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Review

Effects of acetylcholinesterase inhibitors and memantine on resting-state electroencephalographic rhythms in Alzheimer's disease patients

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HIGHLIGHTS

- Symptomatic treatment options for Alzheimer's disease (AD) are currently limited to two therapeutic classes namely, acetylcholinesterase inhibitors (AChEIs) and memantine.
- The present review clarifies the effects of AChEIs and memantine on resting-state electroencephalographic (EEG) rhythms and cognitive function in AD patients to identify EEG markers useful for drug development.
- Based on the field literature, the patient's EEG rhythms most reactive to AChEIs are those at delta (0–3 Hz), theta (4–7 Hz) and alpha (8–12 Hz); the effects of memantine generate a reduction of pathological theta rhythms.

ABSTRACT

Acetylcholinesterase inhibitors (AChEIs) are the most widely used symptomatic treatment for mild to severe Alzheimer's disease (AD) patients, while *N*-methyl-D-aspartic acid (NMDA) receptor antagonist memantine is licensed for use in moderate to severe AD patients. In this article, the effect of these compounds on resting state eyes-closed electroencephalographic (EEG) rhythms in AD patients is reviewed to form a knowledge platform for the European Innovative Medicine Initiative project "PharmaCog" (IMI Grant Agreement No. 115009) aimed at developing innovative translational models for drug testing in AD. Indeed, quite similar EEG experiments and the same kind of spectral data analysis can be performed in animal models of AD and in elderly individuals with prodromal or manifest AD. Several studies have shown that AChEIs affect both resting state EEG rhythms and cognitive functions in AD patients. After few weeks of successful treatment, delta (0–3 Hz) or theta (4–7 Hz) rhythms decrease, dominant alpha rhythms (8–10 Hz) increase, and cognitive functions slightly improve. Beneficial effects of these rhythms and cognitive functions were also found in AD responders to the long-term successful treatment (i.e. 6–12 months). In contrast, only one study has explored the long-term effects of memantine on EEG rhythms in AD patients, showing reduced theta rhythms. The present review enlightens the expected effects of AChEIs on resting state EEG rhythms in AD patients as promising EEG markers for the development of translational protocols both within the PharmaCog project and for wider use.

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Contents

1. Towards the discovery of new markers and drugs for Alzheimer's disease: the PharmaCog project

Alzheimer's disease (AD) is the most prevalent form of dementia seen in the elderly population, and is characterised by memory loss and cognitive and other behavioural abnormalities. AD is related to neurodegeneration within the basal forebrain, parietal, prefrontal, entorhinal cortices, amygdala and hippocampus. It is characterised by an impairment of the cholinergic neurotransmission associated with a pathological production of beta amyloid (Abeta) and phosphorylated tau (Daulatzai, 2010; Shen, 2004).

Clinical diagnosis of AD is normally based on DSM-IV and NINCDS-ADRDA criteria. The following three categories of diagnosis are typically used: (i) possible AD (when a person's dementia cannot be attributable to other causes), (ii) probable AD (when AD is suspected, but there are other possible causes) and (iii) definite AD (when AD is confirmed at autopsy following a microscopic examination of brain tissue). The diagnosis of AD on the basis of overt dementia symptoms reasonably comes after 5–6 years from probable disease onset and this delay is very negative from a therapeutic point of view. Towards an early diagnosis of AD, there has been great progress in identifying the AD-associated structural, functional and molecular changes in the brain and their biochemical footprints well before the symptoms of overt dementia. New research criteria for the diagnosis of prodromal and AD have been advanced in revising the NINCDS-ADRDA criteria (Dubois et al., 2007; Albert et al., 2011; Jack et al., 2011; McKhann et al., 2011; Sperling et al., 2011). The new criteria include fluid and neuroimaging biomarkers of AD. Fluid biomarkers can be extracted from the blood and the cerebrospinal fluid by lumbar puncture (CSF; Clark et al., 2003; Fagan et al., 2006; Schoonenboom et al., 2008; Tapiola et al., 2009). Validated blood biomarkers probe genetic vulnerability for dementia. Genotyping for apolipoprotein E4 (ApoE), cystatin B and homocysteine represent independent risk factors for sporadic late-onset AD, whereas presenilins (PSEN1 and PSEN2) have autosomal dominant inheritance (high penetrance >85%), and lead to Aβ aggregation and early-onset AD (γ-secretase-mediated proteolytic cleavage of APP). Genotyping of ApoE and homocysteine have some impact also for late onset cerebrovascular dementia (VaD) (Dubois et al., 2007). Validated CSF biomarkers probe Aβ amyloid and total phosphorylated tau as signs of the amyloid cascade towards neural injury and neurodegeneration (Tapiola et al., 2009). On the other hand, the validated neuroimaging biomarkers include structural MRI to probe neurodegeneration as revealed by hippocampal atrophy (Frisoni et al., 2010; Silbert et al., 2003; Zarow et al., 2005; Schuff et al., 2009; Van de Pol et al., 2006) and resting-state PET-fluoro-deoxy-glucose (FDG) mapping of temporoparietal and precuneous hypometabolism (Jagust et al., 2007; Minoshima et al., 1997); PET-amyloid Pittsburg Compound B (PIB) is also used for the visualisation of A beta amyloid deposition in the brain (Klunk et al., 2004; Rowe et al., 2007; Ikonomovic et al., 2008). It is important to note that the approaches above are relatively expensive and invasive. Furthermore, they cannot be systematically applied to all elderly subjects with memory complaints or very mild objective decline, due to numerous potential patients and limited financial resources of the public health services. For this reason, new non-invasive and relatively cheap approaches are of extreme interest.

Current symptomatic therapies include cholinergic or glutamatergic agents such as acetylcholinesterase inhibitors (AChEIs; i.e., donepezil) and an antagonist of *N*-methyl-D-aspartic acid (NMDA) receptors (i.e., memantine). They produce, at best, a modest improvement in cognitive symptoms over a relatively short period of time.

In recent years, there has been a high rate of failure of late-stage clinical trials for compounds targeting cognitive symptoms in AD such as positive modulators of nicotinic and muscarinic receptors, serotonergic 5-HT6 receptor antagonists, histamine H3 receptor antagonists and, recently, PDE9 inhibitors (Hutton et al., 2011; Lee et al., 2011). A lack of efficacy rather than pharmacokinetic and toxicological challenges has been increasingly cited as the reason for a compound to fail. There is clearly an urgent need for the development of preclinical assays and models predictive of clinical efficacy. The ability to translate these markers and models and use them in early proof-of-concept clinical studies in healthy volunteers, or even small patient groups, would substantially mitigate the risk involved in taking studies into full-scale expensive phase 2 and 3 trials. Hence, an important objective of current AD research is to develop and validate procedures to allow for early proof-of-concept studies for new symptomatic and disease-modifying agents in humans. This objective may be achieved by several strategies. The European Innovative Medicines Initiative 'PharmaCog' (IMI Undertaking 2008 on neurodegenerative disorders) aims to identify translational, behavioural and physiological biomarkers of cortical activity and cognitive processes sensitive to the effects of symptomatic and disease-modifying drugs for AD. Within PharmaCog, the AChIs (i.e., donepezil) and memantine have been profiled against a matrix of potential biomarkers including EEG.

The current literature is reviewed here in order to evaluate resting-state or spontaneous on-going EEG rhythms as putative biomarkers for the understanding of drug effects on humans. These putative biomarkers are virtually not affected by metalearning relative to task processes, anxiety for performance, emotional variables, skillfulness and subjects' social compliance. Furthermore, recording of the spontaneous on-going EEG rhythms can be repeated countless times along the AD progression with minimal repetition effects on EEG markers used for therapy monitoring. Finally, spontaneous on-going EEG rhythms seem to provide – at least at the group level – useful markers/'end' points to evaluate disease progression and pharmacological intervention in preclini-

cal and clinical stages of AD (Babiloni et al., 2004, 2006a,b,c,d,e,f, 2007a,b,c, 2008a,b, 2009a, 2010a,b, 2011a,b,c).

In the following sections, we will introduce basic concepts on symptomatic treatments for AD, EEG techniques and markers, as well as literature studies.

2. Assessment of the cognitive and functional status in AD patients

The quantitative evaluation of the cognitive and functional deficits in AD patients (i.e., basic and instrumental activities of daily living, hobbies, professional duties and so on) play a key role in the diagnosis or therapy monitoring in clinical trials and are a crucial reference for the evaluation of surrogate instrumental markers to be used in these trials. As far as the assessment of the cognitive deficits is concerned, neuropsychological studies have shown that quantitative and qualitative differences across many cognitive and executive domains can be used to discriminate AD patients from those suffering from other age-associated forms of cognitive decline (Grundman et al., 2004; Ala et al., 2003; Kunik et al., 2000; Elfgren et al., 1994). These differences are especially evident in episodic memory, semantic knowledge and some aspects of executive functions (Reisberg et al., 1984; Braak and Braak, 1991; Salmon and Bondi, 1999; Kirk, 2007). Cognitive decline occurs prior to the development of the clinical AD dementia syndrome. It typically affects episodic memory, which is in line with early neurodegenerative processes involving the medial temporal lobe (Braak and Braak, 1991). However, the efficacy of the pharmacological or rehabilitative intervention in mild-to-moderate AD patients is assessed by evaluation of the global cognition status. For this purpose, a popular tool is the cognitive section of the Alzheimer's Disease Assessment Scale (the so-called ADAS-Cog; Mohs et al., 1983; Rosen et al., 1984; Verhey et al., 2004). Another very popular test of the global cognitive status in mild-to-moderate AD patients is the Mini-Mental State Examination (MMSE; Folstein et al., 1975; Crum et al., 1993), which assesses orientation, memory, attention, naming, comprehension and construction. A typical annual rate of change in AD is about three points of MMSE but this varies across the time course of the illness (Ihl et al., 1992; Reisberg et al., 1996; Brooks et al., 1993; Teri et al., 1990). In patients with severe dementia, the global cognitive status is assessed by the Severe Impairment Battery (SIB; Saxton and Swihart, 1989; Schmitt et al., 2002), composed of 40 simple, one-step commands with gestural cues.

Regarding the functional assessment of AD patients, several scales can be integrated as outcome measures in clinical trials such as (i) the Alzheimer Disease Functional Assessment and Change Scale (ADFACS; Mohs et al., 2001), (ii) the Disability Assessment for Dementia (DAD; Gelinas et al., 1999), (iii) the Alzheimer Disease Cooperative Study-Activities of Daily Living (ADCSADL; Galasko et al., 1997) and (iv) the Progressive Deterioration Scale (PDS; DeJong et al., 1989). These scales are based on an interview of caregivers on daily (feeding, bathing, dressing, continence, etc.), instrumental (ability to use the telephone, shopping, meal preparation, house maintenance, moving, managing medications and administrating finances) and leisure activities. Table 1 lists the main tools for the assessment of cognitive and functional status in AD patients.

3. Standard symptomatic drugs for AD

There have been numerous preclinical and clinical studies published that report positive cognitive symptomatic effects in small-scale clinical studies in AD patients. However, these have failed to translate into significant efficacy in later stage clinical development. Despite decades of research, only two classes of pharmacological agents are currently approved for AD: the AChEIs (approved for all stages of the disease) and the NMDA receptor antagonist, memantine (approved for the later moderate-to-severe stages of AD). These compounds were therefore selected for profiling within PharmaCog and are reviewed below.

The AChEIs exert their beneficial effect by blocking AChE, the enzyme responsible for ACh breakdown (Mesulam et al., 2004), thus prolonging the bioavailability of ACh at the postsynaptic cholinergic receptor with enhancement of cholinergic neurotransmission. The AChEIs act by opposing the cholinergic transmission deficit in AD, a key neurotransmitter system affected by the neurodegenerative processes, particularly in the early stages of the disease (Mesulam et al., 2004). First-generation AChEIs such as tetrahydroaminoacridine (THA) and physostigmine improved cognitive functions in AD patients but had major side effects, possibly because of their impact on the peripheral nervous system

Table 1
Main tools for the assessment of cognitive and functional status in AD patients.

Tool	Domain	Load	Function	Administration	Score	References
ADAS-Cog	Cognitive	11-items test (about 45 min)	Memory, orientation, language, construction, praxis	Patient interview	0–70 (best–worst)	Mohs et al. (1983), Rosen et al. (1984) and Verhey et al. (2004)
MMSE	Cognitive	19-items test (about 10 min)	Memory, orientation, attention, naming, comprehension, construction	Patient interview	0–30 (worst–best)	Folstein et al. (1975) and Crum et al. (1993)
SIB	Cognitive	40 simple one-step commands with gestural cues (about 20 min)	Memory, orientation, language, attention, visuospatial ability, construction	Patient interview	0–100 (best–worst)	Saxton and Swihart (1989) and Schmitt et al. (2002)
ADFACS	Functional	16-items interview (about 20 min)	Activities, instrumental activities and leisure activities	Caregiver interview	0–54 (best–worst)	Mohs et al. (2001)
DAD	Functional	40-items interview (about 20 min)	Activities, instrumental activities and leisure activities	Caregiver interview	0–100 (worst–best)	Gelinas et al. (1999)
ADCSADL	Functional	23-items interview (about 15 min)	Activities, instrumental activities and leisure activities	Caregiver interview	0–78 (worst–best)	Galasko et al. (1997)
PDS	Functional	29-items interview (about 15 min)	Activities, instrumental activities and leisure activities	Caregiver interview	0–100 (worst–best)	DeJong et al. (1989)

(Christie et al., 1981; Mohs et al., 1985; Summers et al., 1986; Stern et al., 1988; Farlow et al., 1992; Kogan et al., 2001). Furthermore, THA caused hepatotoxicity in many patients (Ames et al., 1988; Watkins et al., 1994; Farlow et al., 1992).

Second-generation AChEIs such as donepezil, rivastigmine, tacrine and galantamine seem to be more effective and well tolerated (Burns et al., 1999; Kogan et al., 2001; Farlow, 2002; Birks and Harvey, 2003; Brassen and Adler, 2003; Geldmacher et al., 2003; Lanctôt et al., 2003; Relkin et al., 2003; Rodriguez et al., 2002, 2004; Hsiung and Feldman, 2008). From a biochemical point of view, donepezil and tacrine are both reversible and bind to a similar site of the AChE enzyme. However, donepezil is more selective and therefore has a better side-effect profile. In contrast, rivastigmine is a non-selective quasi-irreversible inhibitor (Enz and Floersheim, 1996).

Recent evidence in 906 mild AD subjects has shown that the donepezil treatment was associated with reduced odds of clinical worsening, defined as an association of cognitive decline, decline in activities of daily living and decline in global function (Wilkinson et al., 2009). In particular, 30% of placebo patients met the criteria for clinical worsening, while only 14% of donepezil-treated patients showed clinical worsening (Wilkinson et al., 2009). Compared to placebo, donepezil also induced a slower decline in instrumental and basic instrumental activities of daily living (ADL) in patients with moderate-to-severe AD (Feldman et al., 2003). Furthermore, AD patients treated with donepezil were associated with less caregiving time and lower levels of caregiver stress (Feldman et al., 2003). Donepezil may help behavioural symptoms by improving attention and concentration (Feldman et al., 2001). Furthermore, donepezil-treated AD patients showed particular benefits for apathy, anxiety and depression (Feldman et al., 2001). In general, a positive response to AChEIs occurs in about 50% of treated AD patients, considered as 'responders' (Tanaka et al., 2003; Hanyu et al., 2003; Bianchetti et al., 2003; Onofrj et al., 2003). However, it has been argued that the number of true responders is closer to 10% when placebo effects are removed (Lanctôt et al., 2003). The cause of this relatively limited response is unclear. To date, responders and non-responders have been found to differ in anatomical features of their pathology (Tanaka et al., 2003), as well as in the patterns of regional cerebral blood flow (rCBF, Hanyu et al., 2003) and resting-state EEG rhythms (Jelic et al., 1998; Babiloni et al., 2006e).

Memantine belongs to the class of low-affinity voltage-dependent uncompetitive NMDA receptor antagonists (Kornhuber and Weller, 1997; Lipton, 2006). It was the first approved drug in a novel class of AD medications acting on the glutamatergic system by blocking NMDA glutamate receptors. It has been associated with a moderate decrease in the clinical deterioration of AD patients (Cappell et al., 2010). Compared with placebo, memantine showed benefits for both basic and instrumental ADL in patients with moderate-to-severe AD, suggesting that memantine treatment may lead to a more interactive and dignified life for patients with moderate-to-severe AD (Winblad et al., 2010). In particular, memantine has been documented to have a positive effect on cognition, mood, behaviour and the ability to perform daily activities in moderate-to-severe AD, but its effect in the mild-to-moderate earlier stages of the disease is poorly understood (Areosa et al., 2005). Concerning cognitive functions, memantine may confer benefits particularly in the domains of orientation, following commands, praxis and comprehension (Mecocci et al., 2009). Furthermore, memantine has also been reported to improve the non-cognitive behavioural symptoms of AD such as delusions, agitation/aggression and irritability (Gauthier et al., 2008). Finally, few existing studies did not support the hypothesis that memantine induces an improvement in the cognitive performance in healthy subjects (Repantis et al., 2010).

The synergistic effect of adding memantine and AChEIs is not clear. An initial study in AD patients showed clear beneficial effects on cognitive and non-cognitive symptoms of AD (i.e., agitation and irritability) when memantine was co-administered with donepezil standard of care (Tariot et al., 2004). However, a more recent study investigating memantine in addition to one of three AChEIs failed to demonstrate any clear cognitive or non-cognitive beneficial effects in AD patients (Porsteinsson et al., 2008).

To summarise the existing literature, whilst positive effects of the AChEIs, memantine and possible synergy between the two have been reported, it is fair to say that the clinical significance of the benefits of these compounds has also been widely questioned. At best, they are generally considered to offer modest improvements over a relatively short period of time. A contrasting viewpoint is, however, that the AChEIs are indeed efficacious but that the choice of outcome measures is flawed (Kaduszkiewicz et al., 2005). One of the aims of PharmaCog is therefore to empirically test these compounds on a range of behavioural, neurobiological, neuroanatomical and neurophysiological (i.e., EEG) markers in patients and healthy volunteers to order to understand the effects of these compounds and identify appropriate markers that can be used in translational studies for drug discovery.

4. Electroencephalographic techniques for research on AD

EEG measures brain electrical activity recorded from electrodes placed on the surface of the head. Spontaneous on-going scalp EEG rhythms reflect synchronous extracellular ion flow due to excitatory and inhibitory postsynaptic potentials in large populations of cortical pyramidal neurons (Nunez, 2000). It is also commonly accepted that scalp EEG voltages mainly correspond to the local field potentials generated in superficial cortical layers; conversely, potentials deriving from deeper cortical layers are attenuated by the resistance of the head volume conductor. Specifically, the synaptic activity of pyramidal neurons located in cortical gyri, whose dendrites are oriented radially to the scalp surface, is reflected by neural currents of the superficial cortical layer, while neural currents of pyramidal neurons located in the cortical sulci that propagate (tangentially to the scalp surface) contribute to a lesser extent to the generation of on-going scalp EEG rhythms (Nunez and Srinivasan, 2006). From the above, it appears that the recording of EEG activity is able to probe the oscillatory nature of the brain, the science of which has only recently started to be understood (Berger, 1929; Nunez, 2000; Michel et al., 2004; Rossini et al., 2007; Rossini, 2009; Babiloni et al., 2009c).

EEG signals are very large-scale measures of brain source activity, reflecting synaptic activity synchronised over macroscopic (centimetre) regional spatial scales and are characterised by a low spatial resolution compared to other measures of brain function such as functional magnetic resonance imaging (fMRI; Nunez et al., 2001; Nunez and Srinivasan, 2006; Michel et al., 2004). Indeed, the different conductivities of head tissues (brain, meninges, skull and scalp) attenuate and blur the spatial distribution of neural currents from brain to scalp electrodes. As a consequence, scalp EEG data present enhanced low-spatial components and negligible values of high-frequency brain oscillations (>40 Hz, gamma rhythms). Although the EEG oscillations decrease in amplitude with increasing frequencies, rhythmic synchronisation at gamma bands related to cognitive functions can be revealed by sophisticated amplifiers and advanced mathematical procedures of spectral analysis (Basar-Eroglu et al., 1996; Engel et al., 2000). Mathematical procedures have also been developed to obtain reference-free measurements with attenuated head volume conductor effects, namely estimation of common average

reference, source current density and inverse EEG source solutions (Nunez and Srinivasan, 2006).

EEG signals have a high temporal resolution (<1 ms) ideal to investigate an emerging property of brain physiology, namely the awake brain rhythms, the immediate (acute) brain responses to sensory, cognitive or motor events and the long-term (chronic) effects of interventions.

The most popular procedures for the estimation of cortical sources of EEG activity use equivalent current dipoles as a model of neural generators. A volume conductor is typically represented by spherical or realistic MRI-based head models. Regularised linear procedures typically serve for solving the inverse problem, which provides an approximation of current density at the source models on the basis of the head volume conductor properties and the voltages/current density at the scalp locations (Pascual-Marqui et al., 1994; Rossetti and Kaplan, 2010; Grech et al., 2008).

Cortical sources of the resting-state EEG rhythms can be reliably estimated by low-resolution brain electromagnetic tomography analysis (LORETA) (Pascual-Marqui et al., 1994, 1999, 2002; http://www.uzh.ch/keyinst/loreta.htm). LORETA is a functional imaging technique estimating maximally smoothed linear inverse solutions accounting for distributed EEG sources within Talairach space (Pascual-Marqui et al., 2002). LORETA computes 3-D linear solutions (LORETA solutions) for the EEG inverse problem within a three-shell spherical head model including scalp, skull and brain compartments. The brain compartments are restricted to the cortical grey matter/hippocampus and are co-registered to the Talairach probability brain atlas, which has been digitised at the Brain Imaging Center of the Montreal Neurological Institute (Talairach and Tournoux, 1988). This compartment includes 2394 voxels (7 mm resolution), each voxel containing an equivalent current dipole. With respect to the dipole modelling of EEG cortical sources, no *a priori* decision of the dipole position is required by the investigators during LORETA estimation. LORETA is also available in a variant allowing statistical standardisation of the source solution, namely the so-called standardised sLORETA (Pascual-Marqui et al., 2002). sLORETA models 3-D distributions of the cortical source patterns generating scalp EEG data (Pascual-Marqui et al., 2002). Compared to LORETA, sLORETA computes 3-D linear solutions (sLORETA solutions) for the EEG inverse problem standardised with respect to instrumental and biological noise, which are mathematically defined in the original paper by Pascual-Marqui et al. (2002). sLORETA solutions are calculated within a three-shell spherical head model including scalp, skull and brain compartments. The brain compartment is restricted to the cortical grey matter/hippocampus of a head model co-registered to the Talairach probability brain atlas. This compartment includes 6239 voxels (5 mm resolution), each voxel containing an equivalent current dipole. The head model for the inverse solution uses the electric potential lead field computed with a boundary element method applied to the MNI152 template (Fuchs et al., 2002). The electrode coordinates are based on the average location of the 10–5 system placement system (Jurcak et al., 2005). It has been shown that sLORETA is relatively efficient when compared to linear inverse algorithms such as the minimum norm solution, weighted minimum norm solution or weighted resolution optimisation (Pascual-Marqui et al., 2002). Furthermore, sLORETA has been successfully used in recent EEG and magnetoencephalographic (MEG) studies (Wagner et al., 2004; Sekihara et al., 2005; Du et al., 2007). However, it should be stressed that sLORETA solutions represent statistical values rather than direct neural currents estimated into the brain source model. There is therefore a possible limitation in their use as a dependent variable for within-group and between-groups comparisons. LORETA is therefore a promising technique for translational research in AD as (i) it has been successfully used in research on AD and EEG markers by independent research groups worldwide (Dierks et al., 2000; Huang et al., 2000; Saletu et al., 2005); (ii) it has been extensively used and validated by two laboratories on EEG data of normal subjects, AD patients, and of patients suffering the pre-clinical condition called mild cognitive impairment (MCI), which refers to an objective cognitive decline in non-demented elderly subjects (Petersen et al., 1995, 1999; Petersen, 2000; Babiloni et al., 2004, 2006a,b,c,d,e,f, 2007a,b,c, 2008a,b, 2009a, 2010a,b, 2011a,b,c); and (iii) it is freeware, and can be freely downloaded by any research unit worldwide for control/replication of the results and for future scientific and clinical applications.

In recent years, great attention has been focussed on the evaluation of quantitative EEG (qEEG) as clinical markers of the early stages of AD (Rossini et al., 2007; Rossini, 2009). In this regard, the recording of resting-state eyes-closed cortical EEG rhythms represents a fully standardised procedure that may be carried out easily and rapidly in a clinical environment. The use of resting-state EEG rhythms does not require stimulation devices or registration of a subject's behaviour, and is not prone to fatigue and anxiety typically associated with task performance. This is ideal when EEG recordings are performed in elderly subjects.

Previous studies unveiled the role of the traditional spectral analysis of the power density of resting-state eyes-closed EEG rhythms at scalp electrodes in the study of ageing and dementia (Goodin and Aminoff, 1986; Giaquinto and Nolfe, 1986; Giannitrapani and Collins, 1988; Giannitrapani et al., 1991; John, 1989; Signorino et al., 1995). Compared to normal elderly (Nold) subjects, demented subjects have been characterised by a topographically widespread increase of slow frequency EEG rhythms (1–6 Hz) and decrease of faster EEG rhythms (about 8–12 Hz) (Giannitrapani and Collins, 1988; Giannitrapani et al., 1991). In particular, this analysis unveiled remarkable difference of the EEG power between Nold and AD subjects (Besthorn et al., 1997; Chiaramonti et al., 1997; Schreiter-Gasser et al., 1993). Compared to Nold subjects, AD patients present a topographically widespread increase of delta (about 1–4 Hz) and theta (about 4–8 Hz) rhythms along with a topographically widespread decrease of alpha (about 8–13 Hz) and beta (about 13–30 Hz) rhythms. These scalp EEG rhythms were also sensitive to the severity of dementia. Delta and/or theta rhythms do increase even in the earlier stages of AD (Schreiter-Gasser et al., 1993) and seem to predict disease progression (Ihl et al., 1996; Nobili et al., 1999). In Nold subjects, the magnitude of alpha rhythm is maximal at occipital electrodes (Giaquinto and Nolfe, 1986). While the alpha rhythm still peaks in posterior scalp areas in mild AD patients, it is either equally distributed over the scalp or localises more anteriorly with disease progression (Ihl et al., 1996). Similarly, the maximum amplitude of the beta rhythms is located more anteriorly in AD patients, as a function of disease severity (Ihl et al., 1996).

More recently, a bulk of studies have shown the following interesting results on the cortical sources of resting-state eyes-closed EEG rhythms in AD, mild cognitive impairment (MCI) and Nold subjects: (1) the cortical (LORETA) sources of dominant alpha rhythms (8–10 Hz) were abnormal in AD subjects when compared to Nold and VaD subjects (Babiloni et al., 2004); (2) the cortical (LORETA) sources of delta (2–4 Hz) and dominant alpha rhythms were related to global cognitive status (i.e., MMSE score) in both MCI and AD subjects (Babiloni et al., 2011a); (3) compared with MCI/AD with non-ApoE4 carriers, MCI/AD with ApoE-4 (i.e., genetic risk factor for AD) showed a stronger decrease of the cortical (LORETA) sources of the dominant alpha rhythms (Babiloni et al., 2006b); (4) haplotype B of CST3 (i.e., genetic risk factor for AD) was related to the cortical (LORETA) sources of delta and dominant alpha rhythms in MCI and AD subjects (Babiloni et al., 2006c); (5) the cortical (LORETA) sources of delta rhythms were related to brain white-matter atrophy in MCI and AD subjects (Babiloni

et al., 2006d); (6) long-term (1 year) cholinergic therapy (i.e., donepezil) slowed the decline of the cortical (LORETA) sources of dominant alpha rhythms in AD subjects (Babiloni et al., 2006e); (7) combined power and linear functional coupling of EEG rhythms predicted conversion from MCI to AD after about 1 year (Rossini et al., 2006); (8) fronto-parietal non-linear functional coupling of EEG rhythms was abnormal in MCI and AD subjects (Babiloni et al., 2006f); (9) cortical (LORETA) sources of delta and dominant alpha rhythms were related to neuropsychological measures of immediate memory based on focussed attention (i.e., digit and spatial span) in MCI and AD subjects (Babiloni et al., 2007a); (10) serum 'free' copper (i.e., a typical biomarker of AD) was related to alterations of EEG rhythms in AD subjects, namely an increase of the cortical (LORETA) sources of pathological delta rhythms (Babiloni et al., 2007b); (11) the cortical (LORETA) sources of delta rhythms were related to the amount of blood serum homocysteine, an amino acid with neurotoxic effects (Babiloni et al., 2007c); (12) power and directionality of functional coupling of EEG rhythms were abnormal in MCI and AD subjects as a function of white matter vascular lesions (Babiloni et al., 2008a,b); (13) hippocampal and cortical grey matter atrophy was related to the decline of the cortical (LORETA) sources of dominant alpha rhythms and cognitive status (i.e., MMSE score) in MCI and AD subjects (Babiloni et al., 2009a, 2012); (14) damage to the cholinergic system was associated with alterations of the cortical (LORETA) sources of the dominant alpha rhythms and of the functional global coupling in MCI subjects (Babiloni et al., 2009b, 2010a); (15) the cortical (LORETA) sources of alpha rhythms were altered in subjects with subjective memory complaints (no objective memory deficits) compared with MCI and Nold subjects (Babiloni et al., 2010b); (16) the cortical (LORETA) sources of the dominant alpha rhythms were related to stability of the cognitive status (i.e., MMSE score) in MCI subjects (Babiloni et al., 2011a); (17) cortical (LORETA) sources of delta and dominant alpha rhythms did not deteriorate with the increase of white-matter vascular lesion in MCI and AD subjects (Babiloni et al., 2011b); and (18) the decrease of the cortical (LORETA) sources of dominant alpha rhythms was higher in AD than in Parkinson's disease subjects (Babiloni et al., 2011c). With respect to the methodology, the difference between the spectral features of the resting-state versus task-related EEG rhythms should be underlined. In healthy human subjects, the 'tonic' (i.e., longlasting) frontal theta rhythms are relatively low in amplitude in the resting-state condition (Klimesch, 1999). During engaging cognitive tasks, the amplitude of the frontal theta rhythms briskly increases ('phasic' theta event-related synchronisation, ERS) in association with a brisk reduction of the amplitude of the posterior low- and high-frequency alpha rhythms ('phasic' alpha event-related desynchronisation, ERD). As mentioned above, several resting-state EEG studies have shown a pathological increase of the 'tonic' posterior delta and theta rhythms in AD subjects, as well as a reduction of the amplitude of the 'tonic' posterior dominant alpha rhythms. On the other hand, a standard auditory attention task (i.e., oddball paradigm) induced a 'phasic' amplitude increment of the frontal theta and delta rhythms accompanying the hand response to rare stimuli in normal elderly (Nold) subjects but not in AD patients (Caravaglios et al., 2008, 2010). In the same line, visual and auditory oddball task induced a 'phasic' amplitude increment of the widespread delta rhythms accompanying mental counting to rare stimuli in Nold subjects but not in AD patients (Yener et al., 2009, 2012). There was no difference between *de novo* AD patients and those treated with ACHEIs (Yener et al., 2009, 2012). The same was true when the functional coupling of these rhythms (i.e., spectral coherence) were considered (Başar et al., 2010).

Keeping in mind the findings mentioned above, we posit that the resting-state eyes-closed EEG rhythms provide reliable neurophysiologic information on MCI and AD subjects. Such information would be related to neurodegenerative processes as indexed by biological (i.e., genetics, homocysteine and free copper) and structural neuroimaging (i.e., hippocampus and cortical grey matter volumes) markers of AD, as well as with the related decline of the subjects' global cognitive status (i.e., MMSE score). Table 2 provides an overview of the main evidence and methodologies on resting-state eyes-closed EEG rhythms in AD, MCI and Nold subjects.

Here we reviewed the literature on the effects of AChEIs and memantine on the resting-state eyes-closed EEG rhythms in AD patients, as a knowledge platform for the development of innovative translational instrumental models for drug discovery in AD. Indeed, quite similar EEG experiments and the same kind of spectral data analysis can be performed in animal models of AD and in elderly individuals with prodromal or probable AD.

5. Acetylcholine effects on EEG rhythms: cellular mechanisms

Cellular mechanisms at the basis of Ach effects on EEG rhythms can be summarised as follows. During slow, synchronised EEG rhythms, cortical pyramidal cells displayed low-frequency intracellular membrane oscillations and pronounced, longlasting inhibitory after-hyperpolarisations following spike discharge (Buzsáki and Gage, 1989; Metherate et al., 1992). Extracellular currents associated with these slow, synchronised membrane electrophysiological events are believed to summate in the extracellular fluid, resulting in the appearance of high-voltage, low-frequency EEG rhythms. By acting on intracortical muscarinic receptors but not nicotinic binding sites, ACh blocks slow intracellular membrane oscillations and the outward potassium current associated with inhibitory after-hyperpolarisations; this mechanism would block slow, synchronised EEG rhythms and would facilitate a shift to a desynchronised pattern of on-going EEG rhythms (Buzsáki and Gage, 1989; Metherate et al., 1992; Steriade et al., 1993a; Steriade, 1993b).

The above data suggest that cholinergic fibres originating from the basal forebrain and targeting the cerebral cortex may play a major role in the desynchronisation of spontaneous on-going EEG rhythms, namely the suppression of high-voltage, low-frequency rhythms in the EEG (i.e., synchronised slow EEG rhythms at 1–6 Hz) and the appearance of low-voltage, fast-frequency EEG rhythms (i.e., desynchronised fast EEG rhythms at >14 Hz; Steriade et al., 1993a; Steriade, 1993b). However, fluctuations of the resting-state EEG rhythms depend not only on the cholinergic systems but also on other neuromodulatory systems that act on both cholinergic systems and directly on the cerebral cortex. Indeed, the basal forebrain cholinergic system is under powerful modulatory activity by fibres arising in the brainstem and diencephalon; these fibres convey noradrenergic, dopaminergic, serotonergic, histaminergic and brainstem cholinergic inputs (Vertes, 1988; Jones and Cuello, 1989; Semba and Fibiger, 1989; Zaborszky, 1989).

6. Pharmacological modulation of resting-state EEG rhythms in human subjects: the effects of AChEIs and memantine

Experiments on the effects of donepezil and memantine on EEG markers in humans have gained great interest owing to biochemical and pharmacological evidence of the crucial role of ACh in cognitive functions. As such, other therapeutic approaches aimed at boosting the cholinergic system are tested in clinical trials. AChEIs sustain the availability of the natural transmitter by limiting its removal from the synapse. Other approaches include administering exogenous agonists that may substitute for the downstream signalling associated with ACh itself. In this way, the issue of the extensive cholinergic cell loss occurring in AD could overcome

Table 2
Overview of the main evidence and methodologies on EEG rhythms in AD, mild cognitive impairment (MCI), and Nold subjects.

Reference	Population	Condition	EEG technique	EEG marker	Main results
Babiloni et al. (2004)	AD, Nold, VaD	Resting state	LORETA source power density	Alpha and theta sources	Amplitude decline of central, parietal, temporal, and limbic alpha 1 (low alpha) sources in AD with respect to Nold and VaD; theta sources abnormal in VaD but not in AD
Babiloni et al. (2006a)	MCI, AD, Nold	Resting state	LORETA source power density	Delta and alpha sources	Occipital delta and alpha 1 sources in parietal, occipital, temporal, and limbic areas had an intermediate amplitude in MCI subjects compared to mild AD and Nold subjects. Correlation between EEG sources and MMSE score across all subjects
Babiloni et al. (2006b)	MCI and AD (APoE4/non-APoE4)	Resting state	LORETA source power density	Alpha sources	Amplitude of alpha 1 and 2 sources in occipital, temporal, and limbic areas was lower in MCI-AD subjects carrying the epsilon4 allele than in those not carrying the epsilon4 allele
Babiloni et al. (2006c)	MCI, AD (CST3 B haplotype/non-CST3 B haplotype)	Resting state	LORETA source power density	Delta and alpha sources	Amplitude of alpha 1 (parietal, occipital, temporal areas) and alpha 2 (occipital area) was lower in MCI-AD subjects carrying CST3 B than in those not carryng the CST3 B. The amplitude of occipital delta sources was stronger in CST3 B carriers than in non-carriers
Babiloni et al. (2006d)	MCI, AD	Resting state	LORETA source power density	Delta sources	A negative correlation was observed between the MRI-based measurement of frontal white matter and the amplitude of frontal delta sources across MCI and AD subjects
Babiloni et al. (2006e)	AD (donepezil responders vs. non-responders)	Resting state	LORETA source power density	Delta and alpha sources	Before donepezil treatment, posterior sources of delta, alpha 1 and alpha 2 frequencies were greater in amplitude in non-responders compared to responders. After treatment (1 year), a lesser amplitude reduction of occipital and temporal alpha 1 sources characterized responders
Rossini et al. (2006)	MCI stable, MCI converted to AD	Resting state	LORETA source power density and spectral coherence	Delta, theta, and alpha sources. Spectral coherence	At baseline, fronto-parietal midline coherence as well as delta, theta, and alpha 1 sources were stronger in MCI converted than in MCI stable subjects. The convertion rate increased when high temporal delta source and high midline gamma coherence were observed
Babiloni et al. (2006f)	MCI, AD, Nold	Resting state	Synchronization likelihood of Laplacian-transformed EEG data	Delta, theta, alpha, beta, and gamma syncrhronization likelihood	Compared to Nold subjects, AD patients presented a marked reduction of the synchronization likelihood (delta to gamma) at both fronto-parietal and inter-hemispherical (delta to beta 2) electrodes. As a main result, alpha 1 synchronization likelihood progressively decreased across Nold, MCI, and mild AD subjects
Babiloni et al. (2007a)	MCI, AD	Resting state	LORETA source power density	Delta and alpha sources	Cortical sources of delta and alpha rhythms correlated with neuropsychological measures of immediate memory based on focused attention in the continuum of MCI and AD subjects
Babiloni et al. (2007b)	AD, Nold, MCI	Resting state	LORETA source power density	Delta, theta, and alpha sources	Alpha sources in parietal, occipital, and temporal areas decreased in amplitude, while the amplitude of the delta and theta EEG sources in parietal, occipital, and temporal areas increased across the continuum of Nold, MCI and AD subjects. Level of serum copper positively correlated with temporal and frontal delta sources
Babiloni et al. (2007c)	MCI, AD (high and low homocisteine)	Resting state	LORETA source power density	Delta, theta, and alpha sources	Delta, theta, alpha 1, and alpha 2 sources were stronger in amplitude in AD patients with high level than in AD patients with low level of homocistein. No difference was found between MCI patients
Babiloni et al. (2008a)	MCI, Nold	Resting state	Direction of EEG functional coupling (DTF)	Fronto-parietal functional coupling at theta, alpha1, alpha2, and beta1	Fronto-parietal functional coupling of EEG rhythms was higher in amplitude in the Nold than in MCI subjects; that coupling was higher at theta, alpha1, alpha2, and beta1 in MCI V+ (high vascular load) than in MCI V− group (low vascular load)
Babiloni et al. (2008b)	MCI, AD, Nold	Resting state	LORETA source power density	Alpha sources	Amplitude of parietal, occipital, and temporal alpha 1 sources was higher in MCI V+ (high vascular load) than in MCI V− (low vascular load) group. A positive correlation was found between the parietal alpha 1 sources and the score of Wahlund scale across all MCI subjects (the more severe white-matter lesions, the higher the amplitude of parietal alpha sources)
Babiloni et al. (2009a)	MCI, AD	Resting state	LORETA source power density	Alpha sources	Amplitude of occipital, parietal, and temporal alpha 1 sources was maximum in MCI h+ (larger hippocampal volume), intermediate in MCI h− (smaller hippocampal volume), and low in AD patients. A significant linear correlation between hippocampal volume and magnitude of alpha 1 sources in the parietal, occipital and temporal areas was found

(*continued on next page*)

Table 2 (*continued*)

Reference	Population	Condition	EEG technique	EEG marker	Main results
Babiloni et al. (2009b)	Amnesic MCI, Nold	Resting state	LORETA source power density	Alpha and theta sources	Amplitude of occipital, parietal, temporal, and limbic theta and alpha 1 sources was maximum in Nold, intermediate in MCI Ch− (low cholinergic damage), and low in MCI Ch+ (high cholinergic damage) patients
Babiloni et al. (2010a)	MCI, Nold	Resting state	Spectral coherence	Total coherence of alpha1 rhythms	Total coherence of alpha1 rhythms was higher in Nold, intermediate in MCI Ch−, and lower in MCI Ch+ groups. The alpha1 total coherence was negatively correlated to (moderate to high) cholinergic lesion across MCI subjects
Babiloni et al. (2010b)	MCI, Nold, subjective memory complaint (SMC), amnestic and non-amnestic MCI	Resting state	sLORETA standardized source power density	Delta, theta, alpha1, and alpha2	Amplitude of delta, theta, and alpha sources was abnormal in SMC when compared to Nold. That of alpha sources was also higher in SMC than in MCI subjects
Babiloni et al. (2011a)	Amnesic MCI	Resting state	LORETA source power density	Alpha sources	Amplitude of alpha sources is related to a long-term (1 year) stable cognitive function in MCI subjects
Babiloni et al. (2011b)	MCI, AD, Nold	Resting state	LORETA source power density	Delta and alpha sources	Amplitude of occipital, temporal, and limbic alpha 1 sources was higher in MCI V+ (high vascular load) than in MCI V− (low vascular load) group. Amplitude of occipital delta sources was lower in AD V+ (high vascular load) than in AD V− (low vascular load) group. Furthermore, central, parietal, occipital, temporal, and limbic alpha sources were higher in amplitude in AD V+ than in AD V− group. Amplitude of these sources was correlated to global cognitive status (MMSE)
Babiloni et al. (2011c)	AD, Parkinson disease related dementia Patients (PDD), Nold	Resting state	LORETA source power density	Delta, theta, alpha, and beta sources	With respect to Nold group, PDD and AD groups mainly pointed to lower amplitude of posterior alpha 1 sources, which were positively correlated to MMSE score across all PDD and AD subjects (the lower the amplitude of alpha sources, the lower the MMSE score). Alpha decrease was greater in the AD than PPD patients
Caravaglios et al. (2008)	AD, Nold	Auditory attention (oddball) task	Auditory event-related oscillatory responses	Event related latencies, delta responses	N200 and P300 latencies were significantly prolonged in AD patients compared to Nold subjects. The difference between Nold and AD subjects was at the level of stimulus-related delta amplitude changes: in all locations a significant enhancement of the delta response is recorded in Nold subjects, while this delta reactivity was not detectable in AD patients
Caravaglios et al. (2010)	AD, Nold	Auditory attention (oddball) task	Auditory event-related oscillatory responses	Theta responses	In AD patients, there was an increased prestimulus theta power, as well as no significant poststimulus theta power increase upon both target and non-target stimulus processing; in Nold, only during target tone processing, an enhancement of both early and late theta responses relative to the prestimulus baseline was found. Moreover, Nold had a frontal dominance of theta power
Yener et al. (2009)	AD (treated and untreated with cholinergic drug), Nold	Visual stimulation	Visual evoked oscillatory responses	Theta responses	Higher theta oscillatory responses in untreated AD subjects were seen in bi-parietal and right occipital areas after simple light stimuli with less, if any, cognitive load. These changes were restricted to the theta frequency range only and were related to location, frequency bands and drug effects.
Yener et al. (2012)	AD (treated and untreated with cholinergic drug), Nold	Visual and auditory stimulation	Visual and auditory evoked oscillatory responses	Delta responses	Auditory delta responses of Nold were higher than in *de novo* or medicated AD groups, without a difference between two AD groups
Başar et al. (2010)	AD (treated and untreated with cholinergic drug), Nold	Visual attention (oddball) task, visual stimulation	Visual evoked and event related coherences	Delta, theta, and alpha event related coherence	The Nold group showed significantly higher values of event related coherence in delta, theta and alpha bands in comparison to treated and untreated AD groups upon application of a target stimuli. In contrast, almost no changes in event related coherences were observed in beta and gamma frequency bands. Furthermore, no differences were recorded between Nold and AD groups upon application of simple light stimuli

the issue of when treatment is given. Moreover, the discovery of different muscarinic receptor subtypes, most notably the M1 sub-type that is primarily involved in the postsynaptic transmission, has offered new opportunities to address the problem in a very specific manner.

In this conceptual framework, donepezil has been found to partially restore the power density of the resting-state eyes-closed EEG rhythms and to improve patients' cognitive performance (see Table 1 for the neuropsychological tools) in mild AD patients at group level (Rodriguez et al., 2002, 2004; Kogan et al., 2001; Reeves et al., 2002; Brassen and Adler, 2003; Onofrj et al., 2003; Babiloni et al., 2006e). In particular, short-term donepezil treatment induced a widespread decrement of the pathological delta rhythms (0–3 Hz; Reeves et al., 2002; 5 mg daily for 1 month), as well as a decrease of the theta rhythms (4–7 Hz) associated with an improvement of the ADAS memory score (Brassen and Adler, 2003; 1- or 2-week standard dose). Furthermore, there was an increment of the alpha rhythms (8–12 Hz)

associated with a significant improvement of the MMSE and ADAS-cog scores (Onofrj et al., 2003; 5–10 mg for 30 days). In contrast, long-term treatment with donepezil induced a decrement of the pathological theta rhythms (Kogan et al., 2001; 5–10 mg day^{-1} for a period of 5.8 ± 3.0 months) and an increment of the alpha/theta ratio, especially in the frontal regions; these changes were associated with a smaller decline of the MMSE score (Rodriguez et al., 2002; 5 mg day^{-1}, 12.3 ± 3.6 months). Furthermore, the mean power across several frontal and posterior resting-state EEG rhythms has been proven to be insensitive to the long-term donepezil effects of treatment in mild-to-moderate AD patients (Rodriguez et al., 2004; 5 mg day^{-1} for about 12 months), possibly due to limitations of the standard EEG approach used. Indeed, long-term (1 year) therapy with donepezil slowed the decline of the cortical (LORETA) sources of dominant alpha rhythms in AD 'responders' showing a stable or improved MMSE score at the follow-up (Babiloni et al., 2006e).

An interesting study investigated resting-state EEG markers as a function of the clinical response in AD patients who did or did not benefit from donepezil therapy, in line with the working hypothesis that responders and non-responders to donepezil treatment may be characterised by different functional features of synchronisation mechanisms at the basis of EEG generation (Babiloni et al., 2006e). Based on the variation of MMSE (MMSEvar) scores between baseline and follow-up (1 year of donepezil treatment), AD patients were classified as responders (MMSEvar >0) and non-responders (MMSEvar <0). Before treatment, posterior sources of delta (<4 Hz), theta (4–8 Hz; trend), low-frequency alpha (8–10.5 Hz) and high-frequency alpha (10.5–13 Hz) were non-selectively greater in amplitude in non-responders than in responders to donepezil treatment (Babiloni et al., 2006e; 5–10 mg day^{-1} for 1 year). After the treatment (1 year), responders and non-responders were characterised by a marked increase of resting-state posterior delta rhythms and a marked decrease of low-frequency temporal, parietal and occipital alpha rhythms, thus suggesting that long-term administration of donepezil was not able to stop the development of neurodegeneration in these AD patients. However, it was observed that the pathological reduction in power of the low-frequency alpha rhythms was lower in magnitude in responders compared to non-responders (Babiloni et al., 2006e). The mechanisms explaining the effect of donepezil on the resting-state EEG rhythms are poorly understood. Donepezil might protect cholinergic neurons and/or potentiate functionally silent cortical synapses, enabling the collective behaviour of basal forebrain–cortical, thalamo-cortical and cortico-cortical mechanisms generating posterior resting-state alpha rhythms (Babiloni et al., 2006e).

Donepezil has been found to act not only on resting-state EEG rhythms but also on sleep EEG rhythms, which are affected by circadian and homeostatic processes (Daan et al., 1984). On the one hand, the circadian process directs the timing of virtually all 24-h behavioural, physiological and molecular processes, including sleep and wakefulness alternation (Rosenwasser and Turek, 2005). Advancing age alters sleep patterns, reducing high-voltage EEG slow-wave activity or delta waves (0.5–4 Hz) in non-rapid eye movement (NREM) sleep, sleep length and delta power during NREM sleep. On the other hand, the sleep homeostatic process regulates the propensity for sleep based on the amount of prior wakefulness; the organism will attempt to regain or compensate for the resource (i.e., sleep) that was previously depleted. During EEG slow-wave activity, slow oscillations, spindles and ripples – at minimum cholinergic activity – coordinate the re-activation and redistribution of hippocampus-dependent memories to neocortical sites; during REM sleep (also called paradoxical sleep), local increases in plasticity-related immediate-early gene activity – at high cholinergic and theta activity – might favour the subsequent synaptic consolidation of memories in the cortex (Diekelmann and Born, 2010). EEG slow-wave activity in NREM sleep has been used as the main quantitative operational measure of sleep homeostasis and is commonly equated with sleep intensity (Steriade, 2005). Decline in slow-wave activity of NREM sleep from early to late sleep and manipulation of this activity by learning before sleep suggest that the average synaptic strength is reflected by NREM slow-wave activity as an effect of homeostatic rather than circadian processes (Tononi, 2009). In this theoretical framework, donepezil treatment for 3–6 months increased the duration of REM during the night and reduced high-voltage slow EEG frequencies (delta and theta) of REM, thus suggesting a possible action upon REM sleep-related cholinergic neurons and the memory consolidation phase of the sleep in patients with AD (Moraes Wdos et al., 2006; standard drug dose). Furthermore, alpha rhythms accompanying paradoxical REM sleep correlated to cognitive response to donepezil (Moraes Wdos et al., 2006).

Significant effects of tacrine on resting-state EEG global field power (i.e., mean of the EEG power density across all electrodes) were observed in AD patients (Jelic et al., 1998). After 3 months, theta global field power was reduced; after 6 months, both theta and delta global field power decreased. Theta global field power was still reduced after 12 months of tacrine treatment when compared to the baseline recording. The untreated control group did not show these effects (Jelic et al., 1998). Similarly, there was a reduction of the resting-state delta and theta rhythms associated with an increase of the alpha and beta rhythms in AD patients exhibiting stable or improved MMSE score after 12 weeks of tacrine treatment (Knott et al., 2000a, 2000b; 30 mg day^{-1}). Furthermore, responders to tacrine treatment showed an increase of the alpha rhythms and of the alpha–theta ratio when compared to non-responders (Alhainen et al., 1991; Alhainen and Riekkinen, 1993). Of note, there is evidence showing that a single dose of tacrine produces changes in the resting-state EEG rhythms that underlie the prediction of therapy response after 4 or 7 weeks of treatment in AD patients (Alhainen et al., 1991; Alhainen and Riekkinen, 1993). In AD responders, a single dose of tacrine induced an increase of resting-state frontal alpha rhythms associated with a reduction of theta rhythms, namely the so-called 'frontal alpha/theta ratio'. This was associated with an enhancement of attention and working memory (Alhainen et al., 1991; Alhainen and Riekkinen, 1993).

Similarly to donepezil and tacrine, rivastigmine affected resting-state EEG rhythms in AD patients (Adler and Brassen, 2001; Brassen and Adler, 2003; Adler et al., 2004; Gianotti et al., 2008). After 3 months of the rivastigmine treatment, resting-state delta and theta rhythms were reduced (Gianotti et al., 2008). Furthermore, a positive correlation between cognitive performance and resting-state EEG rhythms estimated in the left insula was found in AD subjects after 3 months of rivastigmine treatment (Gianotti et al., 2008). Rivastigmine also produced a decrease of the resting-state delta and theta rhythms in AD patients after 5 days of treatment; in these patients, beta rhythms were positively correlated with cognitive performance and negatively correlated with functional impairment (Adler and Brassen, 2001; 3 mg day^{-1}). After 2 weeks of treatment, there was a decrease of the theta rhythms associated with an improvement of the ADAS memory score (Brassen and Adler, 2003). In addition, AD responders to the rivastigmine treatment showed a greater decrease of the global theta rhythms after 1 week of treatment; this effect was associated with improved short-term memory performance and MMSE score (Adler et al., 2004). The effect on theta rhythms was observed after 1 month of treatment as well (Adler et al., 2004).

In contrast to donepezil, tacrine and rivastigmine, the effects of galantamine and memantine on resting-state EEG rhythms are poorly understood. Only one study reported effects on EEG

rhythms in a small number of AD patients (Sneddon et al., 2006). The experimental design included serial EEG recordings combined with a delayed recognition memory task and the use of several techniques of EEG data analysis. On the whole, a reduction of pathological theta rhythms after long-term treatment with galantamine or memantine was demonstrated (Sneddon et al., 2006). Table 3 summarises the main results of the studies on pharmacological modulation of EEG rhythms and assessment of cognitive functions in AD patients.

The translational value of the above data is further substantiated by a bulk of literature evidence on the effects of AChEIs and memantine on spontaneous on-going EEG rhythms in wild-type and transgenic animal models that we will not describe in the present review. A comprehensive review of this literature is re-

Table 3
Overview of the main results of the studies on pharmacological modulation of EEG rhythms and assessment of cognitive functions in AD patients.

References	Drug	Population	End point	EEG marker	Main results
Babiloni et al. (2006e)	Donepezil (5–10 mg/day for 1 year)	AD (responders vs. non-responders)	MMSE score	LORETA sources of delta and alpha power	Before donepezil treatment, posterior sources of delta, alpha 1 and alpha 2 were greater in amplitude in non-responders than in responders. After treatment, a lesser amplitude reduction of occipital and temporal alpha 1 sources characterized responders
Rodriguez et al. (2002)	Donepezil (5 mg/day for 12.3 ± 3.6 months)	AD (treated vs. non-treated)	MMSE score	EEG power ratio (6.5–12/2–6 Hz)	Long-term treatment with donepezil led to a lower deterioration of EEG rhythms in frontal regions
Rodriguez et al. (2004)	Donepezil (5 mg/day for 1 year)	AD	MMSE score	Mean frequency (MF) value of mean power	After donepezil treatment, the MMSE score significantly decreased and qEEG was unchanged; a positive correlation was found between the right frontal MF and brain perfusion (single photon emission computed tomography data) in the left superior parietal lobule
Kogan et al. (2001)	Donepezil (5–10 mg/day for 5.8 ± 3.0 months)	AD	MMSE score	Delta, theta, alpha, and beta power	Reduction of mean absolute power in frontal and temporo-parietal areas after donepezil treatment. In patients with moderate/severe dementia, a significant decrease in the mean absolute beta 1 power particularly in the frontal and occipital areas may be attributed to disease progression
Reeves et al. (2002)	Donepezil (5 mg/day for 1 month)	AD	–	Delta and alpha power	After donepezil treatment, significant decreases in mean alpha and delta power were observed
Brassen and Adler (2003)	Rivastigmine, donepezil (1 or 2 week of standard treatment)	AD	ADAS-Cog score	Global theta power	After donepezil treatment, decrease of global theta power and an improvement in the ADAS memory score were observed
Onofrj et al. (2003)	Donepezil (5–10 mg/day for 1 month)	AD (fluctuating vs. non-fluctuating condition)	ADAS-Cog and MMSE score	The dominant EEG frequency variability, low EEG frequencies amplitude, P300 latency and jitter	Short-term administration of donepezil induced a significant increase in MMSE score, improvement of ADAS-cog score, increase of alpha power and reductions of P300 latency/jitter, and dominant frequency variability in fluctuating cognition group; it also induced significant increase of MMSE score and a decrease of P3 jitter and dominant frequency variability in nonfluctuating group
Jelic et al. (1998)	Tacrine long-term treatment (1 year)	AD	MMSE score	Delta, theta, beta1, and beta2 global field power	After 3 months of tacrine, theta global field power was reduced; after 6 months, both theta and delta global field power decreased. Theta global field power was still reduced after 12 months of treatment when compared to the baseline recording. The untreated control group did not show these effects
Knott et al. (2000a)	Tacrine (30 mg/day for 12 week)	AD	MMSE score	Theta and alpha power	After tacrine treatment, the EEG of patients exhibiting stable or improved MMSE score at 12 weeks showed an increased mean alpha frequency as well as a significant reduction in theta power following the single Tacrine test dose compared to deteriorated patients
Alhainen et al. (1991)	Tacrine (single dose of 50 mg)	AD, Nold	not available	Alpha/theta power ratio	After tacrine treatment, the relative change from the baseline in the alpha-theta power ratio was the most sensitive discriminator of responders and nonresponders
Adler and Brassen (2001)	Rivastigmine (1.5 mg twice daily for 5 days)	AD	MMSE and GDS score	Delta, theta, and beta power	After tacrine treatment, beta power was positively correlated with cognitive performance and negatively correlated with functional impairment. Rivastigmine produced a decrease in delta and theta power
Adler et al. (2004)	Rivastigmine (3–9 mg/day for 1 week)	AD (before and after treatments)	MMSE score	Theta power	After rivastigmine treatment, the MMSE score improved from 20.2 to 21.7. Theta power decreased significantly. Compared to non-responders, responders had a greater decrease in theta power after the treatment and a better short term memory at baseline
Gianotti et al. (2008)	Rivastigmine treatment for 3 months	AD, Nold	MMSE score	LORETA sources of delta, theta, and alpha power	After rivastigmine treatment, a power decrease in delta and theta was observed. LORETA localized rivastigmine effects in a network that includes left fronto-parietal regions, posterior cingulate cortex, bilateral parahippocampal regions, and the hippocampus. Furthermore, a correlation analysis showed better cognitive performance with increased alpha1 sources in the left insula
Sneddon et al. (2006)	Galantamine, memantine, nicotine, and rivastigmine	AD	Memory test score	Theta power	There was a reduction of pathological theta rhythms after long-term treatment; results were independent of the specific medication monitored

ported in an independent review article written with the PharmaCog consortium. In brief, previous studies have shown that a variety of direct and indirect cholinergic agonists induce desynchronisation of spontaneous on-going EEG rhythms at beta/gamma frequencies (Dringenberg et al., 2000a, 2000b, 2002; Dimpfel, 2005), while muscarinic-receptor cholinergic antagonists reduce both the endogenous desynchronisation of on-going EEG rhythms and the desynchronisation elicited by stimulation of cholinergic basal forebrain neurons (Funderburk and Case, 1951; Celesia and Jasper, 1966; Cuculic et al., 1968; Metherate et al., 1992).

7. Conclusions

AChEIs (especially donepezil) are the most important symptomatic treatments for mild-to-severe AD patients, while the NMDA-receptor antagonist memantine is licensed for the administration to moderate-to-severe AD patients. Here, the literature on the effects of these compounds on the resting-state eyes-closed EEG rhythms recorded in AD patients is reviewed as a knowledge platform for the identification of spectral EEG markers to be used for the development of innovative translational models for drug discovery in AD.

The summary of the EEG literature (see Table 3) showed a decrement of the pathological delta (0–3 Hz) and theta (4–7 Hz) rhythms in the AD responders to the chronic administration of AChEIs. These patients also showed an increment of the dominant alpha rhythms (about 8–10 Hz) as well as a slight improvement of the global cognitive status as indexed by ADAS-Cog (particularly the memory section) or MMSE score. In the AD responders to long-term therapy with AChEIs (i.e., from 6 to 12 months), a decrement of the delta and theta rhythms was associated with a reduced loss of the dominant alpha rhythms and with a lesser decline of the global cognitive status when compared to those of the non-responders or not-treated AD patients. In contrast, the only EEG study on the effects of the memantine in AD patients showed a reduction of the pathological theta rhythms after several months of treatment (Sneddon et al., 2006). These data suggest that the spectral EEG markers at delta, theta and dominant alpha frequencies may reflect the beneficial effects of the AChEIs on the neurophysiological substrate of the cognitive status in successfully treated AD patients, whereas further experiments are required to better understand the value of these spectral EEG markers in AD patients treated with memantine. Despite the lack of effects of ACHEIs and memantine on resting-state gamma rhythms, the use of advanced mathematical procedures for an exploratory analysis of high-frequency EEG oscillations in future AD studies is recommended.

An important question is whether the EEG markers can be used as translational markers to assess novel symptomatic drugs that affect the ascending neuromodulation systems at the basis of the generation of the resting-state EEG rhythms: that is, cholinergic, dopaminergic, serotoninergic and glutamatergic pathways. Unfortunately, no definitive conclusion can be drawn based on the data reviewed above. It can be speculated that the spectral EEG markers may be invaluable translational biomarkers at the earlier stages of the drug development, that is, preclinical through to early P1/PII clinical trials. Indeed, quite similar EEG experiments and the same kind of spectral data analysis can be performed in animal models of AD and in elderly individuals with prodromal or manifest AD. Furthermore, the procedure for the recording of the resting-state EEG rhythms in humans can be easily back-translated to the experiments carried out in wild-type and in transgenic animal models of AD. Furthermore, the same FFT procedures can be used for the estimation of the spectral power density in the preclinical and clinical EEG data. Hence, EEG markers may prove a powerful marker of target engagement essential for success in clinical trials for symptomatic drugs. It is of great heuristic value if future clinical trials systematically use spectral EEG markers, especially the cortical sources of the resting-state eyes-closed EEG rhythms), alongside imaging, biochemical and cognitive biomarkers in order to better understand their relationship and predicative validity for new symptomatic and disease-modifying compounds. A number of these studies are being performed within the framework of the PharmaCog project to gain an understanding of the clinical status in patients with prodromal and full AD.

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