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Occipital sources of resting-state alpha rhythms are related to local gray matter density in subjects with amnesic mild cognitive impairment and Alzheimer's disease

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ABSTRACT

Occipital sources of resting-state electroencephalographic (EEG) alpha rhythms are abnormal, at the group level, in patients with amnesic mild cognitive impairment (MCI) and Alzheimer's disease (AD). Here, we evaluated the hypothesis that amplitude of these occipital sources is related to neurodegeneration in occipital lobe as measured by magnetic resonance imaging. Resting-state eyes-closed EEG rhythms were recorded in 45 healthy elderly (Nold), 100 MCI, and 90 AD subjects. Neurodegeneration of occipital lobe was indexed by weighted averages of gray matter density, estimated from structural MRIs. EEG rhythms of interest were alpha 1 (8–10.5 Hz) and alpha 2 (10.5–13 Hz). EEG cortical sources were estimated by low-resolution brain electromagnetic tomography. Results showed a positive correlation between occipital gray matter density and amplitude of occipital alpha 1 sources in Nold, MCI, and AD subjects as a whole group ($r = 0.3$, $p = 0.000004$, $N = 235$). Furthermore, there was a positive correlation between the amplitude of occipital alpha 1 sources and cognitive status as revealed by Mini Mental State Examination score across all subjects ($r = 0.38$, $p = 0.000001$, $N = 235$). Finally, amplitude of occipital alpha 1 sources allowed a moderate classification of individual Nold and AD subjects (sensitivity: 87.8%; specificity: 66.7%; area under the receiver operating characteristic curve:

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0.81). These results suggest that the amplitude of occipital sources of resting-state alpha rhythms is related to AD neurodegeneration in occipital lobe along pathologic aging.

1. Introduction

Amnesic mild cognitive impairment (MCI) is a clinically intermediate state between elderly normal cognition and Alzheimer's disease (AD). MCI subjects show memory complaints and cognitive impairment on neuropsychological tests but do not yet fulfill the clinical criteria for dementia (Flicker et al., 1991; Petersen et al., 1995, 2001). MCI may be considered as a precursor to AD (Arnaiz and Almkvist, 2003; Galluzzi et al., 2001; Scheltens et al., 2002), given the high rate of progression from MCI to AD (Bachman et al., 1993; Gao et al., 1998; Petersen et al., 2001). In cognitively intact elderly subjects, the annual rate of transition to AD ranges from 0.17% to 3.86% (Frisoni et al., 2004; Petersen et al., 2001), but it is much higher in patients with MCI, ranging from 6% to 25% (Petersen et al., 2001). However, the "transition" hypothesis is challenged by the fact that not all MCI subjects deteriorate over time (Bennett et al., 2002; Larrieu et al., 2002), as cumulative incidence rates for AD range from 40% to 60% after about 5 years (Bennett et al., 2002; Fisk et al., 2003; Larrieu et al., 2002).

Neuropsychological markers are extremely important for the assessment of prodromal stages of AD, but there is consensus that a crucial challenge of aging research is a better understanding of the neurobiological basis of the MCI condition, to refine diagnostic procedures and to target new pharmacologic interventions (Albert et al., 2011; Braak and Braak, 1991; Dubois et al., 2007; Nestor et al., 2004; Rogers et al., 1996; Small et al., 1995). In the light of the new international guidelines (Albert et al., 2011; Dubois et al., 2007), prodromal stages of AD in MCI subjects can be diagnosed by abnormal dosages of the "A beta amyloid to tau" ratio in cerebrospinal fluid (CSF) and deposition of A beta amyloid in the brain, as revealed by ligand-based positron emission tomography (PET). Other useful biomarkers are overt signs of neurodegeneration such as atrophy of the hippocampus, on magnetic resonance imaging (MRI), or hypometabolism of the posterior cingulate and/or precuneus, parietal, and temporal regions, as revealed by fluorodeoxyglucose positron emission tomography (Albert et al., 2011; Dubois et al., 2007). However, CSF and PET markers are invasive, and MRI markers of hippocampus volume are relatively expensive for serial screening of large elderly populations at risk of AD. For this reason, other fully noninvasive and more cost-effective procedures have been investigated in the past years.

A promising approach to assess MCI subjects is the recording of resting-state eyes-closed electroencephalographic (EEG) rhythms. This approach is based on low cost and relatively widely available equipment, as well as being is noninvasive. It can also be used to collect serial measurements without incurring misleading effects that are solely because of the repetition of the procedure (Rossini et al., 2007). Prior studies have successfully investigated the resting-state eyes-closed EEG rhythms in MCI and AD subjects. Compared with normal elderly subjects (Nold), AD patients showed an increase in delta (1–4 Hz) rhythms, and a decrement of posterior alpha (8–12 Hz) rhythms (Dierks et al., 2000, 1993; Huang et al., 2000; Jeong, 2004; Ponomareva et al., 2003; Koenig et al., 2005). These EEG abnormalities are associated with altered regional cerebral blood flow and/or metabolism and with impaired global cognitive function as evaluated by the mini mental state examination (MMSE; Jeong, 2004; Rodriguez et al., 1998, 1999a, 1999b; Sloan et al., 1995). Similarly, MCI subjects show a decrease of alpha rhythms compared with normal elderly subjects (Elmstahl and Rosen, 1997; Huang et al., 2000; Jelic et al., 2000; Koenig et al., 2005; Zappoli et al., 1995). However, a certain variability of the brain rhythms in pathologic aging might prevent its use for personalized diagnosis and prognosis, especially in early MCI. For example, recent magnetoencephalographic evidence has not detected a statistically significant difference in brain rhythms in Nold and MCI subjects (Osipova et al., 2006).

When assessing MCI and AD subjects, the practical use of EEG markers would require preliminary validation studies showing that these markers are clearly related to AD neurodegenerative processes as revealed by brain atrophy. In this vein, it has been shown that EEG and structural MRI data complement each other in the modeling of psychomotor speed, global cognition, memory, and language ability in pathologic aging (Strijers et al., 1997). Brain atrophy has been proposed as the primary factor associated with psychomotor speed on the "trail making" test, but variations of alpha rhythms have been associated with a wider range of cognitive functions (Van der Hiele et al., 2007). Furthermore, MCI subjects with different degrees of hippocampal atrophy were characterized by different amplitude of the resting-state EEG rhythms, especially at dominant alpha frequencies (Moretti et al., 2007, 2011).

A step forward in studying the relationship between resting-state EEG rhythms and structural MRI markers of AD neurodegeneration would be the use of EEG and MRI markers, with data co-registered in the same anatomic space. For this purpose, a promising approach is the estimation of the cortical sources of the resting-state EEG rhythms by low-resolution brain electromagnetic tomography (LORETA), (Pascual-Marqui and Michel, 1994; Pascual-Marqui et al., 1999; 2002). For this kind of analysis, software is freely available and has been successfully used in cognitively impaired elderly subjects (Caso et al., 2012; Nishida et al., 2011). With this goal in mind, our research group has repeatedly used LORETA methods to study the cortical sources of the resting-state EEG rhythms in MCI and AD subjects. In these studies, occipital sources of the resting-state alpha rhythms were the most promising EEG markers of prodromal AD in MCI subjects. Specifically, the magnitude of occipital sources of alpha rhythms was positively correlated with the score on the MMSE and attention tasks in MCI and AD subjects (Babiloni et al., 2006a, 2007). Furthermore, it was negatively related to the atrophy of the hippocampal and global cortical gray matter as measured by structural MRIs in MCI and AD subjects (Babiloni et al., 2009a, 2013).

Keeping in mind the previously mentioned data, the present study investigated the relationship between neurodegeneration in the occipital lobe, occipital sources of alpha rhythms, and global cognitive status in Nold, MCI, and AD subjects. We hypothesized that the higher the neurodegeneration in the occipital lobe, the lower the amplitude of occipital sources of alpha rhythms and the lower the global cognitive status. To this aim, resting-state eyes-closed EEG rhythms were recorded in Nold, MCI, and AD subjects. Cortical sources of these EEG rhythms were estimated using the LORETA software. The MMSE score was used to index the global cognitive status (Folstein et al., 1975). Neurodegeneration of the occipital lobe was indexed by gray matter density (GMD) estimated from the subject's MRI, with GMD considered a good index of regional atrophy provoked by neuronal loss (Kassubek et al., 2004; Mummery et al., 2000).