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Hypercapnia affects the functional coupling of resting state electroencephalographic rhythms and cerebral haemodynamics in healthy elderly subjects and in patients with amnestic mild cognitive impairment

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HIGHLIGHTS

- Coherence of resting state EEG rhythms is impaired in MCI patients.
- MCI patients also showed poorer reactivity of resting state EEG rhythms coherence during CO_2 condition compared with Nold subjects.
- VMR was not altered in both Nold and amnesic MCI subjects, while EEG coupling was especially sensitive to the effects of hypercapnia on the amnesic MCI subjects.

ABSTRACT

Objective: Cerebral vasomotor reactivity (VMR) and coherence of resting state electroencephalographic (EEG) rhythms are impaired in Alzheimer's disease (AD) patients. Here we tested the hypothesis that these two variables could be related.
Methods: We investigated VMR and coherence of resting state EEG rhythms in nine normal elderly (Nold) and in 10 amnesic mild cognitive impairment (MCI) subjects. Resting state eyes-closed EEG data were recorded at baseline pre-CO_2 (ambient air, 2 min), during 7% CO_2/air mixture inhalation (hypercapnia, 90 s) and post-CO_2 (ambient air, 2 min) conditions. Simultaneous frontal bilateral near-infrared spectroscopy (NIRS) was performed to assess VMR by cortical oxy- and deoxy-haemoglobin concentration changes. EEG coherence across all electrodes was computed at delta (2–4 Hz), theta (4–8 Hz), alpha 1 (8–10.5 Hz), alpha 2 (10.5–13 Hz), beta 1 (13–20 Hz), beta 2 (20–30 Hz) and gamma (30–40 Hz) bands.
Results: In Nold subjects, 'total coherence' of EEG across all frequency bands and electrode pairs decreased during hypercapnia, with full recovery during post-CO_2. Total coherence resulted lower in pre-CO_2 and post-CO_2 and presented poor reactivity during CO_2 inhalation in MCI patients compared with Nold subjects. Hypercapnia increased oxy-haemoglobin and decreased deoxy-haemoglobin concentrations in both groups. Furthermore, the extent of changes in these variables during CO_2 challenge was correlated with the EEG coherence, as a reflection of neurovascular coupling.

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Conclusions: Hypercapnia induced normal frontal VMR that was detected by NIRS in both Nold and amnesic MCI groups, while it produced a reactivity of global functional coupling of resting state EEG rhythms only in the Nold group.
Significance: In amnesic MCI patients, global EEG functional coupling is basically low in amplitude and does not react to hypercapnia.

1. Introduction

Elderly subjects with amnesic mild cognitive impairment (MCI) are characterised by an objective impairment of memory, without (single-domain) or with (multi-domain) decline of other cognitive functions (Petersen et al., 2001; Petersen, 2004; Petersen and Negash, 2008). In these subjects, the impairment of cognitive and social skills does not yet fulfil the clinical picture of dementia (Petersen et al., 2001; Petersen, 2004; Petersen and Negash, 2008). However, the amnesic MCI condition is a relevant risk factor for Alzheimer's disease (AD) and could be considered its prodromal form (Bachman et al., 1993; Gao et al., 1998; Galluzzi et al., 2001; Petersen et al., 2001; Scheltens et al., 2002; Arnaiz and Almkvist, 2003; Fisk et al., 2003; Frisoni et al., 2004), especially when MCI patients display cerebrospinal fluid, structural and molecular neuroimaging biomarkers of this pathological condition (Albert et al., 1991).

Nowadays, no single biomarker allows a clear-cut early diagnosis of AD. Furthermore, some licensed biomarkers are too invasive (e.g., cerebrospinal fluid) and/or expensive (e.g., molecular biomarkers based on positron emission tomography (PET)) to be examined in serial recordings in elderly subjects at risk of AD. For these reasons, other candidate biomarkers are under evaluation to simplify early diagnosis and disease progression of AD. In this line, an electroencephalogram (EEG) probes general neurophysiological mechanisms of cortical neural synchronisation firing allowing temporal summation of post-synaptic potentials at the basis of scalp EEG rhythms and seems to be an ideal candidate for understanding the progressive loss of connectivity across the neuronal circuitry related to AD neurodegeneration. When compared to normal elderly (Nold) subjects, AD patients were characterised by high power density of delta (0–4 Hz) and theta (4–7 Hz) rhythms and low power density of posterior alpha (8–12 Hz) and/or beta (13–30 Hz) rhythms (Dierks et al., 1993, 2000; Huang et al., 2000; Ponomareva et al., 2003; Jeong, 2004; Babiloni et al., 2004). Furthermore, posterior alpha rhythms showed a decrement of the power density in MCI compared to Nold subjects (Zappoli et al., 1995; Elmstahl and Rosen, 1997; Huang et al., 2000; Jelic et al., 2000; Koenig et al., 2005a,b; Babiloni et al., 2006b; for a review see Rossini et al. (2007)).

The above results on the power density of resting state eyes-closed EEG rhythms have led to the widely supported hypothesis that neuronal networks of time-coordinated brain activity across different regional brain structures underpin cognitive function and denote AD neurodegeneration (see D'Amelio and Rossini (2012) for a review). Failure of integration within a network may lead to cognitive dysfunction in prodromal and clinically defined AD; thus, AD can be viewed, at least, in part, as a disconnection syndrome (Bokde et al., 2009). In this theoretical framework, the spectrum of EEG power density per se may not fully capture the impairment of functional neural connectivity. More specific markers of functional neural connectivity may be derived from the measurement of the functional coupling of resting state eyes-closed EEG rhythms between pairs of electrodes. The linear components of such coupling, functional coordination and mutual information exchange can be evaluated by the analysis of EEG spectral coherence (Gerloff et al., 1998; Gevins et al., 1998; Thatcher et al., 1986; Rappelsberger and Petsche, 1988). Spectral coherence is a normalised value that quantifies the temporal synchronisation of two EEG time series between pairs of electrodes in the frequency domain of the oscillations. It can be derived by fast Fourier transform (FFT) (Rappelsberger and Petsche, 1988; Pfurtscheller and Andrew, 1999), and its theoretical assumption is based on the observation that when the oscillatory activity of two cortical areas is functionally coordinated, their EEG rhythms show linear correlation and high spectral coherence. In general, decreased coherence reflects reduced linear functional coupling and information transfer (i.e., functional uncoupling or unbinding) among cortical areas or the reduced modulation of common areas by a third region. On the contrary, an increase in EEG coherence values can be interpreted as an enhancement of the linear functional connections and information transfer (i.e., functional coupling or binding), thus reflecting the interaction of different cortical structures for a given task. Increased coherence in alpha or higher frequencies reflects a greater 'facilitation' or connectivity, while in delta frequencies it suggests an increase of 'inhibition' or a functional disconnection. It has been demonstrated that EEG spectral coherence is enhanced following perceptive, cognitive and motor processes in the cortical regions involved in task-related processing (Sauseng et al., 2005; Babiloni et al., 2006c; Vecchio et al., 2007, 2010, 2012) as a function of the extension and type of the engaged neural networks (Pfurtscheller and Lopes da Silva, 1999; von Stein and Sarnthein, 2000). In addition, spectral coherence may reflect the integrity of cortical neural pathways (Locatelli et al., 1998).

Functional coupling of resting state eyes-closed cortical EEG rhythms differs across Nold, MCI and AD subjects. Previous EEG studies mainly reported a prominent decrease in the coherence of alpha rhythms in AD subjects compared with Nold subjects (Cook and Leuchter, 1996; Jelic et al., 1997, 2000; Almkvist et al., 2001; Locatelli et al., 1998; Wada et al., 1998a,b; Knott et al., 2000; Adler et al., 2003; Leuchter et al., 1987, 1992). This effect was also associated with ApoE-related genetic risk and was hypothesised to be mediated by a cholinergic deficit (Jelic et al., 1997). However, previous studies showed contradictory results, with either a decrease or an increase in low-band EEG coherence of delta and theta rhythms (Locatelli et al., 1998; Adler et al., 2003; Leuchter et al., 1987; Brunovsky et al., 2003). A recent study has reconciled these conflicting results by computing 'total coherence', obtained by averaging the EEG spectral coherence across all combinations of electrode pairs (Babiloni et al., 2010b). It was reported that delta total coherence gradually decreases from AD to MCI to Nold subjects (Babiloni et al., 2010b). Furthermore, alpha total coherence was lower in AD than in MCI and Nold subjects. Of note, these EEG coherence values were negatively correlated to (moderate to high) cholinergic lesions across MCI subjects (Babiloni et al., 2010b).

What are the physiological mechanisms subtending the abnormal generation of the resting state EEG rhythms in manifest AD and in amnesic MCI patients? One possible mechanism is an abnormal neurovascular coupling and, in particular, an impairment of cerebral haemodynamics in terms of vasomotor reactivity (VMR) to hypoxia and hypercapnia. Hypoxia, even *in vitro*, can increase the production of amyloid beta (Aβ) in different cell types (for a review see Peers et al., 2009). Hypoxia was also described to alter