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Adaptive reorganization of cortical networks in Alzheimer's disease

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HIGHLIGHTS

- Patients with Alzheimer's disease have a profound disruption of alpha-band coherence in the same regions that are also most affected by atrophy and amyloid deposition.
- Patients with Alzheimer's disease also present adaptive network reorganization associated with relatively preserved cognitive function.
- Two different mechanisms of network plasticity: extension to contralateral brain regions and slowing of coherent oscillations.

ABSTRACT

Objective: The impact of neuronal cell loss associated with Alzheimer's disease (AD) on the network organization of the brain is poorly understood. Here we investigated whether modifications in resting-state functional connectivity (FC) are associated with cognitive function of AD patients.
Methods: High-density electroencephalograms (EEGs) were obtained from patients with early stages of AD and elderly healthy controls. Cortical oscillations were reconstructed with an adaptive spatial filter. Maps of imaginary coherence (IC) between brain areas were compared between groups and correlated with cognitive performance.
Results: Parietal and medial temporal lobes of AD patients showed a disruption of alpha band FC to the rest of the brain. However, an adaptive extension of the language network to the right hemisphere could be observed in AD patients and was correlated with better verbal fluency. A shift of FC from alpha frequencies to theta frequencies could be observed in a memory network and was associated with better verbal memory performance.
Conclusions: Not only dysfunctional but also adaptive network reorganization occurs in early AD.
Significance: The network mechanisms for preserved cognitive functioning may inform novel treatment strategies for AD in the future.

1. Introduction

Alzheimer's disease is a progressive neurodegenerative disorder associated with well-known disturbances on molecular, cellular, structural and behavioral levels. Extensive neuronal cell loss and aberrant deposition of neurofibrillary tangles and senile plaques can be observed most prominently in the hippocampus, the entorhinal cortex, and temporo-parietal regions of the neocortex (Minati et al., 2009). The same regions also show a remarkable atrophy and hypometabolism (Morbelli et al., 2010; Raji et al., 2009; Ridha et al., 2008; Sluimer et al., 2009). In accordance with this topography of affected brain structures, cognitive decline starts with deficits in learning, memory and language production and is followed by severe damage of almost all cognitive and motor functions in the late period of illness (Forstl and Kurz, 1999).

The brain is organized into networks of interconnected brain regions, which show temporal correlations in their spontaneous fluctuations even in absence of any specific cognitive activity (Brookes et al., 2011a,b; Damoiseaux et al., 2006; Fox et al., 2005). These networks normally mediate the cognitive functions which are deficient in AD patients. In order to understand the neural basis of the disease, it is therefore important to take a global network approach and study changes in the network organization of AD patients. This can be accomplished by measuring the synchrony of oscillations (i.e., the functional connectivity [FC]) at rest in different brain

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regions (Varela et al., 2001), which allows reconstructing the interactions of the entire brain in a single exam without active participation of the patients (Dubovik et al., 2012; Guggisberg et al., 2008; Martino et al., 2011).

Functional magnetic resonance imaging (fMRI) studies have consistently reported network abnormalities in AD (Buckner et al., 2009; Greicius et al., 2004; Sorg et al., 2007; Wang et al., 2006). In particular, AD patients were found to have disrupted connectivity between the hippocampus and several frontal and parietal areas, and in the so-called default-mode network (Greicius et al., 2004; Raichle et al., 2001; Zhang et al., 2010), which is thought to be involved in high-level and self-referential cognition (Raichle et al., 2001). The grade of disconnection seems to be associated with the progression of the disease, meaning that amnesic mild cognitive impairment patients have more preserved connections than patients who converted to AD (Zhang et al., 2010). Some fMRI studies reported increases of connectivity in AD patients, concerning primarily the connections of PCC with parietal, frontal and prefrontal lobes, suggesting possible network restructuration in early stages of the disease (Bai et al., 2009; Zhang et al., 2009, 2010).

EEG and MEG studies pointed out prominent changes in electrical brain activity associated with AD. One of the most replicated findings is the shift of electrical oscillations towards slow frequency bands with a decrease of alpha and beta power and an increase of slow theta and delta waves in patients compared to elderly controls (Babiloni et al., 2004; Berendse et al., 2000; Czigler et al., 2008; de Haan et al., 2008; Fernandez et al., 2002; van der Hiele et al., 2007). The degree of the EEG slowing correlated with the severity of cognitive impairment (Fernandez et al., 2002; van der Hiele et al., 2007). In line with fMRI studies, EEG and MEG studies also reported both decreases and increases of functional couplings among brain networks in AD patients. A reduction of functional connectivity between both nearby and distant EEG channels has been found in alpha, beta, and gamma bands (Babiloni et al., 2006; Berendse et al., 2000; Besthorn et al., 1994; Czigler et al., 2008; Jiang, 2005; Locatelli et al., 1998; Pijnenburg et al., 2004; Stam et al., 2002, 2003, 2006; Wada et al., 1998), while coherence of slow frequencies was shown to be increased over temporo-parietal, temporo-central and frontal electrodes in some but not all studies (Alonso et al., 2011; Locatelli et al., 1998; Sankari et al., 2011; Stam et al., 2006).

In sum, both fMRI and EEG/MEG studies demonstrate massive changes in resting state brain organization in AD patients, in particular slowing, disruption of network interactions, but also possible network restructuration. However, the significance of these changes for cognitive abilities remains unclear. In particular, we do not know whether they represent disease-induced damages or, on the contrary, compensatory and adaptive mechanisms allowing the patients to maintain certain functions despite neuronal loss.

In the present study, we therefore aimed to investigate the cortical network correlates of memory and language performance in patients with mild AD. To this end, we reconstructed cortical networks from surface EEG recordings with inverse solutions and measures of oscillation synchrony. We have recently shown that EEG analyses of resting-state oscillation coherence capture behaviorally relevant interactions within neural networks (Dubovik et al., 2012). Furthermore, EEG reconstructions allow us to assess not only spatial but also spectral changes in network interactions. In order to probe the significance of observed network interactions for cognitive abilities of the patients, we performed linear correlation analyses between the obtained network maps and standardized scores of memory and language function.

2. Methods

2.1. Patients and healthy control subjects

All procedures were approved by the University Hospital of Geneva Ethics Committee. Fifteen right-handed patients (12 women) diagnosed with probable Alzheimer's disease (AD) according to NINCDS-ADRDA criteria (McKhann et al., 1984) participated in this study (see Table 1). Age ranged from 79 to 94 years (mean 83.9, standard deviation (SD) 4.5); the mini-mental state examination (MMSE) (Folstein et al., 1975) from 17 to 26 (mean 20.6, SD 2.9); the clinical dementia rating (Morris, 1993) was 1 in all patients. Diagnosis was based on medical, neurological, neuropsychological, and psychiatric examination and on exclusion of other causes of dementia with brain imaging and laboratory testing. Fifteen right-handed elderly participants (11 women) without neurological or psychiatric disease were additionally recruited as control group for this study. They were tested for preserved cognitive function with neuropsychological exams. Age ranged from 70 to 88 years (mean 76.7, SD 5.6); MMSE from 25 to 30 (mean 28.4, SD 1.5). The subject with a MMSE of 25 had no memory or language deficits. Ten out of fifteen patients received drug treatment with cholinesterase inhibitors at the time of the experiment. Medication intake was therefore included as confounding covariate in the statistical analyses (see below). Similarly, age was included as covariate because, although patients and control groups had comparable age ranges, they were not age-matched and controls were slightly but significantly younger (Table 1).

2.2. Data acquisition

EEG was recorded with a 128-channel Biosemi ActiveTwo EEG-system (Biosemi B.V., Amsterdam, Netherlands) at a sampling rate of 512 Hz in an awake, resting condition during which subjects kept their eyes closed. Artifacts like eye movements, muscular contractions and electrode artifacts were excluded by visual inspection of the data. "Bad" channels containing artifacts over prolonged periods were completely excluded from further analyses. Five minutes of artifact-free data were recalculated against the average of all remaining channels.

2.3. Clinical assessments

Patients and healthy participants underwent neuropsychological tests evaluating memory and language capacities. Episodic verbal memory was measured with the French version of the Grober and Buschke test (Grober et al., 1988), based on the recollection score defined as the free recall of a list of 16 words memorized approximately 30 min earlier. Language performance was estimated with the semantic verbal fluency test (Wechsler, 1997) which measures the production of words of the same semantic family (e.g. animals or clothes) within 1 min.

2.4. Functional connectivity analysis

FC analysis was carried out in Matlab (The MathWorks Inc., Natick, USA) with NUTMEG (Dalal et al., 2011) (http://www.nitrc.org/plugins/mwiki/index.php/nutmeg:MainPage) and its functional connectivity mapping (FCM) toolbox (Guggisberg et al., 2011). The detailed analysis steps and their validation have been described elsewhere (Guggisberg et al., 2008, 2011). In short, the lead-potential was computed with 10 mm grid spacing using a spherical head model with anatomical constraints (SMAC) (Spinelli et al., 2000) based on the segmented grey matter of the Montreal Neurological Institute (MNI) template brain consisting of the