0.042</b>
MMSE T18-T0	RV-TDP vs RV CP Baseline Covaried		<b>0.006</b>
MMSE T18-T0	RV-TDP vs RV CP uncovaried		<b>0.023</b>

imaging procedures (magnetic resonance imaging, MRI), EEG, and laboratory testing to rule out other causes of cognitive impairment. Patients with cognitive deficits, due to psychic (anxiety, depression, etc.) or physical (hypothyroidism, vitamin B12 and folate deficiency, uncontrolled heart disease, uncontrolled conditions (diabetes, etc.) reasons were excluded. Demographic and cognitive features of the subjects in study are summarized in **Table 1**. All patients were driven to the maximum drug dosage (12 mg/die for RV-CP and 9.5 mg/die for RV-TDP) according to the standard recommended dosage regimen. MMSE scores were determined at the start of the study and at three successive 6-month intervals (T0, T1, T2, and T3).

#### EEG recordings

The EEG activity was recorded continuously from 19 sites by using electrodes set in an elastic cap (Electro-Cap International, Inc.) and positioned according to the 10-20 international systems (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2). In order to keep constant the level of vigilance, an operator controlled on-line the subject and the EEG traces, alerting the subject any time there were signs of behavioural and/or EEG drowsiness. The ground electrode was placed in front of Fz. The left and right mastoids served as reference for all electrodes. The recordings were used off-line to re-reference the scalp recordings to the common average. Re-referencing was done prior to the EEG artifact detection and analysis. Data were recorded with a band-pass filter of 0.3-70 Hz, and digitized at a sam-

pling rate of 250 Hz (BrainAmp, BrainProducts, Germany). Electrodes-skin impedance was set below 5 khz. Horizontal and vertical eye movements were detected by recording the electrooculogram (EOG). The recording lasted 5 min, with subjects with closed eyes. Longer recordings would have reduced the variability of the data, but they would also have increased the possibility of slowing of EEG oscillations due to reduced vigilance and arousal. EEG data were then analyzed and fragmented off-line in consecutive epochs of 2 s, with a frequency resolution of 0.5 Hz. The average number of epochs analyzed was 140, ranging from 130 to 150. The EEG epochs with ocular, muscular and other types of artifact

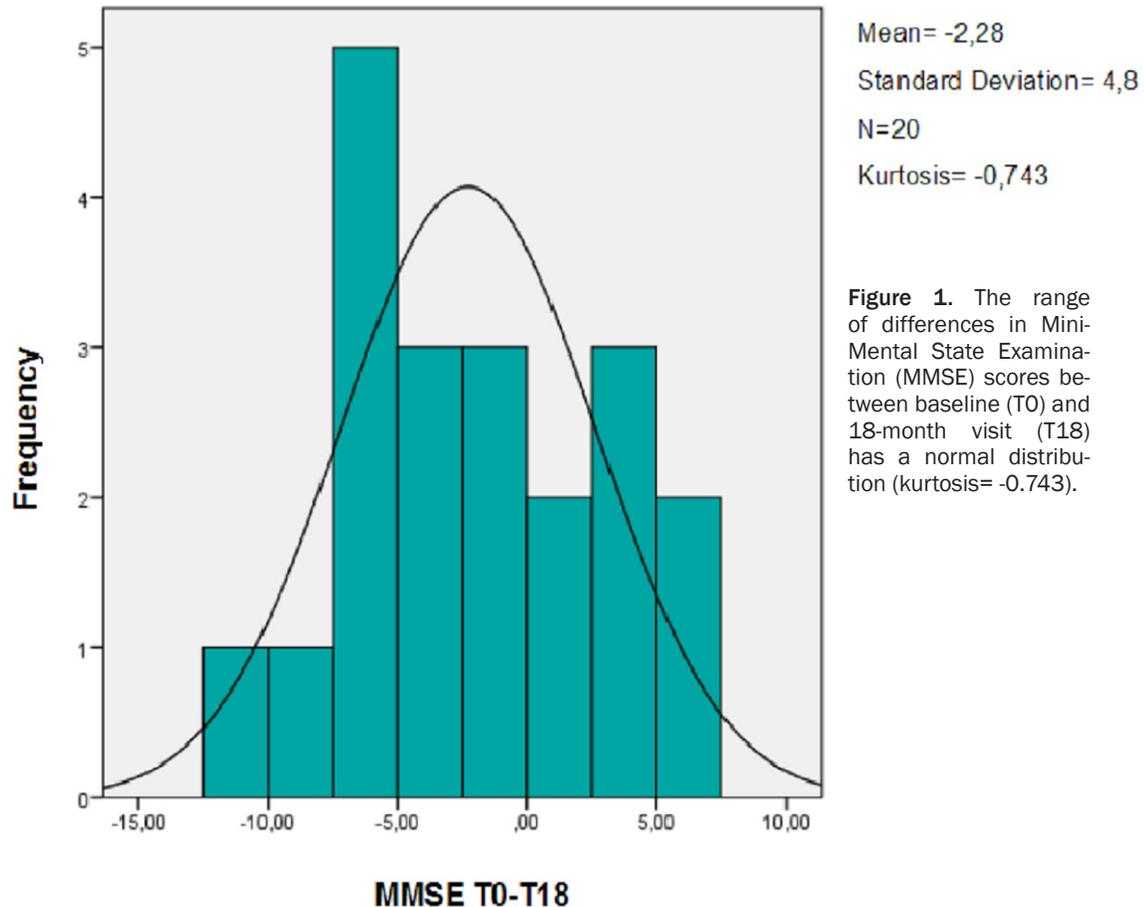
were preliminary identified by a computerized automatic procedure [60-78]. Two expert electroencephalographers manually double-checked and confirmed the automatic selections. The epochs with ocular, muscular and other types of artifacts were discarded. All patients underwent EEG recordings at the beginning and at the end of the 18-month study period using P3, P4, O1 and O2 electrodes each at high (10.5-13.0 Hz) and low (8.0-10.5 Hz) frequency. These electrodes were chosen as the detection in alpha frequency changes is better performed on posterior brain areas.

#### Analysis of individual frequency bands

All recordings were obtained in the morning with subjects resting comfortably. Vigilance was continuously monitored in order to avoid drowsiness. A digital FFT-based power spectrum analysis (Welch technique, Hanning windowing function, no phase shift) computed - ranging from 2 to 45 Hz - the power density of EEG rhythms with a 0.5 Hz frequency resolution. Two alpha frequencies were selected according to the literature guidelines: low alpha (8-10.5 Hz) [35, 36] and high alpha (10.5-13 Hz) [65-77].

#### Statistical analysis

The Wilcoxon signed ranks test was performed to compare EEG spectral power measurements taken at T0 and T18. The Wilcoxon test is a non-parametric alternative to t-test for dependent samples. In a nonparametric test, no assumptions need to be made regarding the distribu-



**Figure 1.** The range of differences in Mini-Mental State Examination (MMSE) scores between baseline (T0) and 18-month visit (T18) has a normal distribution (kurtosis= -0.743).

tion of the values, as non-parametric tests are based on ranking values from low to high. This test has been chosen because there is not a normal distribution in our EEG power data and for the little size of the sample.

The chi-square test has been computed to obtain the *p*-value. As regards the MMSE evaluation, we found that the distribution of the difference between the score at T0 and T18 is like normal (kurtosis= -0.473, see **Figure 1**). As a consequence, the statistical analysis of variance about MMSE score was computed with parametrical test (one-way ANOVA, linear generalized model). In ANOVA analysis, MMSE score difference was the dependent variable, the treatment the independent variable. The results were tested also computing the baseline MMSE score as covariate. All analysis was performed by SPSS statistical software.

#### Study design

This was a clinical, observational, open-label study. Patients were titrated to their target

dose in 4-week steps over 16 weeks, followed by an 8-week maintenance phase. Patients in the rivastigmine patch groups were up-titrated from a 5 cm<sup>2</sup> starting dose in 5 cm<sup>2</sup> steps to a maximum size of 10 cm<sup>2</sup>. Those in the capsule group were up-titrated from 3 mg/day in steps of 3 mg/day to a maximum of 12 mg/day. Patients were maintained permanently at the highest doses until the end of the study. The patch (rivastigmine or placebo) was applied by caregivers to clean, dry, hairless skin on the patient's upper back every morning and worn for 24 h, during which normal activities including bathing were allowed. To minimize possible skin irritation, patch placement on the upper back was alternated between the left and right sides, daily. All patients also took a capsule (rivastigmine or placebo) with breakfast and one with their evening meal.

To allow comparisons between the two groups (oral and transdermal) the following measurement were carried out: 1) high alpha and low alpha frequency power at each electrode sepa-

**Table 2.** Wilcoxon Signed-Rank Test results for EEG power spectra analysis. Significant results are highlighted in bold

Low + High Alpha (8.0-13.0 HZ), P3 Electrode				
	Alpha Power T 18 > Baseline	Alpha Power T 18 < Baseline	Odd-Ratio (95% CI)	Chi Square Test
RV-TDP	80%	20%	0.107	<b>0.025</b>
RV-CP	30%	70%		
Low (8.0-10.5-0 HZ), O1 Electrode				
	Alpha Power T 18 > Baseline	Alpha Power T 18 < Baseline	Odd-Ratio (95% CI)	Chi Square Test
RV-TDP	80%	20%	0.107	<b>0.025</b>
RV-CP	30%	70%		

rately; 2) with total high and low alpha frequency power at each electrode; 3) high alpha frequency power estimated as the sum at all four electrodes; 4) low alpha frequency power estimated as the sum at all four electrodes low; 5) total high and low alpha frequency power estimated as the sum of all four electrodes.

**Results**

**Table 1** shows socio-demographical characteristics of the study sample and ANCOVA MMSE results: 1) MMSE scores significantly improved in patients taking RV-TDP at T1, T2 and T3 (p=0.046, 0.006, 0.001 at the three time points, respectively); 2) at 18 months (T3) differences in MMSE scores between patients taking RV by the transdermal route and oral administration were statistically significant (p=0.023). In particular, MMSE scores decreased in patients taking the oral formulation while remaining unchanged over the 18-month study period in those taking RV-TDP; 3) moreover, when co-varied with the score at baseline results show that differences between MMSE scores at 12 and 18 months, were significantly greater in patients taking RV-TDP compared with those taking RV-CP (p=0.042 and p=0.006, respectively).

**Table 2** shows Wilcoxon Signed-Rank Test results for EEG power spectra analysis: 1) RV-TDP and RV-CP increased spectral power as measured by electrode O1 (low amplitude alpha) in 8 and 3 patients, respectively (p=0.025); 2) spectral power measured with electrode P3 (high and low alpha) was increased in 8 patients receiving RV-TDP and 3 receiving RV-CP (p=0.025).

**Discussion**

In this study we compare the cognitive and neurophysiological outcomes of two groups of patients both assuming rivastigmine, but in different ways, capsules and transdermal. All patients were titrated to the maximum dosage, i.e. 12 mg/die for capsules and 9.5 mg/24 h for transdermal patch. Cognitive performance was evaluated through MMSE score

whereas neurophysiological outcomes were detected by mean of alpha frequency EEG power spectra computation in brain posterior regions.

*Cognitive outcomes*

Our results show that administration of RV-DP is associated with improved cognitive function as evidenced by significant changes in MMSE scores. Of note, MMSE scores as well as age and education were not significantly different at baseline. The improvement in cognitive performance, evaluated by MMSE score, was evident in each of the three follow-up points (at 6, 12 and 18 months of observation) only in the patients assuming TDP rivastigmine. Moreover, the difference of the MMSE score between the groups was significantly different at 12 and 18 months, but at 6 follow-up months. These results suggest that the transdermal patch form induce an improvement of cognitive performance as compared to capsules form, in particular beginning on middle term treatment duration, and that it remains constant over time. On the contrary, in patients assuming RV-CP, there is a progressive deterioration of cognitive performance, along with a progressively stronger difference as compared to MMSE score of RV-TDP patients. Our results confirm and extend previous studies showing potential therapeutic advantages of transdermal vs oral rivastigmine treatment [33, 79]. The transdermal formulation of rivastigmine is a prolonged release drug. This issue avoids dosage fluctuations in drug blood concentration. As a theoretical hypothesis, the constant stimulation of cholinergic receptors could have long-lasting beneficial effects on cognition over the time. Moreover, the maintenance of the cogni-

tive improvement over the time could suggest a neuroprotective effect on the cholinergic system itself, preventing massive degeneration. Further studies are mandatory to confirm this hypothesis.

### *Neurophysiological aspects*

As regards to neurophysiological measures, our results show a major increases of the spectral alpha frequency power (both low and high alpha) in the posterior region in patients assuming RV-TDP after 18 months of treatment. Previous studies have demonstrated the reliability of pharamaco-EEG approach in evaluating both drug and cognitive performance. Analysis of brain field potentials or electrical power recorded as EEG has been proven to be a very sensitive tool to characterize drug effects on the central nervous system [80]. Since the start of this method it became more and more clear that the electrical power of single frequency ranges, as defined by Dimpfel and colleagues, change independently from each other depending on the particular behavioral or drug condition [81, 82]. After drug application the pattern of changes of the brain field potential with respect to these specially defined frequency ranges is called an "electrical fingerprint" of this drug. Meanwhile the "fingerprints" of more than 100 compounds have been obtained including more than 50 standard drugs (e.g. analgesics, antidepressants, neuroleptics, stimulants, tranquilizers, sedatives and narcotics). In general, "fingerprints" show prominent differences for drugs prescribed for different indications and are similar for drugs with a similar indication [83, 84]. A large body of literature has been demonstrated that cholinergic neuromodulation augments the top-down impact of spatial attention on oscillations in human visual cortex, specifically for EEG alpha frequency band. Previous studies show that cholinergic agonists enhance the hemodynamic BOLD response [85, 86] to attended stimuli in visual cortex or spike-rates recorded invasively [30] in primary visual cortex but the studies had not examined oscillatory phenomena. Moreover, the cholinergic impact on alpha frequency related spatial attention effects were correlated to a drug-induced improvement in performance [87]. The specific relation to the drug-enhanced performance speeding here indicates that the cholinergic impact on cognitive alpha frequency related effects is not merely epiphenomenal.

The alpha frequency rhythm is mainly modulated by thalamic and subcortical structure, mostly in the resting state [88]. An intriguing explanation, to be verified, of our results is that the power increase of alpha spectral power in brain areas could be tuned by the peculiar modulation of butyrylcholinesterase on thalamic nuclei. The restoring of the cholinergic system in a nearly physiological way, without strong peak fluctuations of drug concentrations, could prevent the synaptic loss typical of AD. On turn, the better functioning of the cholinergic system are based both the increase of alpha frequency power and the improvement of cognitive performance [66-75].

### *EEG alpha activity and cognitive performance*

A variety of different studies reported a significant relationship between EEG alpha activity and memory performance or intelligence, suggesting that the relationship between the dynamics of alpha frequency and cognitive performance is not correlative but causal in nature. [89-95]. A recent study have demonstrated that the induction of large alpha power by neurofeedback training or repetitive transcranial magnetic stimulation (rTMS) at alpha frequency range mimicked exactly the situation which is typical for good memory performance under normal situations enhancing the cognitive performance [96]. In particular the increase of EEG alpha activity has been correlated a better retrieving of information stored in semantic long-term memory. Moreover, in a different study verbal-semantic and spatial-semantic performance were associated with two different intelligence tests. The results show that more intelligent subjects exhibit a significantly larger alpha activity over the left hemisphere (at centro-parietal regions) as compared to less intelligent subjects [97]. Our results confirm these previous studies, showing an increase of alpha power in subjects without cognitive impairment. Of note, the increase of alpha power was evident of left hemisphere.

### **Conclusions**

RV-DP provides an effective and long-term management option in patients with AD. Furthermore, administration of RV-DP increases the potency of alpha waves in the posterior region and this is associated with improved

cognitive function as evidenced by significant changes in MMSE scores.

### Disclosure of conflict of interest

None to declare.

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