Memory activation enhances EEG abnormality in mild cognitive impairment

K. van der Hiele, MSc3,6
A.A. Vein, MD, PhD2
C.G.S. Kramer, BEng2
R.H.A.M. Reijntjes, BEng2
M.A. van Buchem, MD, PhD4
R.G.J. Westendorp, MD, PhD5
E.L.E.M. Bollen, MD, PhD1
J.G. van Dijk, MD, PhD2
H.A.M. Middelkoop, PhD3,6

From the 1Department of Neurology (sections of 2Clinical Neurophysiology, 3Neuropsychology), 4Department of Radiology, 5Department of General Internal Medicine (Section of Gerontology and Geriatrics), Leiden University Medical Center and the 6Neuropsychology Unit of the Department of Psychology; Leiden University, Leiden, The Netherlands.

Abstract

This exploratory study investigated EEG power changes during memory activation in patients with amnestic mild cognitive impairment (MCI). Twelve MCI patients and 16 age-matched controls underwent EEG registration during two conventional EEG conditions ('eyes closed' and 'eyes open') and three memory conditions ('word memory', 'picture memory' and 'animal fluency'). For all conditions, EEG power in the theta (4-8 Hz), lower alpha (8-10.5 Hz) and upper alpha (10.5-13 Hz) bands were expressed as percentile changes compared to 'eyes closed'. MCI patients showed significantly less decrease in the lower alpha band than controls (p=0.04) during picture memory activation. The word memory task showed a trend towards a similar effect (p=0.09). This study suggests that memory activation reveals EEG differences between MCI patients and controls while conventional EEG conditions do not.
Introduction

Progressive memory loss is considered one of the earliest signs of Alzheimer's disease (AD) [14]. The term amnestic mild cognitive impairment (MCI) has been introduced to define a group of patients with a high probability of conversion to AD [12, 17, 18]. MCI is characterized by isolated memory impairment that does not interfere with activities of daily living. MCI is heterogeneous in nature; some patients develop AD, others another type of dementia and yet others reverse to their premorbid level of functioning. Identifying MCI patients likely to develop dementia is important as in the future this may make early therapeutic intervention possible, thereby reducing health care costs and improving quality of life [10, 12].

Electroencephalography (EEG) has potential as a tool in the diagnostic and treatment work-up of AD, as it is widely available, non-invasive and cost-effective. EEG with eyes closed, as conventionally used in daily clinical routine, revealed no differences between cognitively unimpaired controls and MCI patients [5, 6, 22, 27]. In fact, the EEG only becomes abnormal in at least mildly demented patients [27]. There is evidence to suggest that the yield of EEG for clinical as well as scientific purposes can be enhanced by using activation paradigms, such as haptic tasks [4], category-decision tasks [15] and olfactory stimulation [16]. We hypothesized that memory activation paradigms would be most successful, as memory impairment is the defining criterion for MCI. This concept is supported, firstly, by a known association between oscillations in the alpha and theta bands and memory performance [8, 9]. Secondly, a significant difference between MCI patients and patients with subjective memory complaints was recently found in a study employing a working memory task, using an EEG measure called 'synchronization likelihood' [20].

In this exploratory study, we investigated EEG power changes in MCI patients and healthy age-matched controls during three different memory activation paradigms in a comparison with conventional EEG.

Methods

Subjects

Twenty-six patients with MCI according to the criteria of Petersen [17], consecutively referred to the outpatient memory clinic of the Leiden University Medical Center, were selected for study. Patient histories were reviewed and diagnoses established in multidisciplinary consensus meetings. The diagnosis of MCI was made if the patient met the following criteria: (1) memory complaint, (2) normal activities of daily living, (3) normal general cognitive function, (4) abnormal memory for
age, and (5) not demented. Eighteen healthy controls were recruited through an advertisement in a local newspaper.

All patients and controls underwent a standardized dementia screening, including general medical, neurological, brain Magnetic Resonance Imaging and neuropsychological investigations. In short, neuropsychological testing included an abbreviated version of the Groninger Intelligence Test (GIT) [13], the Cambridge Cognitive Examination (CAMCOG) incorporating the Mini Mental State Examination (MMSE) [2, 21] and the Wechsler Memory Scale (WMS) [26].

Eligible subjects had to be right-handed, aged 60 yrs or above, free of psychotropic medication and without previous history of psychiatric or neurological disorders or substance abuse. Based on these criteria nine MCI patients were excluded because of psychotropic medication (4), psychiatric disorder (4) and left-handedness (1). Seventeen patients were then invited, of which 13 were willing to participate. One control subject was excluded because of below average memory performance. The study was approved by the local Medical Ethical Committee. All subjects gave informed consent.

**EEG recording**

EEGs were recorded using a Nihon Kohden 2110 apparatus with 21 Ag/AgCl electrodes placed according to the 10/20 convention at conventional sites. ECG, respiration and horizontal eye movement leads were recorded to facilitate recognition of artifacts. The EEG was band-pass filtered from 0.16-70 Hz before display and analysis, but recorded unfiltered. Sample frequency was 200 Hz and A-D precision 12 bits. The average reference montage was used to minimize the level of artifact contamination in areas of interest such as the temporal and frontal lobes.

All EEGs were recorded in the afternoon. During recording subjects sat slightly reclined in a comfortable chair, approximately one-and-a-half meters in front of a computer screen. The light in the room was dimmed.

**Experimental procedure**

The EEG was registered during two conventional EEG conditions and during three memory activation paradigms (Fig 1).

The first conventional EEG condition ('eyes closed') concerned a 10-min period where subjects had to close their eyes while remaining awake, and the second a three-min 'eyes open' period. From each period three artifact-free samples, 4-8 s in length, were selected visually for further analysis. The 'eyes closed' condition served as a reference against which spectral power changes in the other conditions were compared.

The first task, a working memory task, concerned word memory. Subjects were consecutively shown 10 common words on a computer
screen. Each word was presented for 2 s and subjects were asked to read aloud and memorize them. After presentation of the words, subjects had to close their eyes and memorize the words for 15 s, which will be referred to as the retention period. Subjects were then asked to open their eyes and name as many words they could remember. This task was performed three times using the same 10 words. From each retention period one EEG sample, 4-8 s in length, was selected for further analysis. The total number of words correctly remembered was noted as the word memory score (maximum:30).

The second task, also a working memory task, addressed picture memory; this task was similar to the word memory task but used pictures of common objects. The total number of pictures correctly remembered was used as the picture memory score (maximum:30).

The final, a semantic memory task, tapped animal fluency; subjects were asked to close their eyes and to think of as many animal names as possible during a 30-s period. From this period three EEG samples, 4-8 s in length, were selected for further analysis. Subjects were then asked to open their eyes and name as many animals as possible during 1 min. The total number of animal names was used as the animal fluency score (no maximum score).

**Fig 1.** Experimental procedure
EEG analysis
As eye movements, blinks and muscle activity may contaminate the EEG, only samples free of such events were selected after visual inspection by the first author, under supervision of the second author. Both were blind to clinical diagnosis. Samples had to be 4 to 8 s in length and were selected during conventional 'eyes closed' and 'eyes open' and the three memory conditions. Frequency analysis was performed using a Fast Fourier Transformation (Focus-EEG imaging and review software, MEGIS software GmdH, München, Germany). As artifact contamination in the beta band (13-30 Hz) lead to a mean value of 31 % missing values across subjects and leads, this band was excluded from further analysis. Furthermore, data of one control subject were excluded because of drowsiness, and of one patient because of an extremely low EEG voltage on most leads. Ultimately, results of 12 MCI patients and 16 controls were submitted to statistical analysis. Absolute power was calculated for the 'eyes closed' period in the theta (4-8 Hz), lower alpha (8-10.5 Hz) and upper alpha (10.5-13 Hz) frequency bands. Because of a skewed distribution, values were normalized using a log-transformation. Spectral power changes during 'eyes open' and the three memory tasks were quantified as the percentage of decrease or increase in absolute band power as compared to 'eyes closed'. This method is similar to that labeled as Event Related Desynchronization (ERD) [19] but for one change; in our analysis an increase in power is denoted by a positive value and a decrease by a negative one. Spectral power changes were calculated for all three frequency bands and for eight scalp locations: left frontal (average of F7 and F3), right frontal (average of F4 and F8), left temporal (T3 and T5), right temporal (T4 and T6), left centroparietal (C3 and P3), right centroparietal (C4 and P4), occipital (O1 and O2) and midline (Fz, Cz, Pz). In all conventional and memory conditions we averaged obtained power measures over all three selected EEG samples.

Statistical analysis
SPSS for Windows (release 11.0.1) was used for data analysis. Differences between groups regarding clinical characteristics were assessed using parametric and non-parametric tests when appropriate. Group differences in EEG measures were evaluated using repeated analysis of variance (ANOVA) with group (two levels; MCI and control) as a between-subjects factor and scalp location (eight levels) as within-subjects factor. We used the Greenhouse-Geisser correction for sphericity [3]. Separate analyses were carried out for each frequency band and condition. Pearson's correlation analysis was used to compute correlations between EEG measures and memory scores. The level of statistical significance
was set at $p \leq 0.05$. P values between 0.05 and 0.10 were considered trend significant.

Results

Clinical characteristics
Age, sex and years of education did not differ between groups (Table 1). Patients with MCI scored significantly lower on the CAMCOG, MMSE and WMS scales than controls. The GIT-age corrected IQ did not differ between groups, indicating preserved general intelligence in the MCI group.

EEG
In the conventional 'eyes closed' condition absolute power did not differ between MCI patients and controls for any band or scalp location. In the conventional 'eyes open' condition the power change as compared to 'eyes closed' (seen as a decrease in theta, lower alpha and upper alpha power) did not differ between patients and controls for any band or scalp location.

In the picture memory task we found a significant group effect in the lower alpha band ($F(1,25)=4.92, p=0.04$), in that MCI patients showed less decrease in lower alpha power than controls (Fig 2). The 'scalp location' and 'scalp location x group' interaction effects were not significant. In the word memory and animal fluency tasks there were no significant differences between groups, but there was a non-significant trend in the word memory task ($F(1,25)=3.19, p=0.09$). As in the picture memory task, MCI patients showed less decrease in lower alpha power than controls.

MCI patients performed significantly worse on the word memory and picture memory tasks, while animal fluency scores did not differ between groups (Table 1). Furthermore, for both groups combined, word and picture memory scores were significantly correlated with lower alpha power ($r$ ranging from -.43 to -.59, $p<0.03$) in that worsening memory performance coincided with less reactivity in the lower alpha band.
Table 1. Clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>male/ female*</td>
<td>7/9</td>
<td>7/5</td>
</tr>
<tr>
<td>age (yrs)</td>
<td>72 (5)</td>
<td>74 (6)</td>
</tr>
<tr>
<td>Education (yrs)</td>
<td>10 (3)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>MMSE (/30)</td>
<td>28 (1)*</td>
<td>25 (3)*</td>
</tr>
<tr>
<td>CAMCOG (/106)</td>
<td>96 (4)**</td>
<td>85 (6)**</td>
</tr>
<tr>
<td>GIT-IQ</td>
<td>121 (10)</td>
<td>123 (10)</td>
</tr>
<tr>
<td>WMS (Memory Quotient)</td>
<td>119 (11)**</td>
<td>96 (8)**</td>
</tr>
<tr>
<td>Word memory score (/30)</td>
<td>21 (3)**</td>
<td>13 (3)**</td>
</tr>
<tr>
<td>Picture memory score (/30)</td>
<td>24 (2)**</td>
<td>15 (3)**</td>
</tr>
<tr>
<td>Animal fluency score</td>
<td>19 (5)</td>
<td>16 (4)</td>
</tr>
</tbody>
</table>

Values in the table are means with SD in parentheses. * p<0.05; ** p<0.01. Independent t-tests were used to assess group differences.

Discussion

This exploratory study shows that memory activation revealed EEG differences between MCI patients and controls, while conventional EEG conditions ('eyes closed' and 'eyes open') did not. We found that picture memory activation caused a decrease in lower alpha power in both MCI patients and controls. However, this decrease was significantly smaller in MCI patients. Furthermore, a correlation was found between lower alpha reactivity and picture memory performance, in that worsening performance coincided with less reactivity in the lower alpha band. In view of the comparable poor performance during the word memory task, a similar EEG effect might be expected, but this was not statistically significant. As there was a trend towards significance in this condition, the limited group size may explain the failure to show an effect in this test.

While the healthy controls generally showed a large decrease in lower alpha power during picture memory activation, we found limited alpha reactivity in MCI patients (Fig 2). Lower alpha band reactivity is thought to reflect attentional processes. While a phasic alpha power increase is usually associated with worsening memory performance, a phasic alpha power decrease is associated with better performance [8, 9]. Our results are consistent with these findings in that poor memory performers (MCI patients) showed a small phasic decrease or even an increase in lower alpha power. The fact that our MCI patients performed significantly worse on the picture memory task strengthens this view. Interestingly, a recent paper [20] also reported differences between MCI patients and...
healthy controls in the lower alpha band (8-10 Hz) using working memory activation, as represented by higher synchronization likelihood in MCI patients. Rather than blaming this on the primary abnormality in MCI, they interpreted the change as a compensation mechanism. Since their MCI patients performed equally well on the memory task as the controls, this seems a plausible explanation. In the current study, using a more difficult memory task, this compensation mechanism might have failed as reflected by the irresponsiveness of the lower alpha band.

The observed EEG differences between MCI patients and controls were present over all scalp locations and might reflect widespread rather than focal cerebral pathology. This finding may be the result of the average reference montage blurring possible regional EEG effects of memory activation. However, recent findings of our research group obtained with volumetric Magnetization Transfer Imaging also demonstrate widespread brain changes in MCI and AD [24, 25].

Theta activity has been linked to episodic memory demands and the encoding of new information. During memory activation theta power usually increases as compared to a reference condition, whereas alpha power decreases [8, 9]. However, in our study we found little theta reactivity. A possible explanation for this lack of reactivity is our choice in memory activation paradigms. Other studies mostly employed event-related paradigms designed to study memory processes in detail. To maximize alpha activity and minimize artifact contamination, we only registered EEG during memory retention, while subjects had their eyes closed. Therefore we might not have captured stimulus encoding as such.

In this study, only the picture memory task was sensitive to EEG differences between MCI patients and controls. The word memory task showed a trend towards a group effect, and the animal fluency task showed no effect. The latter finding can be explained by previous research showing that semantic memory is usually preserved in MCI and the early stages of AD [23]. Regarding working memory, former neuropsychological studies report either impaired picture and/or word memory as a marker for the preclinical phase of AD [1, 7, 11, 14]. Hence, it seems worthwhile to further study the clinical and scientific potential of EEG during both picture and word memory.

Strengths of the current study include the quantitative and individually standardized nature of the EEG parameters. Furthermore, selection of EEG samples was performed blinded to diagnosis. The main limitation of the study is the small sample size, so results will need to be replicated in larger samples. Another methodological issue is our use of fixed instead of variable frequency bands [8, 9]. This was done to increase
clinical usability and to enable a better comparison with other EEG research in memory clinic populations [20], but makes a direct comparison with non-clinical EEG studies using variable frequency bands [8, 9] more difficult.

In conclusion, this study shows that quantitative EEG during picture memory activation is more sensitive to altered brain activity in MCI than conventional EEG. Our finding of diminished alpha reactivity in MCI provides preliminary evidence for a loss of attentional resources during memory activation. Moreover, our results show that the memory-related EEG changes in MCI are a global instead of a regional brain phenomenon. Future research should pursue the value of EEG with memory activation not only in the diagnostic work-up of MCI and AD, but also in evaluating the efficacy of treatment in AD, such as acetyl cholinesterase inhibitor therapy.

Acknowledgements

We thank E.L. Tiesma, P.J. van Someren, J.G. van Vliet-de Regt, M.J. Stijl-Pek, J.C. Albus-de Meza, A.J.C. van der Kamp-Huyts, F.I. Kerkhof and P. Massaar for their help in acquiring the EEG data. We are grateful to A.W.E. Weverling-Rijnsburger for her help in patient recruitment.
Fig 2. Mean absolute power change (%) during 'eyes open' and memory activation as compared to the 'eyes closed' reference, for MCI and control subjects.

Error bars indicate one standard error. * indicates significantly less reactivity in the lower alpha band in MCI patients (p=0.04).
References


Chapter 2


