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Perception-related EEG is more sensitive to Alzheimer's disease effects than resting EEG

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ABSTRACT

To characterize the effects of Alzheimer's disease (AD) on cortical functional connectivity in perception, we analyzed interhemispheric lagged synchronization (ILS) in the source space of high-density EEG recorded in aged controls and patients with amnestic mild cognitive impairment (aMCI) or AD while they viewed collinear and noncollinear bilateral moving gratings. Beta-band ILS was lower in aMCI and AD compared with controls in a large region centered on BA39. As previously reported, in young adults, collinear iso-oriented gratings versus noncollinear gratings synchronizes EEG reflecting perceptual grouping. Only aged controls showed the expected beta-band ILS increase originating in the dorsal visual stream (BA18). The aMCI group only showed a theta-band increase in an adjacent region (BA19). In AD patients, there was no ILS increase. Regression analysis revealed that the posterior callosal area and EEG slowing predict reduction of beta but not emergence of theta ILS response. Considering that we found no between-group differences in resting ILS, perception-related EEG appears to be more sensitive to AD effects, including ILS signs of neurodegeneration and compensation.

1. Introduction

Perceptual dysfunction is an essential aspect of cognitive decline in Alzheimer's disease (AD) and its preclinical stage, amnestic mild cognitive impairment (aMCI). AD/aMCI patients often manifest reduced visuospatial abilities, including impaired recognition of common objects and famous faces, compromised figure-ground discrimination, worsened evaluation of locations and complex figures, difficulties in processing of optic flow, and deteriorated drawing skills (Cronin-Golomb et al., 1991; Mendez et al., 1990; Quental et al., 2013; Tzekov and Mullan, 2014). The loss of visuospatial functions results in profound everyday problems due to spatial disorientation: the inability to read a clock face, confusion while driving, an increased rate of falls, and so forth.

Neurofibrillary tangles and neuritic plaques together with reduced neuronal density and dendritic pathology are widespread in the extrastriate visual areas of AD patients and suggest the structural basis of visuospatial dysfunction in AD (Arnold et al., 1991; Johnson et al., 2012; Lewis et al., 1987; Mavroudis et al., 2011). Moreover, ex vivo, pronounced degeneration of the visual association cortex (BA18, BA19) can be found in more than half of the brains of cognitively normal aged donors and in all the brains of donors with MCI and AD (McKee et al., 2006). Especially, serious damage of the visual association cortex has been described in early-onset AD (Frisoni et al., 2007).

The in vivo imaging studies of AD consistently show the reduction of metabolism and activation in regions that are typically activated by visuospatial processing in healthy subjects; this reduction might be accompanied by the recruitment of additional or alternative regions within the temporal, parietal, and visual association cortices (Fujimori et al., 2000; Mandal et al., 2012; Thiyagesh et al., 2009; Vannini et al., 2008). Considering that higher-order visual functions are implemented by distributed neural networks, the decrease of activation suggests certain disintegration of underlying neurobiological processes. Indeed, an early positron emission tomography study showed that in contrast to healthy aged people, mild AD patients manifest decreased functional connectivity (FC) among ventral visual cortical areas in a face-matching task (Horwitz et al., 1995). Yet, most of studies based on functional magnetic resonance imaging have relied on resting-state FC rather than measuring FC during visuospatial processing.

Furthermore, EEG-based research on FC as a potential biomarker of aMCI/AD is also biased in favor of task-free EEG studies (Giannakopoulos et al., 2009; Jeong, 2004; Pogarell et al., 2005; van Straaten et al., 2014) because activation procedures, while being potentially more sensitive to the AD-related deterioration of cerebral circuitry, are associated with certain health risks for aged patients (e.g., hyperventilation) or are of limited use because of

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mental decline (e.g., cognitive tasks). Passive perceptual tasks can be a solution: they require minimum cognitive efforts and, therefore, can be used with subjects of various ages and health conditions, including AD, to improve the efficacy of EEG markers obtained in the resting state.

In the context of AD, patterned visual stimuli, e.g., gratings, are of special interest because they are processed at the cortical level and integrated via cortico-cortical association and commissural fibers (Kiper et al., 1999; Knyazeva et al., 1999). The latter are especially vulnerable to MCI/AD as manifested by the reduction and microstructural deterioration of the corpus callosum (CC). The consistency of such changes in the posterior CC links them to the visuospatial deficits in AD (Carmeli et al., 2013; Di Paola et al., 2010; Hensel et al., 2002; Rose et al., 2000; Teipel et al., 2003; Wang et al., 2006; Yamauchi et al., 2000). In contrast to the reliable changes of the CC, varying alterations of EEG-based interhemispheric FC in aMCI/AD were reported: some authors showed its reduction, especially in the beta and/or alpha frequency bands (Babiloni et al., 2004; Knott et al., 2000; Locatelli et al., 1998; Wada et al., 1998), whereas others failed to demonstrate such changes (Caminiti et al., 2009; Hsiao et al., 2013; Prichep et al., 2006; Sankari et al., 2011; Stam et al., 2006)

Based on the foregoing considerations, we have chosen a passive visual task, viewing bilateral gratings, for EEG-based testing of interhemispheric FC as a potential dynamic indicator responsive to the effects of prodromal and mild AD on the posterior cerebral cortices. We compare the perception-related FC to a structural marker (the posterior CC area) and a conventional EEG marker (resting-state FC) and estimate this indicator as a supplementary one to the hippocampus volume, a biomarker of brain injury.

2. Methods

2.1. Patients and control subjects

This article presents the data from a sample of 75 subjects, including 19 AD patients and 25 aMCI subjects recruited from the Memory Clinic of the Neurology service of the CHUV in Lausanne and 31 age- and education-matched local residents as control subjects (Table 1). A subsample of 57 subjects including 14 AD patients, 15 aMCI subjects, and 28 controls performed the visual perception task central to this report, during an EEG recording session that also included resting-state EEG (Fig. 1). Fifty-three subjects were scanned on the same MRI scanner, which allowed us to estimate the midsagittal posterior CC area in the control, AD, and aMCI groups (Supplementary Materials, Section II). The intersection of these 2 samples (33 subjects) was the target group for regression analysis. Because the results of resting-state EEG analysis from these subjects were published earlier (Knyazeva, et al., 2010, 2013), as were the MRI-based results from these subjects (Carmeli et al., 2013; Fornari et al., 2012; Rytsar et al., 2011), here we limit ourselves to a short description of the main aspects of the clinical and neuropsychological assessment and diagnostics of the subjects.

Table 1
Demographic data of controls and patients

Feature	Controls	aMCI	AD
No. of subjects	31	25	19
Gender M/W	13/18	14/11	14/5
Age (y)	65.4 ± 11	68 ± 9.8	70.9 ± 10.5
Education 1/2/3	4/15/12	5/12/8	4/9/6
MMSE	29.0 ± 0.8	27.2 ± 2.3	20.4 ± 5.2

Columns present group characteristics (mean with standard deviation). We sorted participants into 3 levels of education: (1) primary and/or secondary school without or with short (<3 years) professional training; (2) primary and/or secondary school with professional training (>3 years); and (3) high school (primary and secondary) and tertiary education.
Key: aMCI, amnestic mild cognitive impairment; M, men; MMSE, Mini-Mental State Examination; W, women.

The AD clinical diagnosis conformed to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria (McKhann et al., 2011). Only patients with mild dementia participated in this study. The clinical aMCI diagnosis was based on the recommendations of the National Institute on Aging and Alzheimer's Association workgroups (Albert et al., 2011). Specifically, individuals with mild cognitive decline (confirmed by a comprehensive neuropsychological examination) who did not satisfy the NINCDS–ADRDA criteria for dementia were selected for MCI diagnosis (McKhann et al., 2011). To this end, all participants performed an extended battery of neuropsychological tests that cover 5 cognitive domains (memory, executive functions, language, praxis, and gnosis) and are validated for a francophone population. An individual was diagnosed with aMCI if (s)he (1) had at least 1 episodic memory task score of $\geq$1.5 standard deviation below normative values; (2) lost $\leq$2 points on daily living activities scores; and (3) had the Mini-Mental State Examination (MMSE) score from 24 to 26 for a low level and from 24 to 28 for a high level of education.

Potential control subjects underwent a brief clinical interview, which included the MMSE and a brain MRI. Only individuals without cognitive complaints, psychoactive drug use, or other diseases that interfere with cognitive functions, and with normal activities of daily living and an MMSE score $\geq$26 for low and $\geq$28 for high level of education, were enrolled in the study.

In addition, clinical laboratory investigations and diagnostic neuroimaging (CT or MRI and Metrizamide SPECT) were performed to exclude subjects with cognitive deficit causes other than AD. Alcohol and/or drug abuse and regular use of neuroleptics, antidepressants with anticholinergic action, benzodiazepines, stimulants, or β-blockers were also exclusion criteria.

As we reported previously (Carmeli et al., 2013, 2014), the aMCI and AD subjects of this sample were characterized by a decreased volume of the hippocampus, which is a structural biomarker of the AD-related pathological process, thus suggesting that their clinical phenotype is associated with the AD pathological process. Specifically, we estimated the hippocampus volume in 53 subjects (Fig. 1) on the basis of T1-weighted MRI scans from the same scanner. Using statistical parametric mapping, the volume of both hippocampi was estimated by applying their mask in Montreal Neurological Institute's (MNI) space based on AAL atlas and calculating the sum of all voxels within the mask. The hippocampus volume was then normalized by total intracranial volume. In the aMCI group, the hippocampus volume was 15% lower ($p = 0.0007$) than that in controls and in AD group 16% lower ($p = 0.0003$), Wilcoxon ranksum test; (Fig. 2).

Subjects can be classified as having "MCI due to AD—Intermediate likelihood" based on a single positive biomarker of neuronal injury (Albert et al., 2011). Here we classified individuals based on the hippocampus volume by means of a linear discriminant analysis using a leave-one-out cross-validation procedure. We classified separately the aMCI versus controls and the AD versus controls. Among 25 subjects who met the core clinical criteria for aMCI, 18 subjects (72%) were correctly classified; and among 9 subjects with clinical AD diagnosis, 8 subjects (89%) were correctly classified.

All investigative methods and procedures applied in this study conform to the Declaration of Helsinki (1964) of the World Medical Association concerning human experimentation and were approved by the local Ethics Committee of Lausanne University. All controls and patients were able to understand the essential information about the research project and to give valid consent.