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Review

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

Claudio Babiloni [a,b,*], Claudio Del Percio [b], Regis Bordet [c], Jean-Luis Bourriez [c], Marina Bentivoglio [d], Pierre Payoux [e], Philippe Derambure [c], Sophie Dix [f], Francesco Infarinato [b], Roberta Lizio [b], Antonio Ivano Triggiani [a], Jill C. Richardson [g], Paolo M. Rossini [b,h]

[a] Department of Physiology and Pharmacology, University "Sapienza" of Rome, Rome, Italy
[b] Department of Neuroscience, IRCCS San Raffaele Pisana, Rome, Italy
[c] L'Université Lille 2 Droit et Santé, Lille, France
[d] Department of Neurological Science (DSNNMM), University of Verona, Verona, Italy
[e] Institut National de la Santé et de la Recherche Médicale U455, Toulouse, France
[f] Eli Lilly, Erl Wood Manor, Windlesham, Surrey, UK
[g] GlaxoSmithKline R&D China Group, Gunnels Wood Road, Stevenage, Hertfordshire, UK
[h] Department of Geriatrics, Neuroscience & Orthopedics, Institute of Neurology Catholic University "Sacro Cuore" Rome, Italy

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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.

* Corresponding author at: Department of Physiology and Pharmacology, University "Sapienza" of Rome, Piazzale Aldo Moro 5, 00185, Rome, Italy. Tel.: +39 0649910989; fax: +39 0649910917.
E-mail address: claudio.babiloni@uniroma1.it (C. Babiloni).

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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-