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Theta oscillations are affected by amnestic mild cognitive impairment and cognitive load

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ABSTRACT

Amnestic mild cognitive impairment (aMCI) is classified primarily via substantial episodic memory deficits in the absence of a dementia diagnosis. To investigate the potential neurophysiological correlates of such deficits we compared QEEG power between 12 participants with aMCI and 12 healthy matched controls. EEG was acquired during performance of a modified Sternberg word recognition task with low and high memory load conditions. While recognition accuracy of aMCI participants was lower than that of controls, this difference was not significant. Nevertheless the aMCI group demonstrated significantly lower theta power at a number of electrode sites and significant correlations were observed between power at these sites and neuropsychological assessment scores. Furthermore in the aMCI sample only, theta power was significantly lower under high versus low memory load. Given current interpretations of the neural generator(s), as well as the role(s), of theta oscillations in cognitive processes, the present data indicate that aMCI may be associated with disruptions in the operation of neurocognitive networks (e.g., MTL-neocortical), particularly under high cognitive load.

1. Introduction

Mild cognitive impairment (MCI) is typically considered a transitional condition between the cognitive changes observed in healthy ageing and the earliest clinical manifestations of dementia (Petersen et al., 1999, 2001a; Petersen and O'Brien, 2006). The amnestic subtype of MCI (aMCI; see Petersen and O'Brien, 2006) is diagnosed when performance is at least 1.5 standard deviations below the mean of an age-matched group on both recall and recognition memory tasks (Backman et al., 2001; Petersen, 2004; Winblad et al., 2004). Annual conversion rates to Alzheimer's Disease (AD) of at least 10–15% have been reported for aMCI and thus, aMCI is quite widely considered to constitute a preclinical stage of AD in many affected individuals (e.g., Ames et al., 2006; Bennett et al., 2002; Ganguli et al., 2004; Lopez et al., 2003; Petersen et al., 1999; Petersen et al., 2001a).

While there is some controversy surrounding the prognostic value of aMCI, the neuroanatomical correlates of this condition (and the broader MCI classification) have been extensively explored. (a)MCI has been associated with atrophy in the medial temporal lobes (Devanand et al., 2007; Jack et al., 2004; Karas et al., 2004; Pennanen et al., 2005), ventricular enlargement, declines in cortical grey matter (e.g., Du et al., 2001; Kantarci et al., 2007) and diminished frontal (Rose et al., 2006) and temporal white matter tract integrity (Fellgiebel et al., 2004; Kantarci et al., 2005; Müller et al., 2005). Furthermore, other studies indicate that various neuropathological features of (a)MCI are intermediate between the changes of normal ageing and early AD (e.g., Jicha et al., 2006; Markesbery et al., 2006; Petersen et al., 2006).

In contrast to the wealth of knowledge on the structural changes associated with aMCI, little is known about other neurophysiological correlates. Electroencephalographic (EEG) studies have occasionally observed differences during rest (e.g. Babiloni et al., 2006, 2007; Huang et al., 2000), however the memory deficits of aMCI may mean that EEG recorded under cognitive task conditions is better suited to identify electrophysiological markers. Theta oscillations are of particular interest in cognitive paradigms because they are known to be related to memory, attention and cognitive control processes (e.g., see Klimesch, 1999; Kahana et al., 2001). Numerous structures in frontal (e.g., Gevins et al., 1997; Onton et al., 2005; Wang et al., 2005) and medial temporal regions (e.g., Kahana et al., 1999; Raghavachari et al., 2001) generate memory related theta oscillations and memory processes are facilitated by theta's role in integrating these structures into coherent neurocognitive networks (see e.g. Klimesch, 1999; von Stein and Sarnthein, 2000 for reviews). Thus, the memory deficits and adverse physiological changes associated with aMCI are likely to be reflected in altered theta activity. In line with this proposal, task-related theta power differences have been observed between control and aMCI samples (Grunwald et al., 2002) as well as between stable and progressively degenerative aMCI cases (Missonier et al., 2006).

Theta oscillations are also known to be sensitive to the manipulation of cognitive load (Gevins et al., 1997; Jensen and Tesche, 2002;

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Krause et al., 2000; Onton et al., 2005; Wilson et al., 1999) and differential theta responses to increased load between healthy young and older adults are thought to reflect the reduced processing efficiency of normal ageing (e.g. Hogan et al., 2003; McEvoy et al., 2001). The theta response to increased load is therefore of interest in aMCI, where further reductions in processing efficiency are observed. However despite these considerations, to date, no studies have varied load and compared the theta power of control and aMCI samples.

The Sternberg (1966) recognition task has been shown to produce heightened levels of activity in the theta band (relative to resting) at frontal and temporal sites (e.g., Jensen and Tesche, 2002). It also allows for separation of the encoding, retention and recognition phases of memory. Hence, by utilising electrodes placed over these areas it should be possible to detect memory (and memory load) related EEG changes that may occur with aMCI. Thus, in the current study EEG theta power during the retention and recognition intervals of a modified Sternberg (1966) task is compared for controls and participants with aMCI. In addition, the effects of (high and low) memory load are assessed by manipulation of study list length.

2. Materials and methods

2.1. Participants

The local ethics committee approved the study and all participants gave informed consent. Unimpaired participants were recruited via newspaper advertisements and from the spouses and friends of participants with amnestic mild cognitive impairment (aMCI) and Alzheimer's Disease (AD). The majority of impaired participants were community dwelling individuals who were recruited via the same newspaper advertisements, the remainder were recruited from the memory clinic of a major hospital in Brisbane, Australia. A consensus meeting of a neurologist and two certified neuropsychologists was used to categorise participants on the basis of medical history, clinical and radiological examination, and neuropsychological assessment.

General exclusion criteria included: a) evidence of significant prior head trauma (LOC>30 min), b) infectious or endocrine causes of cognitive dysfunction, c) significant cerebrovascular disease evident on MRI brain scans (based in part on Hachinski scores and Wahlund age-related white matter changes) (Wahlund et al., 2001), d) a primary psychiatric diagnosis, such as major depressive disorder or schizophrenia (or a history of major psychiatric illness), e) a geriatric depression scale (GDS, a self-report mood assessment) (Yesavage et al., 1983) score>16, f) alcohol consumption>30 g/day for men and >20 g/day for women, g) a history of habituation to drugs such as benzodiazepines or narcotics or, h) a full scale IQ (general intellectual functioning) that fell outside the normal range.

Each of the participants was administered a comprehensive battery of neuropsychological tests devised to detect cognitive impairment in the elderly, including a 7-subtest short form of the Wechsler Adult Intelligence Scale — 3rd edition (WAIS-III; Axelrod et al., 2001; Wechsler, 1997a), the Logical Memory, Paired Associates and Face Recognition subtests of the Wechsler Memory Scale — 3rd edition (WMS-III; Wechsler, 1997b), the Mini Mental State Exam (MMSE; Folstein et al., 1975), the Rey Auditory Verbal Learning Test (RAVLT; Spreen and Strauss, 1998), the Rey Osterrieth Complex Figure (Spreen and Strauss, 1998), the Boston Naming Test (BNT; Kaplan et al., 1983), letter and category verbal fluency tests (the Controlled Oral Word Association Test; Spreen and Strauss, 1998), Trail Making Test forms A and B (TMT; Reitan and Wolfson, 1993), the Number Location, Dot Counting and Cube Analysis subtests of the Visual Object and Space Perception Battery (VOSP; Warrington and James, 1991), the Stroop Neuropsychological Screening test (Spreen and Strauss, 1998) and the cognitive section of the Alzheimer's Disease Assessment Scale (ADAS-Cog; Rosen et al., 1984).

aMCI was diagnosed according to the stringent diagnostic criteria outlined by the Mayo Clinic Alzheimer's Disease Research Centre (Petersen et al., 1999, 2001b; Petersen, 2004) and required the following: (a) subjective memory impairment according to the patient or an informant, (b) objective memory impairment indicated by a delayed recall score on the Wechsler Memory Scale — 3rd edition Logical Memory subtest and a Rey Auditory Verbal Learning Test (RAVLT) score of at least 1.5 SD below age and education adjusted norms, (c) no significant impairment (i.e., performance below 1.5 SD from the mean obtained from normative data) on tests measuring other cognitive domains and (d) no significant impairment in the activities of daily living. Participants were excluded if they satisfied a diagnosis for dementia as defined by either, the Diagnostic and Statistical Manual of Mental Disorders — 4th edition (DSM-IV, 1994) or, the National Institute of Neurological and Communicative Disorders and Strokes in conjunction with the Alzheimer's Disease and Related Disorders Association workgroup (NINCDS-ADRDA; McKhann et al., 1984).

The resulting control sample included 12 healthy cognitively intact individuals (7 males, 5 females) with a mean age of 67.80 years (SD=8.30, Range=56–80) and an average of 11.50 years of education (SD=3.10). MMSE scores ranged from 27 to 30, with a mean score of 28.25 (SD=.87). The sample of aMCI participants included 12 individuals (8 males, 4 females) with a mean age of 70.17 years (SD=8.90, Range=58–84) and an average of 10.30 years of education (SD=3.30). MMSE scores ranged from 21 to 29, with a mean score of 26.58 (SD=2.35). While the control and aMCI groups differed significantly on MMSE scores ($t(22)=2.30$, $p=.04$) they did not differ significantly in age ($t(22)=-.66$, $p=.52$), gender ratio ($p=1.00$, Fisher's exact test) or education ($t(22)=.96$, $p=.35$).

2.2. Procedure and materials

All participants were tested between late morning and early afternoon[1]. EEG data was recorded while participants performed a modified version of the Sternberg (1966) recognition task. The procedural details of this task are illustrated in Fig. 1. Each of the words that appeared throughout the task was five letters in length and had a normative frequency of 10 to 100 occurrences per million (source: *The Sydney Morning Herald* word database). Study list lengths were either four (short list — low memory load) or eight (long list — high load) unique words. Each study list was followed by a single test word. Fifty percent of the test cue words appeared once in a random position (other than as the last word) in the immediately preceding study list (old). The other fifty percent of test cue words did not occur at any other time throughout the experiment (new). In total there were 20 trials with each of the possible study–test combinations (short–old, short–new, long–old, long–new). Within this constraint order of presentation of trial type varied randomly. Participants were informed of the load conditions and of the requirement to determine whether each test cue word was in the immediately preceding study list (old) or not (new). They were further instructed to rest one index finger on each of the two horizontal arrow keys of a standard keyboard throughout the task and to respond by pressing the arrow that corresponded to the displayed laterality (varied at random from trial to trial) of their decision type ("yes": seen; "no": unseen). In order to minimize motor-related artifacts in the EEG data during the period of interest, participants were instructed to withhold their yes/no recognition responses until the appearance of the words "yes" and "no" on the screen. To provide participants with the opportunity for a break, the experiment was broken into four blocks of twenty trials. Each block commenced with depression of the space bar. Upon completion of the task, three minutes of EEG data were recorded while participants rested with their eyes open.

[1] This procedure was adopted to minimize the influence of circadian fluctuations in arousal and theta band activity (e.g. Aeschbach et al., 1999; Higuchi et al., 2001).