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EEG network connectivity changes in mild cognitive impairment — Preliminary results

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ABSTRACT

Resting state EEGs were compared between patients with amnestic subtype of mild cognitive impairment (aMCI) and matched elderly controls at two times over a one year period. The study aimed at investigating the role of functional connectivity between and within different brain regions in relation to the progression of cognitive deficit in MCI. The EEG was recorded in two sessions during eyes closed and eyes open resting conditions. Functional brain connectivity was investigated based on the measurement of phase synchronization in different frequency bands. Delta and theta synchronization characteristics indicated decreased level of local and large-scale connectivity in the patients within the frontal, between the frontal and temporal, and frontal and parietal brain areas which was more pronounced 1 year later. As a consequence of opening the eyes connectivity in the alpha1 band within the parietal lobe decreased compared to the eyes closed condition but only in the control group. The lack of alpha1 band reactivity following eye opening could reliably differentiate patients from controls. Our preliminary results support the notion that the functional disconnection between distant brain areas is a characteristic feature of MCI, and may prove to be predictive in terms of the progression of this condition.

1. Introduction

The term "mild cognitive impairment" (MCI) conventionally applies to a condition in which the decline of cognitive abilities is more apparent than that seen in normal aging, but it still does not satisfy the criteria of dementia. Individuals with predominating memory problems are referred to as amnestic MCI (aMCI) (Petersen et al., 2001). While MCI may be regarded as a transitional state from which Alzheimer disease (AD) may develop ("MCI-converters"), this conversion does not occur in all MCI patients ("MCI-nonconverters", or "stable MCI" patients) (Decarli, 2003). Eckerström et al. (2008) suggested that the left hippocampal volume loss was predictive for the possible development of AD and non-AD dementia in individuals with MCI. The practical importance of a predictive biomarker by which conversion from aMCI to AD is emphasized by the fact that the rate of conversion to AD is much higher in MCI than in normal aging individuals (Petersen et al., 2001; Petersen, 2004). Therefore, the investigation of a neurophysiological marker which is sensitive to the progression of MCI or conversion into AD is of crucial importance. Despite the obvious importance of the functional disconnection of brain regions in MCI and AD, there are only few longitudinal studies in which the relationship between the progression of MCI and changes of functional connectivity characteristics was considered from this perspective (Giannakopoulos et al., 2009; Fernández et al., 2012). The present study aimed for the first time at investigating the role of functional connectivity of brain regions in relation to the progression of cognitive deficit in MCI.

Since neurodegenerative diseases such as AD or aMCI are considered to be disconnection syndromes, functional connectivity analysis would seem to be an optimal approach for the purpose of their investigation (Missonnier et al., 2007; Buscema et al., 2007). Functional connectivity is defined as the temporal interdependence of neuronal activity of anatomically separated brain regions (reflected by hemodynamic and/or electrophysiological responses), and its analysis enables the quantification of the interaction between and within different neural systems (Rodriguez et al., 1999). Recent findings indicate disturbed network organization in aMCI and AD: reduced level of functional communication between distant brain regions and altered patterns of functional brain organization were observed, already apparent during resting state, and not just under high cognitive load (Bokde et al., 2009). Resting state (Raichle et al., 2001) denotes a state in which an individual is awake and alert, but is not actively involved in an attention demanding or goal directed task ("psychological baseline"). Neuroimaging studies

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up till now described around eight networks of anatomically distinct brain regions that show a high level of functional connectivity during rest, including the so-called default mode network (DMN), consisting of the precuneus, the medial frontal, inferior parietal and temporal regions. The DMN is assumed to be exclusively crucial for the maintenance of cognitive functioning and is presumably altered in mental disorders (Broyd et al., 2009). In functional neuroimaging (fMRI — functional magnetic resonance imaging) studies peculiar features of the DMN were observed in MCI subjects distinguishing this condition from healthy aging (Qi et al., 2010; Liu et al., 2012). A consistent pattern of deactivation was observed in DMN during cognitive processes (Raichle et al., 2001).

Since the EEG signal represents directly the ongoing neural activity from which both global and local properties characterizing physiological and/or pathological function can be extracted this method is appropriate for the investigation of resting state networks related to various oscillatory frequency bands. EEG oscillations are generated locally in different brain regions and mediate coordinated interactions within and between different neuronal systems (Rodriguez et al., 1999). Functional connections are reflected by the temporal correlation – synchrony – between the oscillatory firing patterns of neuronal assemblies. Numerous EEG studies reported lower EEG synchrony (indicating decreased functional connectivity) in MCI and AD patients in resting condition compared to age matched control subjects (Koenig et al., 2005; Stam, 2010; Park et al., 2008). Babiloni et al. (2010) found characteristic changes in MCI and AD patients with respect to sources of the delta, theta and alpha1 and alpha2 bands when compared to healthy elderly. Delta oscillation (related to large-scale cortical integration with homeostatic processes and also to attentional processes) sensitively reflects brain structural damage (lesions) and a wide range of neurodegenerative disorders (Parkinson's disease, AD, and schizophrenia depression (for review see Knyazev, 2012)). Pathological changes of theta oscillation are mainly reported in association with memory deficits (important for a variety of cognitive functions such as declarative memory and attentional control processes). Low alpha rhythm as a characteristic oscillation of resting state (the “idling rhythm”, but which may also have a role in inhibiting neural task irrelevant regions) is shown to be abnormal in dementia and AD and MCI (Scheeringa et al., 2012).

The observed loss of synchrony was interpreted as functional disconnection between different cortical regions which cannot simply be due to the loss of cortical neurons (Jeong et al., 2001; Schliebs and Arendt, 2011). Interestingly, in the few studies when the EEG of MCI and AD patients was analyzed in conditions with cognitive load such as a working memory task a frequency band dependent increase of EEG synchrony was found in the patient groups (Jiang and Zheng, 2006; Pijnenburg et al., 2004). The results obtained by the computational neural mass model of de Haan et al. (2012) used for the investigation of the relation between the level of neural activity and hub vulnerability in Alzheimer's disease supported these latter findings. The model predicted a range of AD hallmarks (loss of spectral power and long-range synchronization, hub vulnerability, disrupted functional network topology) and reproduced the transient increase of functional connectivity in preclinical AD patients followed by subsequent breakdown of functional connections in definite AD. In healthy adults, corroborating the above mentioned neuroimaging findings on DMN sensory activation, attentional focusing was found to be associated with decreases in alpha power in the corresponding sensory area (Niedermeyer, 1999).

In the present preliminary study functional connectivity was investigated with respect to the progression of aMCI status as an attempt to identify reliable electrophysiological markers that are able to capture the decline of MCI patients. As a putative electrophysiological marker the spatial distribution of EEG phase synchronization (phase lag index, a method that eliminates the distorting bias of volume conduction), (Stam et al., 2007) was analyzed to characterize the longitudinal pathophysiological changes in aMCI. EEG data of aMCI patients and age matched control subjects were recorded in two sessions (one year in between) in eyes closed and eyes open resting conditions. First, aMCI patients and elderly controls were compared to assess the differences of functional connectivity between and within different brain regions. The difference of these connectivity characteristics between the two recording sessions was used to identify pathophysiological changes of aMCI over time. Discrimination analysis was applied in order to determine which of the electrophysiological connectivity characteristics the best predictors of aMCI status are. Furthermore, the effect of sensory stimulation (due to opening the eyes) on resting state functional connectivity was investigated by the comparison of eyes closed and eyes open resting conditions. It was hypothesized that connectivity measures will be sensitive indices of 1) deterioration of connectivity and 2) decline of reactivity in aMCI which, compared to healthy controls, was supposed to increase with elapsing time.

2. Methods

2.1. Participants

Elderly adults (N = 14; women 8; age: 64.8, ±2.5) and patients (N = 9; women 6; age: 67.5, ±3.2) with the diagnosis of amnestic subtype of MCI (aMCI) took part in the study. The participants signed a written informed consent form and received financial compensation for taking part in the study that was approved by the relevant institutional ethical committee. None of the control subjects had any neurological or mental disorders. Dementia, sedative medication and antipsychotic-based medical treatment were exclusion criteria in both groups. The aMCI patients were recruited from the Department of Psychiatry and Psychotherapy in Budapest. The diagnosis of aMCI was based on neurological and psychiatric examination and neuroimaging scans, including subjectively reported and neuropsychologically assessed memory impairment (Petersen's criteria standard clinical protocol, Petersen, 2004). The test results in the patients were the following: Mini Mental State Examination (MMSE) mean 1 session: 27.4; SD: ±1.8, 2. session: 26.9; SD: ±2.2; Addebrooke's Cognitive Test mean: 83.0; SD: ±8.6; Global Deterioration Scale mean: 3.0; SD: ±0. The MCI diagnosis of the patients was confirmed one year later by the same clinical department. Follow-up electrophysiological and behavioral data collection was performed in the patients and matched (age, sex) elderly controls in the Institute of Cognitive Neuroscience and Psychology. Prior to the EEG recordings in all participants the IQ (Wechsler Adult Intelligence Scale [WAIS]) was tested and the Mini Mental State Examination was performed in the aMCI patients. The IQ and MMSE results were used to assess possible cognitive decline over time in the aMCI patients by taking it two times over a one-year period.

The participants were seated in an acoustically attenuated and electrically shielded room. The EEG was recorded with 33 Ag/AgCl electrodes (positioned according to the international 10–20 system) using Neuroscan software and amplifiers (Scan 4.3., Nuamps, bandpass: DC-70 Hz, FIR, sampling rate: 1000 Hz). Vertical and horizontal eye movements were recorded. The tip of the nose was used as reference and an electrode placed between Cz and Fz as ground. The EEG data of elderly adults and patients with aMCI were recorded two times over a one-year period. The time between the two recording sessions in the elderly group was 13.2 (SD: 2.1) months, and in the case of the aMCI group 12.6 (SD: 4.1) months. 4 min of spontaneous EEG was recorded both in eyes closed (EC) and also in eyes open (EO) conditions.

2.2. Data analysis

The EEG epochs recorded at the two sessions (session 1, session 2) in EC and EO conditions were analyzed separately. A single epoch length was 2048 data points (2048 ms). The EEG epochs were filtered in six frequency bands (delta: 0.5–4 Hz, theta: 4–8 Hz, alpha1: 8–10 Hz, alpha2: 10–13 Hz, beta: 13–30 Hz, gamma: 30–45 Hz). Visual screening, and ICA (using EEGLab 10.2.5.8b ADJUST plugin) were used to exclude blinks