Early Event-Related Potential Changes During Working Memory Activation Predict Rapid Decline in Mild Cognitive Impairment

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Background. The conversion of mild cognitive impairment (MCI) to Alzheimer’s disease is associated with substantial compromise of neocortical circuits subserving rapid cognitive functions such as working memory. Event-related potential (ERP) analysis is a powerful tool to identify early impairment of these circuits, yet research for an electrophysiological marker of cognitive deterioration in MCI is scarce. Using a ”2-back” activation paradigm, we recently described an electrophysiological correlate of working memory activation (positive-negative working memory [PNwm] component) over parietal electrodes.

Methods. Ours was a longitudinal study of 24 MCI patients with ERP analysis at inclusion and neuropsychological follow-up after 1 year. We used ERP waveform subtraction analysis between the n-back and control tasks. Analysis of variance (ANOVA) was used to compare electroencephalograph latencies between progressive MCI (PMCI) and stable MCI (SMCI), and univariate regression was used to assess the relationship between neuropsychological measures at baseline and clinical outcome.

Results. Thirteen (54%) MCI patients showed PMCI, and 11 (46%) remained stable (SMCI). In SMCI, a PNwm component with significantly larger density compared to baseline was identified when subtracting the detection task for both the 1- and 2-back tasks. In contrast, in PMCI, the PNwm component was absent in both 1-back and 2-back conditions. Neuropsychological variables and n-back test performance at inclusion did not predict cognitive deterioration 1 year later.

Conclusions. In conjunction with recent functional imaging data, the present results support the notion of an early dysfunction of neural generators within the parietal cortex in MCI. They also reveal that the absence of the PNwm component may provide an easily applicable qualitative predictive marker of rapid cognitive deterioration in MCI.

Mild cognitive impairment (MCI) has been described as a transitional state between normal aging and dementia. It has attracted great interest from researchers seeking to identify individuals at high risk of developing dementia before the occurrence of significant structural deficits, as such patients are deemed to be the best candidates for therapeutic intervention. MCI patients progress to dementia—in particular, Alzheimer’s disease (AD)—at a greatly accelerated rate compared to normal controls. However, not all MCI patients progress to clinically defined AD or decline at identical rates, and a significant proportion of patients remain stable for several years, or even improve (1).

Electroencephalography (EEG) is an easily accessible and low-cost modality that might prove to be a particularly powerful tool for the identification of predictive markers of cognitive deterioration in MCI. Yet, the number of contributions in this field remains very low (2–8). Although prospective studies have proposed that various quantitative EEG parameters may be possible predictors of dementia (5,7,8), most cross-sectional comparisons have failed to identify EEG differences under resting conditions between MCI patients and elderly controls (2,3,6). A recent study (4) confirmed this situation but found significant theta power differences during haptic tasks implying for the first time, to our knowledge, that activation paradigms may improve the prediction of MCI conversion to AD. In fact, because AD symptomatology is mainly due to the progressive damage of neocortical association areas [for review, see (9) and (10)], event-related potential (ERP) analysis, which makes it possible to investigate the functional activation of neocortical circuits with a very high temporal resolution, may represent a particularly sensitive method to identify early alterations of neuronal networks predictive of AD evolution among MCI patients (4,11).

Working memory, the capacity to store information and simultaneously manipulate it, is one of the cognitive processes which are mainly subserved by neocortical circuits. In agreement with a previous study suggesting an early activation of neural generators in parietal cortex during the successful performance of spatial and verbal working memory tests (12), we recently identified in healthy individuals an ERP component (a waveform labelled positive-negative working memory [PNwm]) over parietal electrodes, lasting from 140 to 280 ms after the onset of a new visual stimulus.
and showed that it represents an electrophysiological correlate of working memory load (13). This 1-year longitudinal study reveals that it is possible to predict cognitive deterioration in an MCI group on the basis of the PNw according to working memory load (13). This 1-year longitudinal study reveals that it is possible to predict cognitive deterioration in an MCI group on the basis of the PNw component.

**Methods**

**Inclusion Procedure and Follow-Up**

Patients were recruited in a large acute and intermediate care geriatric hospital. All admissions were screened with the Mini-Mental State Examination (MMSE) (14). Patients with MMSE scores between 25 and 28 underwent an additional clinical evaluation which included the Hospital Anxiety and Depression Scale (15) and Lawton’s Instrumental Activities of Daily Living (16). Depressive comorbidity was excluded on the basis of a Hospital Anxiety and Depression Scale score consistently less than 8. Extensive neuropsychological testing of the following was performed: attention (17); orientation (MMSE items); short-term memory [Mattis Dementia Rating Scale (DRS) items; (18), Digit Span Forward (19), Corsi’s Block-Tapping Test (20)]; episodic memory [Buschke’s Double Memory Test (21), Shapes test (22)]; executive functions [verbal fluency test (23), Trail Making Test (24)]; language [Boston Naming Test (25)]; ideomotor (26), reflexive (27), and constructional praxis (28); and visual gnosis (Ghent overlapping figures test) (29). Global cognitive function was assessed by the Clinical Dementia Rating scale [CDR; (30)] and the Mattis DRS. Patients having a test score more than 1.5 standard deviations below the age-appropriate mean in any of the above tests and a CDR score of 0.5 but no dementia, were diagnosed as possible MCI (1). These cases were reviewed independently by two highly experienced clinicians blinded to each other’s findings, and were included in the MCI group only if both clinicians concurred on this diagnosis. All participants had normal or corrected-to-normal visual acuity, and none reported a history of sustained head injury, or neurological or psychiatric disorders. Participants with regular use of psychotropics, stimulants, or β-blockers were also excluded. After formal approval of the local Ethics Committee, informed written consent was obtained from all patients included in this study. The final sample included 24 MCI patients (mean age: 83.0 ± 2.5 years, age range: 78–86 years) who underwent a detailed neuropsychological follow-up evaluation 1 year after inclusion using the same neuropsychological battery.

**Experimental Design**

Patients watched a continuous stream of letters (pseudo-random sequences of consonants and vowels) common to the French alphabet on a computer screen and pressed a computer-controlled pushbutton with the index finger of their right hand as soon as a target appeared (response trials). For nontarget trials, no motor response was required (no-response trials). Targets were defined according to the n-back design (Figure 1).

Stimuli consisted of white letters, in “Arial” typeface (2° × 2.5° visual angle), with 10% gray noise, embedded in a 50% random-noise gray rectangular background patch (6° × 6.7° visual angle). They were presented for a duration of 0.5 seconds, separated by 5-second intervals (onset to onset), during which a dot helped patients to maintain fixation. Three different tasks were used: in a simple detection task (control), sequential letters or background patches without letters were presented. Patients responded as fast as possible when background patches without letters appeared. In the 1-back task, the target was any letter identical to the one immediately preceding it. In the 2-back task, the target was any letter that was identical to the one presented two trials back. Thus, working memory load increased from control (memory-free condition) to 1-back (moderately demanding) and 2-back tasks (highly demanding).

Each task was tested in three stimulus sequences of 30 images each, adding up to 90 trials per task. Before each sequence block, patients were informed about the nature of the task, and several warm-up trials were performed. A control task block was followed by one block of the 1-back condition, three blocks of the 2-back condition, two blocks of the 1-back condition, and two blocks of the control task. No feedback on performance was provided. Electrophysiological and neuropsychological assessments were performed in the morning.

**Electrophysiological Recordings**

Continuous electroencephalography (Brain Quick system 98, BQ 3200; Micromed, Treviso, Italy) was recorded, using 20 surface electrodes placed over the scalp according to the International 10–20 System of Electrode Placement (31). Linked earlobes were used as a reference. Skin impedance was kept below 5 Ω. Physiological signals were sampled at 1024 Hz, the lower cutoff was 0.33 Hz, and the upper cutoff was 120 Hz (DC amplifiers; Micromed). Right, left, supra-, and infra-orbital electrodes monitored horizontal and vertical electro-oculograms. Synchronized with stimulus onset, Transistor-Transistor Logic (TTL)-pulses were used off-line to segment the continuous EEG data into epochs. Reaction times and patients’ performances were recorded.

**Waveform Analysis**

Data were analyzed with NeuroScan software (NeuroScan, Herndon, VA). After artefact removal and off-line correction of ocular artefacts (threshold reduction algorithm), data from trials with correct answers were averaged according to the task condition (control, 1-back, 2-back). All correct answers were combined (response to a target and no response in the absence of a target), because working memory is required in both situations and because prior research has shown that there is no difference between response and no response conditions during the time window used to study the ERPs (13). Combined ERPs were then averaged over a time window of 700 ms with a 200-ms prestimulus onset and were band-pass filtered between 0.33 Hz and 30 Hz, 24 dB/octave for low-pass filter. Latencies of the ERP components were measured at the time of the peak maximum.

**Data Analysis**

The visual P100 component latency was measured at the O1, Oz, and O2 electrode sites. The maximal peak latencies of the N160, P200, and N200 components occurred at fron-
tal, midline, and posterior (Fz, Cz, and Pz) electrode sites in the two groups, and these sites were thus selected for their measurement (Figure 2).

To isolate the PNwm component, we performed an ERP waveform-subtraction analysis between the n-back tasks and the control task. Electrodes F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4 were selected for analysis in keeping with the anteroposterior distribution of the PNwm component. The intersection between the detection waveform and either the 1-back or 2-back waveforms in the 175- to 317-ms time-range window was used to define the temporal limits for the measurement of density (area in μV²). These temporal limits were not identical in both tasks. To correct for this difference, the density of the PNwm component was divided by the measurement time range defined by the temporal limits for each task in all patients; it was then normalized through logarithmic transformation.

Statistical Comparisons Between Progressive and Stable MCI

Neuropsychological values at baseline and upon follow-up were compared in progressive MCI (PMCI) and stable MCI (SMCI) groups using the Wilcoxon nonparametric test. Differences in reaction times and performances between SMCI and PMCI groups were assessed using the Mann–Whitney nonparametric U test. Univariate regression analysis was also performed to examine whether neuropsychological measures at baseline predict further cognitive decline after 1 year in the present MCI cohort. Analyses of variance (ANOVAs) were used to compare EEG latency and densities among the different task conditions (control, 1-back, and 2-back). The significance values were determined using the Greenhouse–Geisser correction. The Scheffé test was used for post hoc analyses. Two-tailed differences of \( p < 0.05 \) were considered significant.

RESULTS

Upon follow-up examination which took place 1 year after baseline (range 12.0 ± 0.4 months), 13 (54%) of the original MCI patients demonstrated significant cognitive decline and constituted the PMCI group. The remaining 11 patients (46%) showed no change in cognitive function and were included in the SMCI group. PMCI patients showed deterioration in one or more of the following domains: executive function, attention, and memory. No patients in the SMCI group developed AD 1 year later (Table 1).

There was no statistical difference in baseline scores for any of the neuropsychological tests between SMCI and PMCI patients. This finding was confirmed by the univariate regression analysis, which showed that neuropsychological parameters at baseline did not predict cognitive deterioration 1 year later. Age, sex distribution, educational level, func-
Global assessment (spectively) (Figure 2). Differences in the PMCI and SMCI groups for any of the tasks (Table 3). The PNwm Component
Sensory ERPs
of the trials. Performance was related to task difficulty (p < .01). However, this increase was similar in both PMCI and SMCI patients (Table 3). All MCI patients performed well in both 1-back and 2-back tasks and responded correctly in more than 80% of the trials. Performance was related to task difficulty (p < .001); this effect was restricted to the 2-back condition (Scheffe p < .001). More importantly, performance of PMCI and SMCI patients was not significantly different (Table 3).

Sensory ERPs
Latencies of sensory P100 and N160 ERPs were no different in the PMCI and SMCI groups for any of the tasks (116.4 ms vs 115.4 ms and 162.1 ms vs 167.5 ms, respectively) (Figure 2).

The PNwm Component
Figure 3 shows the PNwm component, obtained by subtracting ERP waveforms for the detection task from the 2-back (Figure 3A) and 1-back (Figure 3B) tasks. In the SMCI group, a PNwm component is clearly visible. Its density was significantly larger than baseline for both the 1- and 2-back tasks (p < .01 and p < .001, respectively). In the PMCI group, no significant PNwm component could be identified. No electrode site effect or interactions between group and electrode sites were observed (Figure 3).

DISCUSSION
Strengths of the present study include the large series of longitudinally studied MCI patients, confirmation of the clinical diagnosis of MCI by two independent clinicians blind to the study purposes, as well as control for medications which influence ERP. The present data indicate that the absence of an early ERP component (i.e., PNwm component) during working memory activation is associated with rapid cognitive deterioration in MCI. Neither neuropsychological measures nor n-back performances at baseline were related to the clinical outcome, suggesting that the
observed ERP change may be an independent predictor of MCI decline. Importantly, all PMCI patients displayed high performances in n-back task at baseline and only few additional specific cognitive deficits on follow-up (with preserved global scores such as MMSE and Mattis DRS), indicating that the inability to visualize a PNwm component in this group represents an early EEG phenomenon which may predict even subtle decrease in the cognitive abilities of MCI patients. In this context, the successful completion of the task in PMCI patients may be due to the compensatory activation of additional cortical areas. This possibility is supported by a recent functional imaging study (32) showing that high- but not low-performing elderly individuals may compensate for the neural decline of parietal areas during working memory tasks, through the activation of distinct neurocognitive networks within prefrontal and limbic areas.

The only other longitudinal ERP study focusing on memory in MCI reported that a significant reduction of late potential repetition (P600) in a word repetition paradigm may help to distinguish PMCI from SMCI in a 2-year follow-up (11). This study included only 14 MCI patients and used post hoc determined cutoff values of the P600 to separate converters from nonconverters. More importantly, it focused on verbal episodic memory processes thought to reflect mesial temporal lobe function. However, several lines of evidence suggest that metabolic or electrophysiological changes within the mesial temporal lobe may be not the best candidates for the prediction of MCI conversion to AD. In fact, this brain region is a site of very early neurofibrillary tangle (NFT) formation which was quite comparable in patients with no cognitive impairment and in patients with questionable dementia [CDR score of 0.5, (33,34)]. In addition, MCI patients display extensive (up to 50%) neuron loss in layer II of entorhinal cortex, and NFT counts in this area are elevated in these patients even in comparison to those in AD patients with several years of evolution (33,35). In contrast, the progression of NFT within neocortical association areas is clearly associated with clinical signs of dementia (for review, see 9,10,34,35). These neuropathological observations are also confirmed by a recent prospective single photon emission tomography (SPECT) study which showed that reduction of regional cerebral blood flow in the medial temporal lobe has no value as predictor because it also occurs in SMCI (36). In contrast, two recent functional imaging studies proposed that decreased metabolism in parietal areas is a sensitive early marker of MCI progression toward AD (37,38). In line with these observations and our previous work (13), the prediction of MCI decline based on the early impairment of neural generators within the parietal

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Table 2. Demographic and Clinical Characteristics of SMCI and PMCI Patients at Inclusion

<table>
<thead>
<tr>
<th>Variable</th>
<th>SMCI Patients (N = 11)</th>
<th>PMCI Patients (N = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>84.91 ± 4.78</td>
<td>83.54 ± 4.31</td>
</tr>
<tr>
<td>Sex, f/m</td>
<td>8/3</td>
<td>11/2</td>
</tr>
<tr>
<td>Educational level*</td>
<td>1.64 ± 0.81</td>
<td>1.31 ± 0.48</td>
</tr>
<tr>
<td>IADL1</td>
<td>12.91 ± 4.46</td>
<td>12.77 ± 4.28</td>
</tr>
<tr>
<td>HAD1 (anxiety)</td>
<td>5.00 ± 2.53</td>
<td>5.46 ± 2.60</td>
</tr>
<tr>
<td>HAD1 (depression)</td>
<td>4.45 ± 2.16</td>
<td>3.54 ± 2.37</td>
</tr>
</tbody>
</table>

Notes: Data are presented as mean ± standard deviation.
*Educational levels from 1 to 3.
1Hospital Anxiety and Depression (HAD) scales, cutoff is 8 for both anxiety and depression. The two diagnostic groups were comparable with respect to the above mentioned variables.

SMCI = stable mild cognitive impairment; PMCI = progressive mild cognitive impairment.

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Table 3. Reaction Times (ms) and Performances (%) With Standard Errors (±SE) for the Control, 1-Back, and 2-Back Tasks in SMCI (N = 11) and PMCI (N = 13) Patients

<table>
<thead>
<tr>
<th>Tasks</th>
<th>Reaction Times (Mean ± SE)</th>
<th>Performances (Mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMCI</td>
<td>PMCI</td>
<td>p</td>
</tr>
<tr>
<td>Control</td>
<td>977.67 ± 4.13 1081.22 ± 4.06 NS 98.89 ± 0.44 97.78 ± 0.44 NS</td>
<td>Control</td>
</tr>
</tbody>
</table>

Notes: There was no statistically significant difference in reaction times and performances between the two diagnostic groups. See text for details.
SMCI = Stable mild cognitive impairment; PMCI = progressive mild cognitive impairment; NS = not significant.

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Figure 3. Frontal (Fz), central (Cz), and parietal (Pz) grand average waveforms of the positive-negative working memory (PNwm) component, representing event-related potential (ERP) differences between 2-back task and control task (A) and between 1-back task and control task (B), respectively, for stable mild cognitive impairment (SMCI) (dashed lines) and progressive mild cognitive impairment (PMCI) (solid lines) patients. Response and no-response conditions were averaged. No PNwm component was observed in PMCI patients.
cortex reported here further supports a key role for this area in MCI transition to AD.

Numerous structural and functional neuroimaging reports addressed the issue of a predictive marker of further cognitive deterioration in MCI with conflicting data. Early longitudinal and cross-sectional MRI studies supported the value of hippocampal (39–44) and entorhinal cortex (40,45) atrophy in MCI with regard to subsequent cognitive decline. However, volumetric alterations in hippocampus and entorhinal cortex reflect the presence of an already substantial loss of pyramidal neurons (46) and cannot thus be considered as early predictors of the degenerative process in brain aging. Because functional alterations are thought to occur prior to structural deficits in the course of MCI, recent studies have attempted to identify an early functional marker of MCI deterioration. Decreased parietal and increased prefrontal regional cerebral blood flow (37), posterior cingulate (38), and right temporoparietal cortex hypometabolism (47,48) have all been associated with MCI conversion to AD. These variable results have led to increasing scepticism about the validity of positron emission tomography in the prediction of AD. Furthermore, poor time resolution, low practicability, and cost-effectiveness of PET and SPECT in clinical settings. In contrast, the PN_wm component may provide an easily applicable qualitative predictive EEG marker of rapid cognitive deterioration in MCI. Two main limitations should, however, be considered when interpreting these data. First, no distinction was made between different MCI subgroups (i.e., vascular vs AD MCI) in the present series. Second, as it is frequently the case in imaging studies (49), the definition of an individual risk is still not possible on the basis of the present activation paradigm due to the relatively low signal-to-noise ratio. Additional ERP studies in large, prospectively studied MCI subgroups with a longer follow-up period are needed to determine how future paradigm changes including an increased number of n-back trials and improved noise-filtering methodology could lead to predictive models of MCI conversion to PMCI and ultimately dementia that could be applied to a single individual.

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