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Highlights

- In this study we performed a thorough investigation on the use of event-related potentials (ERP) and event-related (de)synchronization (ERD/ERS) for early Alzheimer's disease (AD) diagnosis.
- We compared behavioural results (reaction time and accuracy), ERP and ERD/ERS responses when healthy elderly (HE) controls, Mild Cognitive Impairment (MCI) and mild AD patients were performing a three-level N-Back working memory task
- Our most important finding was that ERD/ERS analyses have revealed themselves more valuable than ERP, since they showed significant differences in all three group comparisons: HE vs. MCI, HE vs. AD, and MCI vs. AD.

Early Diagnosis of Mild Cognitive Impairment and Alzheimer's with Event-Related Potentials and Event-Related Desynchronization in N-Back Working Memory Tasks

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Abstract

Background and Objective: In this study we investigate whether or not event-related potentials (ERP) and/or event-related (de)synchronization (ERD/ERS) can be used to differentiate between 27 healthy elderly (HE), 21 subjects diagnosed with mild cognitive impairment (MCI) and 15 mild Alzheimer's disease (AD) patients. *Methods:* Using 32-channel EEG recordings, we measured ERP responses to a three-level (*N-back, N=0,1,2*) visual working memory task. We also performed ERD analysis over the same EEG data, dividing the full-band signal into the well-known delta, theta, alpha, beta and gamma bands. Both ERP and ERD analyses were followed by cluster analysis with correction for multicomparisons whenever significant differences were found between groups. *Results:* Regarding ERP (full-band analysis), our findings have shown both patient groups (MCI and AD) with reduced P450 amplitude (compared to HE controls) in the execution of the non-match *1-back* task at many scalp electrodes, chiefly at parietal and centro-parietal areas. However, no significant differences were found between MCI and AD in ERP analysis whatever was the

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task. As for sub-band analyses, ERD/ERS measures revealed that HE subjects elicited consistently greater alpha ERD responses than MCI and AD patients during the *1-back* task in the match condition, with all differences located at frontal, central and occipital regions. Moreover, in the non-match condition, it was possible to distinguish between MCI and AD patients when they were performing the *0-back* task, with MCI presenting more desynchronization than AD on the theta band at temporal and fronto-temporal areas. In summary, ERD analyses have revealed themselves more valuable than ERP, since they showed significant differences in all three group comparisons: HE vs. MCI, HE vs. AD, and MCI vs. AD. *Conclusions:* Based on these findings, we conclude that ERD responses to working memory (*N-back*) tasks could be useful not only for early MCI diagnosis or for improved AD diagnosis, but probably also for assessing the likelihood of MCI progression to AD, after further validated by a longitudinal study.

Keywords: Alzheimer's disease; mild cognitive impairment; working memory; event-related potentials; event-related (de)synchronization

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Introduction

The treatment and diagnosis of dementia has become a serious public health problem in both developed and developing countries. Research to identify reliable markers that can effectively promove early diagnosis is very active, especially in the case of Alzheimer's disease (AD). Waiting for the appearance of more pronounced symptoms to start treatment is risky, since it may be too late to achieve full effectiveness of the drugs capable of controlling disease progression. As such, early diagnosis of AD has become a pressing need, with the United Nations and Alzheimers Disease International calling on all governments to implement national dementia plans focusing on (i) raising public awareness about the disease and reducing stigma, (ii) improving early diagnosis, and (iii) providing better care and more support to caregivers. Very early detection allows for treatments to slow disease progression to be administered early, thus

making them more effective and reducing healthcare costs. The Alzheimer Society of Canada, for example, has reported that delaying the onset of AD by two years would result in 34% fewer individuals in long-term care [1].

Several studies have pointed out mild cognitive impairment (MCI) as an important risk factor in the development of AD [2, 3, 4, 5]. Statistics reveal that about half the people who reported MCI symptoms to a clinician will develop AD in a couple of years, with a 12% average annual conversion rate [6]. Therefore, there is an urgent need to find low-cost, highly sensitive and highly specific biomarkers for the early identification of subjects at risk of developing AD within the next two to three years. Quantitative analysis of electroencephalographic signals is potentially one of the best candidates among possible markers because EEG equipment is relatively cheap, non-invasive, and safe. More importantly, EEG biomarkers can investigate the neurophysiological "reserve" in patients with dementia disorders. This was defined as the residual capacity of the brain to ensure the synchronization of neural activity at different spatial and frequency scales between subcortical and cortical neural networks [7].

The literature on EEG or MEG use in assisting AD diagnosis is clearly divided into two main approaches [8, 9, 10]. The first one deals with EEG or MEG signals registered when participants are awake at rest, with eyes open or closed (resting-state) [11, 12, 13, 14, 15, 16], while the other is dedicated to the analysis of signals recorded with subjects performing some pre-defined tasks (task-oriented)[17, 18, 19, 20, 21]. Both paradigms can be analyzed in time and frequency domains, bringing information about cognitive functions related to the characteristics of brain signals [22, 23, 10].

Although resting-awake protocols have a good prognosis for early diagnosis of AD [24], this study explores the use of EEG analysis during an executive function test, since deficits in such tasks are characteristic in MCI [25, 26]. The neurological basis of executive dysfunction in MCI and AD remain somewhat unclear, although some authors have postulated that alterations in functional neural networks might have some influence [27, 28]. In fact, research has shown that the risk of developing AD is higher in MCI-like patients who present at

least one other cognitive impairment in addition to memory loss [29] . To investigate these functional neural networks, event-related potential (ERP) analysis has been explored [30, 31, 32], with some success in discriminating between healthy controls, MCI, MCI-Progression-to-AD, and AD. ERP analysis, however, discards sub-band information that has been shown to be invaluable to discriminate AD patients from healthy elderly in the resting-awake EEG protocol [33, 34, 35, 36, 37].

In this article, we seek to overcome this limitation of full band analysis using not only ERP, but also a complementary technique called synchronization / (de) synchronization (ERS / ERD), which is associated with the classical EEG frequency bands [38, 39]. To detect the so-called ERPs, signal averaging techniques are usually used. The fundamental hypothesis is that the evoked activity has a somehow fixed time-delay with respect to the stimulus, while the background EEG activity acts as additive noise. Thus, the idea behind the averaging procedure is that it will significantly increase the signal-to-noise ratio. However, it has also been shown, for instance, that visual stimuli can reduce ongoing EEG amplitude [40], thus implying that the basic model that an ERP can be represented by a signal added to uncorrelated noise is not valid for all cases. Some types of changes are synchronized with the event, but not with the same phase and therefore cannot be extracted by a simple linear method, such as the averaging procedure, but can only be detected by frequency analysis of the so-called induced oscillations [41, 42].

In order to get a better understanding of how ERP and ERD could be complementarily used to discriminate MCI and AD patients from age-matched elderly controls, in this study we employed both methods for the analysis of EEG signals in response to working memory tasks. The *N-back* task is widely used to investigate the neurological basis of working memory. Previous studies using the *N-back* paradigm have consistently found that this kind of task activates several brain regions: dorsolateral and ventrolateral prefrontal cortex, premotor cortex, supplementary motor area and reaching even parietal posterior areas [43, 44, 45]. The *N-back* visual identification letter task requires participants to

maintain information in working memory in order to decide whether a currently presented stimulus matches a stimulus presented N trials previously [46].

Likewise ERP, ERD/ERS and other types of oscillatory analysis of event-related responses, like event-related oscillations (ERO) [47], have been used with success to differentiate AD and/or MCI patients from healthy elderly. Some of these EEG studies found AD patients with reduced delta (1-4 Hz) ERO in the classic auditory oddball paradigm [48, 49]. Further investigations revealed that MCI patients also presented lower delta ERO both in the auditory [50] as well as in the visual [51] oddball paradigm. Previously (2007), using ERO in the same visual oddball paradigm, Yener et. al. [52] had found Alzheimer patients with weaker phase-locking in the theta (4-8 Hz) band. Using the very same *N-back* working memory tasks we used in this study, Deiber et al. showed that induced theta activity was lower in progressive MCI as compared to elderly controls and stable MCI [53]. Still in the same theta band and also with EEG recorded during execution of working memory tasks, but using a modified Sternberg word recognition task instead of *N-back*, Cummins et al. [54] encountered 12 MCI patients with significantly lower theta power when compared to 12 healthy matched controls.

Moving to the next band, using MEG recordings of participants performing a go/no-go task, Babiloni et al. found that AD and vascular dementia (VaD) patients presented stronger alpha ERD peak when compared to elderly normal subjects [55]. More recently and more close-related to our study, Deiber et al. [56] found altered theta (4-7 Hz), alpha (8-13 Hz), and beta (14-25 Hz) ERS/ERD in MCI cases compared to controls using EEG recordings during performance of a *2-back* working memory task. With MEG recorded during execution of the Sternberg's memory recognition task by patients with early AD, patients with MCI and by age-matched healthy controls, Kurimoto et al. [57] found significant group differences in beta and gamma frequency bands: patients with AD presented lower beta ERD compared to controls and reduced gamma ERD compared to MCI patients. Using a simple visual oddball paradigm, Güntekin et al. [58] showed that both beta ERO and EEG-evoked beta power were significantly

higher in elderly controls when comparing responses to target with responses to non-target stimuli, while in age- and education-matched MCI patients no differences were found between the two types of stimuli. Finally, in a recent study (2016), Basar et al. investigated ERO gamma responses in a classical visual oddball paradigm and found that gamma target ERO latency was significantly delayed in AD patients when compared to age-, gender- and education-matched healthy controls [59].

In a previous study, using EEG recorded during execution of the same *N-back* working memory tasks used in this paper, we also found ERS/ERD differences between MCI, AD and age-, gender- and education-matched healthy elderly, but only in the alpha, beta and gamma bands [20]. However, as mentioned above, other researchers encountered significant differences between patients (AD and/or MCI) and elderly controls in the low-frequency delta and theta bands [54, 48, 53, 49, 51, 50]. Consequently, we wondered whether this was due to the methods used to calculate the ERS/ERD measures, since there are several different forms of computing these type of even-related responses [60, 61, 62]. In order to investigate this issue, we decided to try out a different method for obtaining the ERS/ERD: instead of getting both the synchronized induced and the in-phase evoked oscillations [41, 42], as we did in our recently published paper [20], we decided to use the first original Pfurtscheller's methodology [39] to analyze ERD/ERS, which gets only the induced response and discards the in-phase evoked response, as will be described in the next section.

Methods

Participants

The experiment was attended by 63 volunteers. From these participants, 15 were diagnosed with probable Alzheimer's disease (AD), 21 had mild cognitive impairment (MCI) and 27 were healthy elderly (HE) controls. All patients (subjects with MCI and AD) were diagnosed and enrolled at the Memory Clinic of the Sir Mortimer B. Davis-Jewish General Hospital (JGH) in Montreal, Canada,

which is a tertiary care referral center of McGill University. The healthy elderly were selected from research databases at Concordia University and the JGH Memory Clinic. Ethical approval was obtained from both Concordia University and the General Jewish Hospital. The 63 participants provided written consent.

Patients underwent a general health questionnaire to select participants and exclude neurological conditions other than MCI or AD, such as medical conditions that can affect cognition (e.g., B12 deficiency, uncontrolled thyroid dysfunction, alcohol abuse) and psychiatric disorders (other than mild depression). Furthermore, Geriatric Depression Scale - GDS [63] was administered and only participants with a score lower than six were admitted to this study.

Healthy controls were recruited after undergoing the Montreal Cognitive Assessment test - MoCA [64], which is a cognitive screening tool sensitive to detect MCI and able to perform a full review of their overall cognitive function. If an individual scored under 26 on this measure, he/she was excused and therefore excluded from the HE group.

Mild cognitive impairment patients (or his/her kin companion) were required to make a subjective report about their cognitive decline, which is part of the procedure to achieve a proper diagnosis according to agreed-upon criteria [65, 66]. All MCI subjects reported a gradual cognitive decline in the past six months, since this was a pre-requisite to be included in the experiment. Additionally, in order to guarantee the absence of significant impairment in daily life activities, "candidates" to be incorporated in the MCI group underwent an objective verification of cognitive impairment made through neuropsychological tests. Also, failure to meet the ADRDA-NINCDS criteria for dementia [67] had to be assured, which was determined by the assessing physician in the Memory Clinic. In summary, patients were diagnosed as amnestic MCI [26], demonstrating a deficiency in episodic memory measures and some also demonstrated deficits in other cognitive domains.

To be included in the AD group, participants had to demonstrate an established progressive cognitive decline and the absence of any other condition capable of producing a dementia syndrome, according to the ADRDA-NINCDS

criteria for probable AD [67]. Finally, only those patients who were competent to sign the consent form without any assistance were included in the AD group. This additional measure ensured that all subjects diagnosed with AD who participated in the study had only a mild degree of the disease, thus no moderate or severe cases were included.

N-back task description

Participants performed a three-level visual *N-back* task ($N = 0, 1, 2$) [46]. These tasks are designed to carry out a working memory (WM) test with increasing levels of memory load, where the individual must indicate (by pressing a button) if the current (visual) stimulus displayed on a screen (in this case, a digit in the 1-9 range) is the same or different from (I) a digit the participant has been asked to remember (*0-back*), (II) the digit he/she saw in the preceding trial (*1-back*) or (III) the digit seen two trials previously (*2-back*). Any particular trial is labelled as "match" or "non-match", based on whether or not it matches the digit presented N trials before (or the target digit in the *0-back* case), respectively.

The digits (1-9) were presented each time on a computer screen in white letters (Arial font point 150) on a black background. Each condition of the three-level *N-back* task (in ascending WM load: $N = 0, 1, 2$) consisted of 100 trials, with 60 non-match trials (match/non-match stimuli were distributed pseudorandomly). Every single digit was presented with the same probability in a pseudorandom order, restricted by the requirements of the 40/60 match/mismatch ratio. Each stimulus remained on screen for 600 ms, where the next stimulus appeared after a 1,400 ms blank-screen interval. Every time a new stimulus appeared on screen, the individual should respond by pressing the left or right button on a keyboard with the index finger of each hand. The designation of which button (left or right) was the match or the non-match key was counterbalanced across participants. Figure 1 illustrate the task performing for the *1-back* condition. Immediately before each condition, subjects completed a short practice block, which was repeated on demand until the participant understood the

task completely. Only during the practice blocks a beep warned subjects every time they made a mistake on their match/mismatch decision. During the tests, button pressing from all trials were registered to further calculate reaction times and accuracy for each participant performing the three-level *N-back* task. Participants also completed other tasks of executive function during the testing session, but they are not relevant to this study and therefore will not be reported herein.

EEG recording and pre-processing

EEG signals were registered with a 32-channel Neuroscan device operating at a 500 Hz sampling rate. The 32 Ag/AgCl electrodes were mounted in an elastic Easycap according to the international 10-20 placement system. During EEG recording impedance was maintained below 8 kΩ and the reference electrode was positioned in the left earlobe, but for offline analysis all signals were re-referenced to the average of the left and right ear electrodes. Of the existing 32 channels, we used two for monitoring vertical (blinks) and horizontal (saccades) eyeball movements, and a third one was attached to the right earlobe and used for referencing purposes (as mentioned above), thus resulting in 29 EEG channels.

We passed EEG data through a lowpass filter (57 Hz), then down-sampled signals to 125 Hz and high-pass filtered (1.2 Hz) them to remove drifting effects. Following, using the Independent Component Analysis tool of the EEGLAB software [68], we removed eye blinks, saccades, heart beats and other muscular as well as electrode artifacts. In the last pre-processing step preceding ERP and ERS/ERD analysis, since the inter stimulus interval (ISI) was exactly 2.0 seconds, we partitioned the sub-band signals into 2-second epochs (trials) in the -300 ms to 1700 ms interval, where 0 ms designates the time when visual stimuli appeared on screen.

ERP and ERD/ERS analyses

Before performing both ERP and ERD/ERS analyses, the 2-second epochs of each of the 63 participants were separated into six blocks of data corresponding

to each of the six *N-back* tasks (match and mismatch trials of the three-level WM load). To avoid misjudgment issues, we did not analyze any trials where the subject has provided incorrect responses (match or non-match), since we do not know the underlying brain processes that led to the wrong answer. To obtain the ERPs of each data block, we simply averaged the 29-channel EEG signals across epochs with correct responses, which mathematically corresponds to obtaining the point-to-point inter-trial mean, according to equation 1

$$ERP_i(t) = \bar{x_i}(t) = \frac{1}{M}\sum_{m=1}^{m=M} x_{im}(t), \tag{1}$$

where $x_{im}(t)$ stands for the 29-channel ($i = 1, 2, , 29$) EEG signal of the 2-second epoch ($-300ms \leq t \leq 1700ms$) of the m-th trial.

Event-related synchronization (ERS) / desynchronization (ERD) are related respectively to the increase / decrease in firing synchrony of neurons involved in frequency-specific event-related brain processes. According to Pfurtscheller, "ERD characterizes cortical areas involved in task-relevant processing and ERS marks cortical areas in an idling state" [69]. In order to obtain ERS/ERD patterns, first the 29-channel full-band 2-second signals $x_{im}(t)$ of each trial m ($m = 1, 2, ..., M$) are band-pass filtered into the five classical sub-bands, i.e.: delta ($4 - 8$ Hz), theta ($4 - 8$ Hz), alpha ($8 - 12$ Hz), beta ($12 - 30$ Hz) and gamma ($30 - 45$ Hz) [70], generating the signals $s_{bim}(t)$ for each of the five sub-bands ($b = 1, 2, 3, 4, 5$). Next, we proceed to the calculation of the point-to-point inter-trial variance [39], given by equation 2

$$VAR_{bi}(t) = \frac{1}{M-1}\sum_{m=1}^{m=M} [s_{bim}(t) - \bar{s_{bi}}(t)]^2, \tag{2}$$

where $\bar{s_{bi}}(t)$ is the point-to-point inter-trial mean of the bandpass signals $s_{bim}(t)$ calculated with the same equation 1 used to generate the ERPs. It is important to remark that after performing this step there is no more in-phase information in the $VAR_{bi}(t)$ signals, since the "bandpass ERPs", which are nothing more than the inter-trial means $\bar{s_{bi}}(t)$, were completely removed. In this way, we can be sure that ERS/ERD signals will carry information that is not present

in the ERPs, thus assuring that ERP and ERD are complementary and not redundant measures. In order to reduce the signal variability and therefore get more robustness against noise [39], the sub-band $VAR_{bi}(t)$ signals passed through a smoothing (lowpass) filter with 10 Hz cutoff frequency to produce the five ($b = 1, 2, 3, 4, 5$) bandpass energy signals $E_{bi}(t)$ of the i-th channel ($i = 1, 2, ..., 29$). Following the original study from Pfurtscheller [39], to compute the ERS/ERD first of all we have to calculate the pre-stimulus baseline, which is the average energy of the smoothed bandpass energy signals from -300 to 0 ms, where 0 ms is the instant when the stimulus was presented. This baseline energy measure is herein called R_{bi}. Lastly, the percentage power increase (%ERS) or decrease (%ERD) were computed exactly as in [39]:

$$\%ERS_{bi}(t) = 100 \times \frac{E_{bi}(t) - R_{bi}}{R_{bi}}. \quad (3)$$

Therefore, when $\%ERS_{bi}(t)$ is negative it means the power has decreased after the stimulus as compared to the baseline, otherwise it means power increase, respectively indicating activity or inactivity on frequency band b at the underlying cortical area covered by electrode i [69]. The computation of ERS/ERD patterns in this study follows the same steps used in [69, 71].

Cluster Analysis

A common procedure most researchers use to compare EEG data results from different subjects is to assume that scalp channel sites are spatially equivalent for all of them. However, this assumption is actually an idealization, since the spatial connection of any physical electrode location to the underlying cortical areas producing the activities covered by that channel may be quite different across subjects. It means that data recorded from equivalent channel locations in different subjects may convey information from different cortical EEG sources, a point commonly overlooked in several EEG studies. To overcome this issue, the EEGLAB software package [68] has recently launched a new tool to perform cluster analysis [72]. This alternative form of analysing electrophysiological data were successfully used in several EEG and MEG stud-

ies [73, 74, 75, 76, 77]. It uses Principal Component Analysis (PCA) to find meaningful clusters across EEG data from different subjects, which leads to a much more accurate statistical analysis when comparing different groups of participants in a study [78]. The first step is identifying which scalp channels are spatially equivalent, using clusters of the independent components previously calculated through the EEGLAB ICA tool. In order to do that, we used the well-known k-means clustering algorithm [79] with the rule of thumb of one cluster per each subject participating in the study. After clustering, once the ICA components are grouped, it is possible to calculate statistical differences at scalp electrodes between the conditions (WM tasks) and groups (HE, MCI and AD).

Statistical Analysis

Statistical significance was established at 5% level for all tests. We used Kolmogorov Smirnov test to determine if the data come from a normal distribution; when normality holds, parametric ANOVA tests were used to determine if there are significant differences between groups (AD, MCI and HE). When the hypothesis that the data come from a normal distribution was rejected, the non-parametric Kruskal Wallis test was used instead. Whenever significant differences were found, we used multiple comparisons tests (Bonferroni correction) to verify the existence of actual differences between the pairs of groups AD-MCI, AD-HE and MCI-HE. To compare groups after cluster analysis of EEG data, the interactive EEGLAB tool was used, which on its turn uses the "Cluster-based permutation tests on event related fields" *Fieldtrip* software plugin [80] to implement the Monte Carlo method with statistical permutation.

Results

Participant demographics

Before starting the analysis of any measures taken from HE, MCI and AD participants, we must have a look at participant demographics, since if there

were any significant differences between groups regarding age and education, that could be a source of bias and would cast doubt on the validity of other comparisons between groups emerging from the analysis of *N-back* task responses [81]. In Table 1 we show the average demographic data (gender distribution, mean and standard error of age and years of education) of the three groups. One-way ANOVA did not reveal significant group differences neither in age ($F = 1.39$, $p = 0.2565$) nor in years of education ($F = 0.49$, $p = 0.618$). Regarding gender distribution, the AD group has proportionally less females than the MCI and HE groups, but we do not see this as an issue, since recent research on large databases has shown men and women with AD performing similarly in the great majority of neuropsychological tests [81].

N-back Behavioural Results

The primary goal of this study is to explore if event-related potentials (ERP) together with (de)synchronisation (ERD/ERS) can be used to distinguish between healthy controls, MCI and AD patients. However, it is also important to investigate the behavioural responses (reaction time and accuracy in match/non-match discrimination) for both the match and non-match trials because, if these measures alone were enough to make a clear distinction between groups, there is no need to further analyse electrophysiological measures. Since the mental effort in the *N-back* task increases with an increase in N, we have observed that the number of correct answers decreased substantially with increasing N, as can be seen in Table 2, where we show the average performance (reaction time in ms and accuracy in % correct responses) of each group for both the match and non-match tasks. Just the opposite, there was a steady increase in the reaction times of all participants with greater memory load.

In Table 3 we display the results of post-hoc multiple-comparisons following one-way ANOVA tests, using diagnosis (HE, MCI or AD) as a factor and keeping constant the memory load ($N = 0, 1, 2$) and the match/non-match type. Differences in reaction times were found only when $N = 1$ (match and non-match) and just for the ADxHE comparison. As for accuracy, we have found

several differences when comparing AD with HE (HE > AD) but only two in the ADxMCI comparison (MCI > AD). In figures 2 and 3, one can clearly see that both for the match- as for the non-match-type, reaction times rise and accuracies drop, respectively, for the three groups (HE, MCI and AD) as the memory load increases (from $N = 0$ to $N = 2$), as expected. To get an overview of the behavioural results in graphical form, we also show in the same figures the *N-back* tasks where significant differences (marked with an asterisk) were found in the pairwise group comparison tests (Bonferroni correction).

ERP Analysis

Since our ERP data did not have normal distribution, we used the nonparametric Kruskal Wallis test and observed significant differences in the ERP of the three groups (AD, MCI and HE) at several electrode locations. In order to know between which pairs of groups (AD vs. MCI, AD vs. HE and MCI vs. HE) there were real differences, statistical tests were performed for multiple comparisons using cluster analysis, which allowed us to find significant differences between the AD vs. HE and MCI vs. HE comparisons in *0-back* non-match, *1-back* non-match and *1-back* match tasks.

Table 4 lists all significant differences encountered on the #-level WM-task match (M#) and non-match (N#) trials after post-hoc comparisons using cluster correction. Most differences were found in the AD vs. HE group comparison for the N0, N1 and M1 tasks. However, several significant differences were also found in the MCI vs. HE comparison for the N1 and M1 tasks. No differences were found in ERP cluster analysis for the AD vs. MCI comparison.

Observing Table 4, it is interesting to note that, differently from AD patients, who present significant differences in the ERP both in the *0-back* and the *1-back* tasks, MCI patients, having less cognitive impairment than the AD subjects, have shown differences only for the *1-back* tasks, which are more demanding since they have a higher level of memory load. Finally, no differences were found when participants were performing the *2-back* tasks, probably because the memory load was so high that even the HE controls had difficulty to

properly perform the tasks.

Figure 4(a) shows the grand average ERP at parietal electrode P4 representative of all subjects during execution of the *0-back* non-match task; the post-stimulus time interval where ERP of HE controls is significantly higher than AD patients is highlighted in yellow. Similarly, in Fig. 4(b) one can see that at the same electrode there is also a significant difference between HE and MCI individuals, but now only when participants were performing the *1-back* non-match task.

ERD/ERS Analysis

Herein we show the frequency sub-bands, time intervals and scalp locations where significant group differences were found in the ERD/ERS analysis. Table 5 reports the results obtained in cluster analysis (post-hoc comparisons) for the "match" trials when participants performed the three *N-back* tasks. As can be seen in the table, the first level of memory load (*0-back*) elicited significant differences between the HE and MCI groups in the high-frequency gamma band. On the contrary, significant differences between HE and AD groups were shown in lower frequency bands (theta and delta) and for more demanding WM tasks (i.e., N=1 and 2).

Table 6, on the other hand, presents findings related to the "non-match" trials. As observed, MCI and AD groups showed significant (post-hoc) differences in the *0-back* task. HE and MCI, in turn, showed significant differences across frequency bands (delta, alpha, beta) and across all three WM task levels. On the other hand, the HE and AD groups did not show any significant differences under the non-match scenario.

Figure 5 depicts a representative grand average (from all participants) ERS/ERD pattern of the high-frequency sub-band gamma at the right temporal-parietal location TP8, where significant $ERD\%$ differences (highlighted in yellow) were observed for the HE vs. MCI post-hoc comparison with subjects performing the *0-back* match task. Figure 6, in turn, shows differences between MCI and AD groups on the low-frequency band theta at the left hemisphere (electrode T3),

when participants were performing the *0-back* non-match task.

Discussion

To the best of our knowledge, this is the second study combining ERP (in-phase evoked) and ERS/ERD (synchronized induced) responses to working memory tasks for both Alzheimer's and Mild Cognitive Impairment investigation, thus builds on the cross-sectional and longitudinal study performed by Missonnier *et al.* in 2007 [31]. Other research on the topic was done either with ERP alone [82, 30, 32] or only with ERS/ERD [83, 84]. Our first finding herein was that behavioural measures were not sufficient to discriminate groups, with reaction times separating only AD from HE and accuracy in the match/mismatch choice capable of distinguish both patient groups from controls, but unable to tell MCI apart from AD.

Regarding our results on in-phase evoked electrophysiological responses, they revealed that ERPs where able to differentiate patients (MCI and AD) from controls at latencies between 450 and 550 ms, with both patient groups showing reduced amplitude of the P450 component (Table 4 and Fig. 4). This is consistent with previous literature findings reporting alterations of the P450 wave on visual tasks related to working memory update [85, 86]. Although the P450 component is somehow different from the P300 component, since the latter is elicited in the context of an oddball task and the former in working memory tasks, some researchers did not formally differentiate them both [82]. Given that, since higher P300 amplitude has been always interpreted in literature [18, 21] as the subject having more attentional resources devoted to the task, our finding corroborates such interpretation because it means that patients (MCI and AD) present less attentional skills than healthy controls, as expected.

In a recent study (2016), Zunini *et al.* [82] used EEG recorded during visual *N-back* tasks to compare MCI patients to healthy older adults. Their ERP analysis revealed lower P450 (they called it P300) amplitudes in MCI for all theee *N-back* conditions ($N = 0, 1, 2$), a result quite similar to ours, with the difference

that theirs was a two-group study, as they did not evaluate AD patients.

Proceeding to synchronized induced responses, our findings in delta band showed AD patients during execution of *2-back* match trials with more ERD (more negative ERS) than HE controls at temporal and temporal-parietal electrodes. The same effect was observed at parietal and centro-parietal electrodes in the HE vs. MCI comparison (HE with more ERD than MCI). These results cannot be directly compared with previous literature, since most studies in this band used ERO instead of ERD and observed reduced delta ERO in both MCI and AD groups when compared to HE, with participants performing simple visual or auditory oddball tasks instead of working memory tasks [48, 49, 51, 50].

In our experiment we have found significant differences in theta band ERD/ERS patterns (match condition, Table 5) between HE and AD, but no differences were found on this band for the HE vs. MCI comparison. Similar to what happened in the case of delta band, these results cannot be directly compared with some important findings of previous literature because several studies on theta band used ERO instead of ERD [52, 54, 53]. Notwithstanding, in a relatively recent study, ERS analysis during an attention/prediction task has shown decreased theta ERS in the MCI group relative to controls [87]. Missonnier *et al.* (2007) obtained similar results with *N-back* tasks, where significant lowering of theta ERS for progressive MCI patients relative to stable MCI was found [31]. As such, we hypothesize that our study did not find any significant differences in the HE vs. MCI comparison on theta band probably because the MCI patients were likely stable. Since we did not monitor the cognitive decline of our MCI patients, we are not able at this time to validate this hypothesis. However, there is an important finding of our study that helps to corroborate this: we find significant differences between MCI and AD patients only on that very theta band, when participants were performing the *0-back* non-match task (Table 6). The reasoning goes as follows: as we did not find any difference between HE and MCI patients on theta band like previous studies [87, 31] did, but on the other hand found significant differences in the MCI vs. AD comparison on the same band, it seems that our MCI participants were closer to the HE than to the

AD group, thus unlikely to progress to AD in a short period of time, therefore they were probably stable MCI patients. Nevertheless, as we were not able to monitor the cognitive decline of the MCI patients include in this study, perhaps this effect was observed simply because it was a mixed group of MCI patients, some of which will remain stable and some that will progress, thus masking the effect due to heterogeneity within the group.

It has been extensively shown in the literature that alpha band rhythm presents desynchronization (ERD) over broad scalp regions in judgement and memory tasks [88, 89, 90, 91] performed by healthy individuals. More specifically, a previous study by Krause *et al.* [92] suggested that long-lasting desynchronization could be observed in the low alpha bands (i.e., 6-10 Hz) during a *2-back* task. In a previously mentioned study, Missonnier *et al.* [31] observed the effectiveness of beta-band ERD resultant from the visual *2-back* task to discriminate progressive MCI from stable MCI. The ERD (negative ERS) values we observed on alpha band when HE and MCI participants were performing the *1-back* match task (Table 5) corroborate such findings. Furthermore, it has also been previously reported that an increase in task complexity and/or attention results in greater ERD (more negative) magnitudes on high-frequency bands (alpha and beta) [93, 94], an effect also observed in this study, but only for the match tasks and just for the alpha band, with gamma band showing an opposite result (ERS instead of ERD) for HE in the match condition (Table 5).

Surprisingly, in the non-match condition, we observed that MCI patients presented greater alpha ERD than HE controls, who in fact presented ERS (Table 6), at frontal and fronto-parietal scalp locations, which was just the opposite of what we have found in the match trials, where HE have more ERD than MCI at frontal, central and occipital electrodes (Table 5). Such opposite findings could be due to the fact that, based on our behavioural results (Table 2), the non-match condition seems to be a bit easier than the match condition, since HE participants had better performance (accuracy) in the former one. Since a previous study [92] found long-lasting alpha ERD in a high-demanding memory task (*2-back* task), it is just consistent that a least demanding task (the

non-match condition, in our case) would present ERS instead of ERD. However, this somehow unexpected result in the *2-back* non-match trials (MCI with more alpha ERD than HE) was similar to the findings of Babiloni et al., who showed that AD and vascular dementia (VaD) patients have stronger alpha ERD peak when compared to healthy elderly [55].

Interestingly, in the match condition (Table 5), several significant differences were found in the HE vs. MCI and in the HE vs. AD post-hoc comparisons, but none were found between the AD and MCI groups. Such findings suggest that ERD/ERS during *N-back* match tasks could potentially be used for early MCI diagnosis or for improved AD diagnosis, but not for differentiating MCI from AD. Similar findings have been obtained with an auditory-verbal Sternberg memory task [95], where significant alpha ERD/ERS differences were found between the control and MCI groups during the encoding phase and between the control and AD groups during retrieval [38].

In beta band we found differences between HE and MCI only in the non-match condition (*0-back* task), with patients presenting ERD and controls showing ERS at temporal and temporal-parietal electrodes (Table 6). As for gamma, exactly the same result was observed (HE with ERS and MCI with ERD) for the same *0-back* task and at the same scalp locations, but now just for the match trials. Comparing our results to previous literature, in a three-group (HE, MCI and AD) study somehow similar to ours and also using working memory tasks, Kurimoto et al. [57] found AD patients with reduced beta ERD in the right central area compared to HE, and reduced gamma ERD in the left prefrontal and medial parietal cortex compared to MCI during during execution of a modified version of the Sternberg's memory recognition task [95]. These results in beta and gamma bands are quite different from ours, perhaps because herein we used *N-back* tasks instead of Sternberg's task and calculated ERS/ERD according to Pfurtscheller's methodology [39], which completely removed the in-phase evoked responses.

Finally, since we have recently published an ERS/ERD study [20] using the same database we used in this paper, but without removing the in-phase evoked

response as we did herein, we must now compare the findings of both studies. The first remarkable difference between the results of that publication [20] and the findings of this one is we did not find any significant difference between patients (MCI and AD) and controls (HE) in the low-frequency delta and theta bands in our previous investigation. Just the opposite, in this study we got plenty of differences in delta for the MCI vs. HE comparison and in theta the MCI vs. AD comparisons in the non-match condition (Table 6). Also, several differences between HE controls and AD patients in both bands were found in the match trials (Table 5). Such mismatch between the studies results can only be explained by the fact that the in-phase evoked response, which was not removed in our previous study [20], has somehow masked the differences between groups in these low-frequency bands.

Regarding the high-frequency alpha, beta and gamma bands, in our 2017 paper [20] we found alpha ERD differences between patients and controls (HE ERD > MCI and AD ERD) in just a few electrodes and only when participants were performing the *2-back* match task, while herein we found similar differences (HE ERD > MCI ERD) in the match condition at much more scalp locations. However, as mentioned above, in this study we found and opposite result (HE ERD < MCI ERD) in the non-match trials, an effect that can only be explained (again) by the different methodologies we used to calculate ERS/ERD responses. An opposite result was also observed in the beta band: in our previous ERS/ERD study [20] we had HE ERD > MCI ERD in the *0-back* non-match task, while herein we have HE ERD < MCI ERD exactly in the same condition. Lastly, in this study we got ERS/ERD gamma differences between HE and MCI (HE ERD < MCI ERD) in just a few temporal and temporal-parietal electrodes and only in the match trials, while in our previous study [20] we got plenty of gamma differences both in the match as well as in the non-match condition. In this case, however, the findings of both studies pointed in the same direction, with HE controls presenting less gamma ERD than patients.

A limitation of our study is that, since we did not evaluate patients suffering from other types of dementia, we cannot comment on whether these findings

would differentiate AD/MCI from other causes of cognitive impairment. Another limitation comes from the fact our sample was small, so tests over larger databases would be useful to further validate our results. In summary, our main findings were: 1) behavioral measures (reaction time and accuracy on match/mismatch judgement) were not enough to fully differentiate the three groups, since no differences were found in the MCI vs. AD comparison; 2) ERP analysis, while important because it corroborated the recent (2016) research result [82] of P450 reduction for MCI (and AD too, in our study), also did not find any difference between MCI and AD patients; 3) ERS/ERD analysis was the most valuable because it showed significant differences in all three group comparisons (HE vs. MCI, HE vs. AD and MCI vs. AD). The distinction between MCI and HE our ERS/ERD analyses have provided means that responses to a working memory (*N-back*) task could be useful for early MCI diagnosis. On the other hand, the differentiation the same analyses provided between MCI and AD will probably also help for assessing the likelihood of MCI progression to AD, after such differences were further validated by a longitudinal study. Finally, in order to verify the true discriminating power of the ERP and ERS/ERD features derived herein, it would be interesting to employ such features to train an automatic three-class (HE, MCI and AD) classifier (using machine learning techniques) and evaluate the results in terms of sensibility and specificity for MCI and AD early diagnosis.

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References

References

[1] S. E. Black, S. Gauthier, W. Dalziel, R. Keren, J. Correia, H. Hew, C. Binder, Canadian Alzheimer's disease caregiver survey: baby-boomer caregivers and burden of care, Int J Geriatr Psychiatry 25 (8) (2010) 807–13. doi:10.1002/gps.2421.

[2] R. C. Petersen, G. E. Smith, S. C. Waring, R. J. Ivnik, E. G. Tangalos, E. Kokmen, Mild cognitive impairment: clinical characterization and outcome, Arch Neurol 56 (3) (1999) 303–8.

[3] R. C. Petersen, J. C. Stevens, M. Ganguli, E. G. Tangalos, J. L. Cummings, S. T. DeKosky, Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). report of the quality standards subcommittee of the american academy of neurology, Neurology 56 (9) (2001) 1133–42.

[4] K. Tifratene, P. Robert, A. Metelkina, C. Pradier, J. F. Dartigues, Progression of mild cognitive impairment to dementia due to ad in clinical settings, Neurology 85 (4) (2015) 331–8. doi:10.1212/WNL.0000000000001788.

[5] K. Budolfson, M. Malek-Ahmadi, C. M. Belden, J. Powell, K. Davis, S. Jacobson, M. N. Sabbagh, Neuropsychological correlates of the Alzheimer's questionnaire, Journal of Alzheimer's disease : JADdoi: 10.3233/jad-142388.
URL http://dx.doi.org/10.3233/JAD-142388

[6] W. Thies, L. Bleiler, Alzheimer's Association, 2013 alzheimer's disease facts and figures, Alzheimers Dement 9 (2) (2013) 208–45. doi:10.1016/j.jalz.2013.02.003.

[7] C. Babiloni, C. D. Percio, R. Lizio, G. Noce, S. Lopez, A. Soricelli, R. Ferri, F. Nobili, D. Arnaldi, F. Famà, D. Aarsland, F. Orzi, C. Buttinelli, F. Giubilei, M. Onofrj, F. Stocchi, P. Stirpe, P. Fuhr, U. Gschwandtner, G. Ransmayr, H. Garn, L. Fraioli, M. Pievani, G. B. Frisoni, F. D'Antonio, C. D. Lena, B. Güntekin, L. Hanoğlu, E. Başar, G. Yener, D. D. Emek-Savaş, A. I. Triggiani, R. Franciotti, J. P. Taylor, L. Vacca, M. F. D. Pandis, L. Bonanni, Abnormalities of Resting State Functional Cortical Connectivity In Patients With Dementia Due To Alzheimer's and Lewy Body Diseases: An EEG Study, Neurobiology of Agingdoi:https://doi.org/10.1016/j.neurobiolaging.2017.12.023. URL http://www.sciencedirect.com/science/article/pii/S0197458017304207

[8] S. Hulbert, H. Adeli, Eeg/meg- and imaging-based diagnosis of alzheimer's disease, Rev Neurosci 24 (6) (2013) 563–76. doi:10.1515/revneuro-2013-0042.

[9] J. Dauwels, F. Vialatte, A. Cichocki, Diagnosis of alzheimer's disease from eeg signals: where are we standing?, Curr Alzheimer Res 7 (6) (2010) 487–505.

[10] J. Jeong, Eeg dynamics in patients with alzheimer's disease, Clin Neurophysiol 115 (7) (2004) 1490–505. doi:10.1016/j.clinph.2004.01.001.

[11] E. C. van Straaten, P. Scheltens, A. A. Gouw, C. J. Stam, Eyes-closed task-free electroencephalography in clinical trials for alzheimer's disease: an emerging method based upon brain dynamics, Alzheimers Res Ther 6 (9) (2014) 86. doi:10.1186/s13195-014-0086-x.

[12] P. A. M. Kanda, L. R. Trambaiolli, A. C. Lorena, F. J. Fraga, L. F. I. Basile, R. Nitrini, R. Anghinah, Clinician's road map to wavelet EEG as an Alzheimer's disease biomarker, Clin EEG Neurosci 45 (2) (2014) 104–12. doi:10.1177/1550059413486272.

[13] F. J. Fraga, T. H. Falk, L. R. Trambaiolli, E. F. Oliveira, W. H. L. Pinaya, P. A. M. Kanda, R. Anghinah, Towards an EEG-based biomarker for Alzheimer's disease: Improving amplitude modulation analysis features, in: 2013 IEEE International Conference on Acoustics, Speech and Signal Processing, 2013, pp. 1207–1211. doi:10.1109/ICASSP.2013.6637842.

[14] R. Cassani, T. H. Falk, F. J. Fraga, P. A. Kanda, R. Anghinah, Towards automated EEG-Based Alzheimer's disease diagnosis using relevance vector machines, in: 5th ISSNIP-IEEE Biosignals and Biorobotics Conference (2014): Biosignals and Robotics for Better and Safer Living (BRC), 2014, pp. 1–6. doi:10.1109/BRC.2014.6880978.

[15] P. A. M. Kanda, E. F. Oliveira, F. J. Fraga, EEG epochs with less alpha rhythm improve discrimination of mild Alzheimer's, Computer Methods and Programs in Biomedicine 138 (2017) 13–22. doi:https://doi.org/10.1016/j.cmpb.2016.09.023.
URL http://www.sciencedirect.com/science/article/pii/S0169260716305314

[16] M. M. A. Engels, W. M. van der Flier, C. J. Stam, A. Hillebrand, P. Scheltens, E. C. W. van Straaten, Alzheimer's disease: The state of the art in resting-state magnetoencephalography, Clin Neurophysiol 128 (8) (2017) 1426–1437. doi:10.1016/j.clinph.2017.05.012.

[17] C. Morrison, S. Rabipour, F. Knoefel, C. Shepard, Auditory event-related potentials in mild cognitive impairment and alzheimer's disease: A literature review, Curr Alzheimer Resdoi:10.2174/1567205015666180123123209.

[18] R. V. Pedroso, F. J. Fraga, D. I. Corazza, C. A. A. Andreatto, F. G. d. M. Coelho, J. R. Costa, R. F. Santos-Galduróz, P300 latency and amplitude in Alzheimer's disease: a systematic review, Brazilian Journal of Otorhinolaryngology 78 (2012) 126–132.

[19] G. Q. Mamani, F. J. Fraga, G. Tavares, E. Johns, N. D. Phillips, EEG-based biomarkers on working memory tasks for early diagnosis of Alzheimer's disease and mild cognitive impairment, in: 2017 IEEE Healthcare Innovations and Point of Care Technologies (HI-POCT), 2017, pp. 237–240. doi:10.1109/HIC.2017.8227628.

[20] F. J. Fraga, L. A. Ferreira, T. H. Falk, E. Johns, N. D. Phillips, Event-related synchronisation responses to n-back memory tasks discriminate between healthy ageing, mild cognitive impairment, and mild Alzheimer's disease, 2017 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP) (2017) 964–968doi:10.1109/ICASSP.2017.7952299.

[21] R. V. Pedroso, F. J. Fraga, C. Ayán, J. Cancela Carral, L. Scarpari, R. F. Santos-Galduróz, Effects of physical activity on the P300 component in elderly people: a systematic review, Psychogeriatrics (2017) n/a–n/adoi:10.1111/psyg.12242.
URL http://dx.doi.org/10.1111/psyg.12242

[22] R. Ishii, L. Canuet, Y. Aoki, M. Hata, M. Iwase, S. Ikeda, K. Nishida, M. Ikeda, Healthy and pathological brain aging: From the perspective of oscillations, functional connectivity, and signal complexity, Neuropsychobiology 75 (4) (2017) 151–161. doi:10.1159/000486870.

[23] M. J. Kas, B. Penninx, B. Sommer, A. Serretti, C. Arango, H. Marston, A quantitative approach to neuropsychiatry: The why and the how, Neurosci Biobehav Revdoi:10.1016/j.neubiorev.2017.12.008.

[24] C. Laske, H. R. Sohrabi, S. M. Frost, K. López-de Ipiña, P. Garrard, M. Buscema, J. Dauwels, S. R. Soekadar, S. Mueller, C. Linnemann, S. A. Bridenbaugh, Y. Kanagasingam, R. N. Martins, S. E. O'Bryant, Innovative diagnostic tools for early detection of alzheimer's disease, Alzheimers Dement 11 (5) (2015) 561–78. doi:10.1016/j.jalz.2014.06.004.

[25] M. A. Hird, P. Egeto, C. E. Fischer, G. Naglie, T. A. Schweizer, A systematic review and meta-analysis of on-road simulator and cognitive driving assessment in Alzheimer's disease and mild cognitive impairment, J Alzheimers Disdoi:10.3233/JAD-160276.

[26] E. K. Johns, N. A. Phillips, S. Belleville, D. Goupil, L. Babins, N. Kelner, B. Ska, B. Gilbert, F. Massoud, C. de Boysson, H. D. Duncan, H. Chertkow, The profile of executive functioning in amnestic mild cognitive impairment: disproportionate deficits in inhibitory control, J Int Neuropsychol Soc 18 (3) (2012) 541–55. doi:10.1017/S1355617712000069.

[27] D. P. Salmon, M. W. Bondi, Neuropsychological assessment of dementia, Annu Rev Psychol 60 (2009) 257–82. doi:10.1146/annurev.psych.57.102904.190024.

[28] A. L. W. Bokde, M. Ewers, H. Hampel, Assessing neuronal networks: understanding Alzheimer's disease, Prog Neurobiol 89 (2) (2009) 125–33. doi:10.1016/j.pneurobio.2009.06.004.

[29] R. Duara, D. A. Loewenstein, M. T. Greig, E. Potter, W. Barker, A. Raj, J. Schinka, A. Borenstein, M. Schoenberg, Y. Wu, J. Banko, H. Potter, Pre-MCI and MCI: neuropsychological, clinical, and imaging features and progression rates, Am J Geriatr Psychiatry 19 (11) (2011) 951–60. doi:10.1097/JGP.0b013e3182107c69.

[30] R. M. Chapman, J. W. McCrary, M. N. Gardner, T. C. Sandoval, M. D. Guillily, L. A. Reilly, E. DeGrush, Brain ERP components predict which individuals progress to Alzheimer's disease and which do not, Neurobiology of Aging 32 (2011) 1742–1755. doi:DOI10.1016/j.neurobiolaging.2009.11.010.

[31] P. Missonnier, M. P. Deiber, G. Gold, F. R. Herrmann, P. Millet, A. Michon, L. Fazio-Costa, V. Ibanez, P. Giannakopoulos, Working memory

load-related electroencephalographic parameters can differentiate progressive from stable mild cognitive impairment, Neuroscience 150 (2007) 346–356. doi:DOI10.1016/j.neuroscience.2007.09.009.

[32] P. Missonnier, G. Gold, L. Fazio-Costa, J.-P. Michel, R. Mulligan, A. Michon, V. Ibáñez, P. Giannakopoulos, Early event-related potential changes during working memory activation predict rapid decline in mild cognitive impairment, J Gerontol A Biol Sci Med Sci 60 (5) (2005) 660–6.

[33] D. V. Moretti, C. Babiloni, G. Binetti, E. Cassetta, G. Dal Forno, F. Ferreric, R. Ferri, B. Lanuzza, C. Miniussi, F. Nobili, et al., Individual analysis of EEG frequency and band power in mild Alzheimer's disease, Clinical Neurophysiology 115 (2) (2004) 299–308.

[34] L. R. Trambaiolli, A. C. Lorena, F. J. Fraga, P. A. M. Kanda, R. Anghinah, R. Nitrini, Improving Alzheimer's disease diagnosis with machine learning techniques, Clin EEG Neurosci 42 (3) (2011) 160–5.

[35] R. Cassani, T. H. Falk, F. J. Fraga, P. A. M. Kanda, R. Anghinah, The effects of automated artifact removal algorithms on electroencephalography-based Alzheimer's disease diagnosis, Front Aging Neurosci 6 (2014) 55. doi:10.3389/fnagi.2014.00055.

[36] T. H. Falk, F. J. Fraga, L. Trambaiolli, R. Anghinah, EEG amplitude modulation analysis for semi-automated diagnosis of Alzheimer's disease, EURASIP Journal on Advances in Signal Processing 2012 (1) (2012) 192. doi:10.1186/1687-6180-2012-192.
URL https://doi.org/10.1186/1687-6180-2012-192

[37] F. J. Fraga, T. H. Falk, P. A. M. Kanda, R. Anghinah, Characterizing Alzheimer's disease severity via resting-awake EEG amplitude modulation analysis, PLoS One 8 (8) (2013) e72240. doi:10.1371/journal.pone.0072240.

[38] M. Karrasch, M. Laine, J. Rinne, P. Rapinoja, E. Sinerva, C. Krause, Brain oscillatory responses to an auditory-verbal working memory task in mild cognitive impairment and Alzheimer's disease, International Journal of Psychophysiology 59 (2006) 168–178. doi:DOI10.1016/j.ijpsycho.2005.04.006.

[39] G. Pfurtscheller, F. da Silva, Event-related EEG/MEG synchronization and desynchronization: basic principles, Clinical Neurophysiology 110 (1999) 1842–1857.

[40] P. C. M. Vijn, B. W. van Dijk, H. Spekreijse, Visual stimulation reduces EEG activity in man, Brain Research 550 (1) (1991) 49–53. doi:https://doi.org/10.1016/0006-8993(91)90403-I.
URL http://www.sciencedirect.com/science/article/pii/000689939190403I

[41] C. Başar-Eroglu, D. Strüber, M. Schürmann, M. Stadler, E. Başar, Gamma-band responses in the brain: a short review of psychophysiological correlates and functional significance, International Journal of Psychophysiology 24 (1-2) (1996) 101–112. doi:10.1016/S0167-8760(96)00051-7.
URL https://www.sciencedirect.com/science/article/pii/S0167876096000517?via{%}3Dihub

[42] C. S. Herrmann, M. H. J. Munk, A. K. Engel, Cognitive functions of gamma-band activity: memory match and utilization, Trends Cogn Sci 8 (8) (2004) 347–55. doi:10.1016/j.tics.2004.06.006.

[43] M. D'Esposito, G. K. Aguirre, E. Zarahn, D. Ballard, R. K. Shin, J. Lease, Functional mri studies of spatial and nonspatial working memory, Brain Res Cogn Brain Res 7 (1) (1998) 1–13.

[44] A. Baddeley, Working memory: looking back and looking forward, Nat Rev Neurosci 4 (10) (2003) 829–39. doi:10.1038/nrn1201.

[45] F. Collette, M. Hogge, E. Salmon, M. Van der Linden, Exploration of the neural substrates of executive functioning by functional neuroimaging, Neuroscience 139 (1) (2006) 209–21. doi:10.1016/j.neuroscience.2005.05.035.

[46] T. Braver, J. Cohen, L. Nystrom, J. Jonides, E. Smith, D. Noll, A parametric study of prefrontal cortex involvement in human working memory, Neuroimage 5 (1997) 49–62.

[47] E. Başar, C. Başar-Eroğlu, B. Güntekin, G. G. Yener, Brain's alpha, beta, gamma, delta, and theta oscillations in neuropsychiatric diseases: proposal for biomarker strategies, Suppl Clin Neurophysiol 62 (2013) 19–54.

[48] G. Caravaglios, E. Costanzo, F. Palermo, E. G. Muscoso, Decreased amplitude of auditory event-related delta responses in Alzheimer's diseasedoi:10.1016/j.ijpsycho.2008.04.004.
URL https://ac.els-cdn.com/S0167876008001050/1-s2.0-S0167876008001050-main.pdf?{_}tid=3f98be61-95ed-4541-9711-cb46d2939bc8{&}acdnat=1523474734{_}5be169c487668e6a44bcf5d66d993c56

[49] G. G. Yener, B. Güntekin, D. N. Örken, E. Tülay, H. Forta, E. Başar, Auditory delta event-related oscillatory responses are decreased in Alzheimer's disease, in: Behavioural Neurology, 2012. doi:10.3233/BEN-2012-0344.

[50] P. Kurt, D. D. Emek-Savaş, K. Batum, B. Turp, B. Güntekin, S. Karşdağ, G. G. Yener, Patients with mild cognitive impairment display reduced auditory event-related delta oscillatory responses, Behav Neurol 2014 (2014) 268967. doi:10.1155/2014/268967.

[51] G. G. Yener, P. Kurt, D. D. Emek-Savaş, B. Güntekin, E. Başar, Reduced visual event-related delta oscillatory responses in amnestic mild cognitive impairment, Journal of Alzheimer's Disease 37 (4) (2013) 759–767. doi:10.3233/JAD-130569.

[52] G. Yener, B. Güntekin, A. Öniz, E. Başar, Increased frontal phase-locking of event-related theta oscillations in Alzheimer patients treated with cholinesterase inhibitors, International Journal of Psychophysiology 64 (1) (2007) 46–52. doi:10.1016/J.IJPSYCHO.2006.07.006.
URL https://www.sciencedirect.com/science/article/pii/S0167876006002121?via{%}3Dihub

[53] M.-P. Deiber, V. Ibañez, P. Missonnier, F. Herrmann, L. Fazio-Costa, G. Gold, P. Giannakopoulos, Abnormal-induced theta activity supports early directed-attention network deficits in progressive MCI, Neurobiology of Aging 30 (2009) 1444–1452. doi:10.1016/j.neurobiolaging.2007.11.021.
URL http://www.neurobiologyofaging.org/article/S0197-4580(07)00453-8/pdf

[54] T. D. Cummins, M. Broughton, S. Finnigan, Theta oscillations are affected by amnestic mild cognitive impairment and cognitive load, International Journal of Psychophysiology 70 (1) (2008) 75–81. doi:10.1016/J.IJPSYCHO.2008.06.002.
URL https://www.sciencedirect.com/science/article/pii/S0167876008006995?via{%}3Dihub

[55] C. Babiloni, E. Cassetta, P. Chiovenda, C. Del Percio, M. Ercolani, D. V. Moretti, F. Moffa, P. Pasqualetti, V. Pizzella, G. L. Romani, F. Tecchio, F. Zappasodi, P. M. Rossini, Alpha rhythms in mild dements during visual delayed choice reaction time tasks: A MEG study, Brain Research Bulletin 65 (6) (2005) 457–470. doi:10.1016/J.BRAINRESBULL.2005.01.014.
URL https://www.sciencedirect.com/science/article/pii/S0361923005000742?via{%}3Dihub

[56] M. P. Deiber, H. B. Meziane, R. Hasler, C. Rodriguez, S. Toma, M. Ackermann, F. Herrmann, P. Giannakopoulos, Attention and Working Memory-Related EEG Markers of Subtle Cognitive Deterioration in Healthy El-

derly Individuals, Journal of Alzheimer's Disease 47 (2) (2015) 335–349. doi:10.3233/JAD-150111.

[57] R. Kurimoto, R. Ishii, L. Canuet, K. Ikezawa, M. Iwase, M. Azechi, Y. Aoki, S. Ikeda, T. Yoshida, H. Takahashi, T. Nakahachi, H. Kazui, M. Takeda, Induced oscillatory responses during the Sternberg's visual memory task in patients with Alzheimer's disease and mild cognitive impairment, NeuroImage 59 (4) (2012) 4132–4140. doi:10.1016/J.NEUROIMAGE.2011.10.061.
URL https://www.sciencedirect.com/science/article/pii/S1053811911012250

[58] B. Güntekin, D. Durusu Emek-Savaş, P. Kurt, G. G. Yener, E. Başar, Beta oscillatory responses in healthy subjects and subjects with mild cognitive impairment doi:10.1016/j.nicl.2013.07.003.
URL https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3791295/pdf/main.pdf

[59] E. Başar, D. D. Emek-Savaş, B. Güntekin, G. G. Yener, Delay of cognitive gamma responses in Alzheimer's disease, NeuroImage: Clinical 11 (2016) 106–115. doi:10.1016/J.NICL.2016.01.015.
URL https://www.sciencedirect.com/science/article/pii/S221315821630016X

[60] A. Mouraux, G. D. Iannetti, Across-trial averaging of event-related EEG responses and beyond, Magn Reson Imaging 26 (7) (2008) 1041–54. doi:10.1016/j.mri.2008.01.011.

[61] L. Leocani, G. Comi, Movement-related event-related desynchronization in neuropsychiatric disorders, Prog Brain Res 159 (2006) 351–66. doi:10.1016/S0079-6123(06)59023-5.

[62] G. Pfurtscheller, C. Andrew, Event-related changes of band power and coherence: methodology and interpretation, J Clin Neurophysiol 16 (6) (1999) 512–9.

[63] J. A. Yesavage, T. L. Brink, T. L. Rose, O. Lum, V. Huang, M. Adey, V. O. Leirer, Development and validation of a geriatric depression screening scale: a preliminary report, J Psychiatr Res 17 (1) (1982) 37–49.

[64] Z. S. Nasreddine, N. A. Phillips, V. Bédirian, S. Charbonneau, V. Whitehead, I. Collin, J. L. Cummings, H. Chertkow, The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment, J Am Geriatr Soc 53 (4) (2005) 695–9. doi:10.1111/j.1532-5415.2005.53221.x.

[65] B. Winblad, K. Palmer, M. Kivipelto, V. Jelic, L. Fratiglioni, L.-O. Wahlund, A. Nordberg, L. Bäckman, M. Albert, O. Almkvist, H. Arai, H. Basun, K. Blennow, M. de Leon, C. DeCarli, T. Erkinjuntti, E. Giacobini, C. Graff, J. Hardy, C. Jack, A. Jorm, K. Ritchie, C. van Duijn, P. Visser, R. C. Petersen, Mild cognitive impairment–beyond controversies, towards a consensus: report of the international working group on mild cognitive impairment, J Intern Med 256 (3) (2004) 240–6. doi:10.1111/j.1365-2796.2004.01380.x.

[66] R. C. Petersen, R. O. Roberts, D. S. Knopman, B. F. Boeve, Y. E. Geda, R. J. Ivnik, G. E. Smith, C. R. Jack, Jr, Mild cognitive impairment: ten years later, Arch Neurol 66 (12) (2009) 1447–55. doi:10.1001/archneurol.2009.266.

[67] G. McKhann, D. Drachman, M. Folstein, R. Katzman, D. Price, E. M. Stadlan, Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease, Neurology 34 (7) (1984) 939–44.

[68] A. Delorme, S. Makeig, EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis, J Neurosci Methods 134 (1) (2004) 9–21. doi:10.1016/j.jneumeth.2003.10.009.

[69] G. Pfurtscheller, Event-related synchronization (ERS) - an electrophysiological correlate of cortical areas at rest, Electroencephalography and Clinical Neurophysiology 83 (1992) 62–69.

[70] S. Sanei, J. Chambers, EEG signal processing, Wiley-Interscience, 2007.

[71] G. Pfurtscheller, B. Graimann, J. E. Huggins, S. P. Levine, L. A. Schuh, Spatiotemporal patterns of beta desynchronization and gamma synchronization in corticographic data during self-paced movement, Clinical Neurophysiology 114 (7) (2003) 1226–1236.

[72] B. Everitt, Cluster analysis, 5th Edition, Wiley series in probability and statistics, Wiley, Chichester, West Sussex, U.K., 2011.
URL http://catalogimages.wiley.com/images/db/jimages/9780470749913.jpg

[73] E. Maris, R. Oostenveld, Nonparametric statistical testing of EEG- and MEG-data, J Neurosci Methods 164 (1) (2007) 177–90. doi:10.1016/j.jneumeth.2007.03.024.

[74] Y. Xu, G. P. Sudre, W. Wang, D. J. Weber, R. E. Kass, Characterizing global statistical significance of spatiotemporal hot spots in magnetoencephalography/ electroencephalography source space via excursion algorithms, Stat Med 30 (23) (2011) 2854–66. doi:10.1002/sim.4309.

[75] D. M. Groppe, T. P. Urbach, M. Kutas, Mass univariate analysis of event-related brain potentials/fields ii: Simulation studies, Psychophysiology 48 (12) (2011) 1726–37. doi:10.1111/j.1469-8986.2011.01272.x.

[76] D. M. Groppe, T. P. Urbach, M. Kutas, Mass univariate analysis of event-related brain potentials/fields i: a critical tutorial review, Psychophysiology 48 (12) (2011) 1711–25. doi:10.1111/j.1469-8986.2011.01273.x.

[77] J. A. Urigüen, B. García-Zapirain, J. Artieda, J. Iriarte, M. Valencia, Comparison of background eeg activity of different groups of patients with id-

iopathic epilepsy using shannon spectral entropy and cluster-based permutation statistical testing, PLoS One 12 (9) (2017) e0184044. doi:10.1371/journal.pone.0184044.

[78] N. J. Williams, S. J. Nasuto, J. D. Saddy, Method for exploratory cluster analysis and visualisation of single-trial erp ensembles, J Neurosci Methods 250 (2015) 22–33. doi:10.1016/j.jneumeth.2015.02.007.

[79] T. Kanungo, D. M. Mount, N. S. Netanyahu, C. D. Piatko, R. Silverman, A. Y. Wu, An efficient k-means clustering algorithm: analysis and implementation, IEEE Transactions on Pattern Analysis and Machine Intelligence 24 (7) (2002) 881–892. doi:10.1109/TPAMI.2002.1017616.

[80] R. Oostenveld, P. Fries, E. Maris, J.-M. Schoffelen, Fieldtrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data, Computational Intelligence and Neuroscience 2011 (2011) 9. URL http://dx.doi.org/10.1155/2011/156869%]156869

[81] S. Weintraub, L. Besser, H. H. Dodge, M. Teylan, S. Ferris, F. C. Goldstein, B. Giordani, J. Kramer, D. Loewenstein, D. Marson, D. Mungas, D. Salmon, K. Welsh-Bohmer, X.-H. Zhou, S. D. Shirk, A. Atri, W. A. Kukull, C. Phelps, J. C. Morris, Version 3 of the alzheimer disease centers' neuropsychological test battery in the uniform data set (UDS), Alzheimer disease and associated disordersdoi:10.1097/wad.0000000000000223. URL https://doi.org/10.1097/WAD.0000000000000223

[82] R. A. López Zunini, F. Knoefel, C. Lord, F. Dzuali, M. Breau, L. Sweet, R. Goubran, V. Taler, Event-related potentials elicited during working memory are altered in mild cognitive impairment, Int J Psychophysiol 109 (2016) 1–8. doi:10.1016/j.ijpsycho.2016.09.012.

[83] P. Missonnier, G. Gold, F. R. Herrmann, L. Fazio-Costa, J.-P. Michel, M.-P. Deiber, A. Michon, P. Giannakopoulos, Decreased theta event-related

synchronization during working memory activation is associated with progressive mild cognitive impairment, Dement Geriatr Cogn Disord 22 (3) (2006) 250–9. doi:10.1159/000094974.

[84] M.-P. Deiber, V. Ibañez, P. Missonnier, F. Herrmann, L. Fazio-Costa, G. Gold, P. Giannakopoulos, Abnormal-induced theta activity supports early directed-attention network deficits in progressive MCI, Neurobiol Aging 30 (9) (2009) 1444–52. doi:10.1016/j.neurobiolaging.2007.11.021.

[85] S. E. Bruce, K. B. Werner, B. F. Preston, L. M. Baker, Improvements in concentration, working memory and sustained attention following consumption of a natural citicoline-caffeine beverage, Int J Food Sci Nutr 65 (8) (2014) 1003–7. doi:10.3109/09637486.2014.940286.

[86] H. A. D. Keage, C. R. Clark, D. F. Hermens, L. M. Williams, M. R. Kohn, S. Clarke, C. Lamb, D. Crewther, E. Gordon, ERP indices of working memory updating in ad/hd: differential aspects of development, subtype, and medication, J Clin Neurophysiol 25 (1) (2008) 32–41. doi:10.1097/WNP.0b013e318163ccc0.

[87] G. Caravaglios, E. G. Muscoso, G. Di Maria, E. Costanzo, Theta responses are abnormal in mild cognitive impairment: evidence from analysis of theta event-related synchronization during a temporal expectancy task, J Neural Transm 120 (7) (2013) 1093–107. doi:10.1007/s00702-012-0921-9.

[88] G. Pfurtscheller, W. Klimesch, Functional topography during a visuoverbal judgment task studied with event-related desynchronization mapping, J Clin Neurophysiol 9 (1) (1992) 120–31.

[89] W. Klimesch, H. Schimke, G. Pfurtscheller, Alpha frequency, cognitive load and memory performance, Brain Topogr 5 (3) (1993) 241–51.

[90] W. Klimesch, H. Schimke, J. Schwaiger, Episodic and semantic memory:

an analysis in the EEG theta and alpha band, Electroencephalogr Clin Neurophysiol 91 (6) (1994) 428–41.

[91] M. Sterman, D. Kaiser, B. Veigel, Spectral analysis of event-related EEG responses during short-term memory performance, Brain Topography 9 (1) (1996) 21–30. doi:10.1007/BF01191639.
URL http://dx.doi.org/10.1007/BF01191639

[92] C. M. Krause, L. Sillanmäki, M. Koivisto, C. Saarela, A. Häggqvist, M. Laine, H. Hämäläinen, The effects of memory load on event-related EEG desynchronization and synchronization, Clin Neurophysiol 111 (11) (2000) 2071–8.

[93] F. Boiten, J. Sergeant, R. Geuze, Event-related desynchronization: the effects of energetic and computational demands, Electroencephalogr Clin Neurophysiol 82 (4) (1992) 302–9.

[94] K. Dujardin, P. Derambure, L. Defebvre, J. L. Bourriez, J. M. Jacquesson, J. D. Guieu, Evaluation of event-related desynchronization (ERD) during a recognition task: effect of attention, Electroencephalogr Clin Neurophysiol 86 (5) (1993) 353–6.

[95] S. Sternberg, High-speed scanning in human memory, Science 153 (3736) (1966) 652–4.

Tables and Figures

Table 1: Group (HE, MCI and AD) mean and standard error estimates of demographic data (age and years of education) from subjects participating in the study. The number of participants and their gender distribution are displayed in the first and second rows.

Group	HE	MCI	AD
No. Particip.	27	21	15
No. Female	16	10	5
Age	77.6±1.0	79.9±1.1	79.7±1.3
Education	14.9±0.7	13.8±0.8	14.1±1.0

Table 2: Group (HE, MCI and AD) mean and standard error estimates of behavioural results (reaction time in ms and accuracy in % correct responses) from participants performing the match and non-match *N-back* ($N = 0, 1, 2$) tasks.

Measure	Reaction time (ms)			Correct responses (%)		
Group	HE	MCI	AD	HE	MCI	AD
0-back match	487.4±13.7	499.5±15.5	491.6±17.7	96.5±3.0	94.8±3.4	79.7±3.9
1-back match	539.7±21.4	601.4±24.3	638.7±28.8	90.7±2.3	82.9±2.6	76.5±3.1
2-back match	720.4±38.1	756.9±43.4	797.8±48.6	76.5±3.4	65.9±3.9	60.7±4.4
0-back non-match	497.7±13.9	504.9±15.8	515.5±18.1	95.3±1.2	94.4±1.4	94.2±1.6
1-back non-match	580.5±26.3	667.0±29.8	690.9±35.3	95.5±2.1	88.5±2.4	83.2±2.9
2-back non-match	737.4±36.9	787.4±42.1	846.3±47.1	80.1±3.7	68.7±4.2	49.1±4.8

Table 3: Pairwise group comparison (p-values after Bonferroni correction) of behavioural performance (reaction time and accuracy) of participants performing the match and non-match *N-back* ($N = 0, 1, 2$) tasks. Only comparisons with significant differences ($p < 0.05$) are shown.

Measure	Reaction time (ms)		Correct responses (%)	
Task	ADxHE p	ADxMCI p	ADxHE p	ADxMCI p
0-back match	—	—	0.00356	0.01542
1-back match	0.02320	—	0.00138	—
2-back match	—	—	0.01765	—
0-back non-match	—	—	—	—
1-back non-match	0.04451	—	0.00324	—
2-back non-match	—	—	0.00001	0.00982

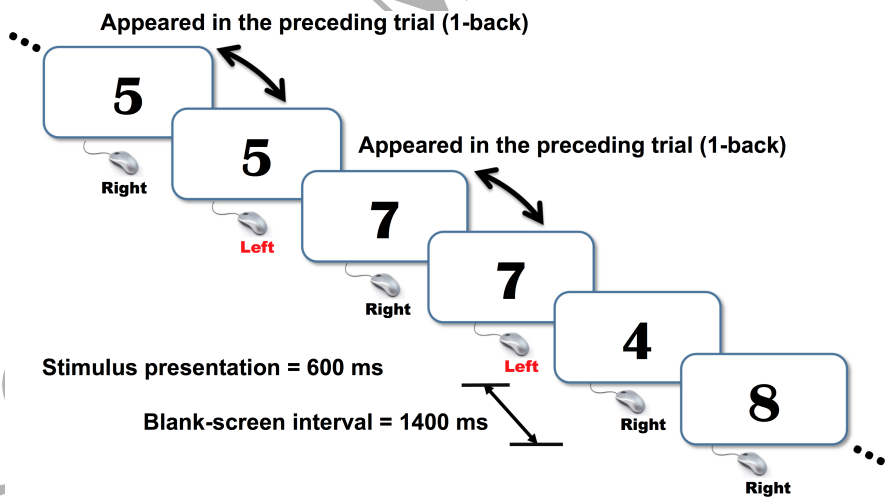

Figure 1: Illustration of *N-back* ($N = 0, 1, 2$) task execution for the case $N = 1$, where the participant should press the left button after the two match trials (digits 5 and 7) and the right button after the four non-match trials (digits 5, 7, 4 and 8)

Table 4: Mean group (HE, MCI and AD) potentials (μV), time intervals (ms) and electrode locations where significant ERP differences in post-hoc group comparisons (cluster analysis) were found during execution of of *N-back* tasks for match (M#) and Non-match (N#) conditions after cluster correction, where # is the WM load level of the task.

Task	Interval (ms)	Electrode	HE	MCI	AD
M1	824-920	P3	-0.69		0.19
	816-920	Pz	-0.85		0.21
	864-896	P4	-0.49		0.43
	824-864	P3	-0.79	0.01	
	816-888	Pz	-0.85	0.04	
	816-848	P4	-0.48	0.30	
N0	472-496	C4	0.99		0.34
	464-552	CPz	1.70		0.51
	448-560	CP4	1.16		0.28
	480-544	P3	0.96		0.12
	440-552	Pz	1.39		0.22
	456-544	P4	1.09		0.13
N1	504-600	C4	0.40		-0.28
	496-592	CPz	1.00		0.17
	496-624	CP4	0.58		-0.37
	496-600	Pz	0.81		-0.03
	472-576	P4	0.59		-0.31
	480-584	CPz	0.95	0.24	
	512-576	CP4	0.72	0.15	
	488-536	P3	0.59	-0.01	
	488-544	Pz	0.88	0.07	
	488-576	P4	0.61	0.01	

Table 5: Frequency sub-bands, time intervals and electrode locations where we found $ERS\%$ differences (negative percentages indicate ERD) in the post-hoc group comparisons for "match" trials when participants were performing the *0,1,2-back* tasks.

Task	Sub-band	Interval (ms)	Electrode	HE $ERS\%$	MCI $ERS\%$	AD $ERS\%$
0-back	Gamma	560-616	T3	13.46	-6.15	
		528-584	TP7	9.90	-4.81	
		456-576	TP8	7.29	-9.13	
		520-576	T5	12.62	-5.96	
		456-560	T6	9.65	-8.35	
1-back	Theta	336-640	CP4	-42.06		-23.73
		120-616	T5	-48.75		-25.75
		176-480	P3	-46.69		-27.79
		336-376	P4	-40.38		-26.22
		384-432	T6	-45.75		-29.25
		160-424	O1	-46.89		-26.79
	Alpha	848-992	Fz	-56.07	-36.78	
		784-992	F4	-52.52	-31.03	
		808-992	C3	-54.79	-38.74	
		784-992	Cz	-49.68	-23.61	
		832-992	C4	-52.41	-36.45	
		776-992	O1	-61.10	-36.28	
		800-992	O2	-62.53	-38.19	
2-back	Delta	72-184	T3	-71.39		-54.27
		40-200	TP7	-71.56		-53.05
		152-232	TP8	-76.09		-65.02
		32-240	T5	-71.83		-59.28
		80-240	T6	-71.24		-57.96

Table 6: Frequency bands, time intervals and scalp locations where significant differences were observed between groups in cluster analysis for the non-match condition, when participants were performing the three-level *N-back* task.

Task	Sub-band	Interval (ms)	Electrode	HE *ERS*%	MCI *ERS*%	AD *ERS*%
0-back	Theta	112-448	FT7		-44.29	-26.96
		344-592	FT8		-48.80	-33.93
		136-480	T3		-43.05	-23.98
		136-424	T5		-46.72	-30.21
	Beta	176-592	FT8	5.35	-8.52	
		312-400	T3	3.50	-10.73	
		432-496	TP7	3.05	-9.66	
		440-736	TP8	2.44	-12.81	
		344-376	T5	3.55	-8.67	
		448-528	T6	-0.45	-16.97	
1-back	Delta	448-992	CP3	-63.67	-51.68	
		536-592	CPz	-56.79	-45.89	
		528-544	CP4	-54.57	-42.32	
		240-992	P3	-64.18	-48.49	
		272-304	Pz	-68.98	-61.73	
2-back	Alpha	288-536	FP1	17.83	-8.89	
		280-536	FPz	20.29	-12.03	
		304-528	FP2	15.98	-13.75	
		168-472	F7	18.50	-6.88	
		240-360	F3	16.34	-3.90	
		232-480	Fz	17.34	-6.64	
		288-416	F4	10.04	-10.07	

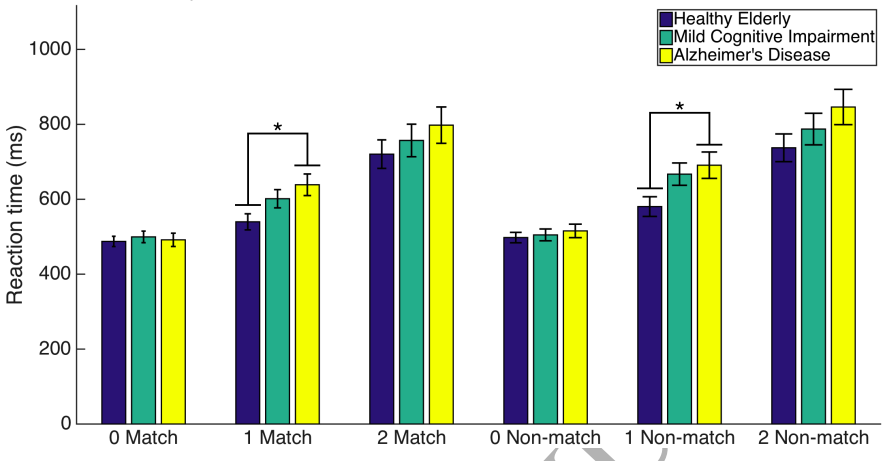

Figure 2: Average reaction times (in ms, with error bars) in match/non-match discrimination for each group (HE, MCI and AD) and *N-back* ($N = 0, 1, 2$) task. Post-hoc multiple-comparisons where significant differences were found are marked with an asterisk.

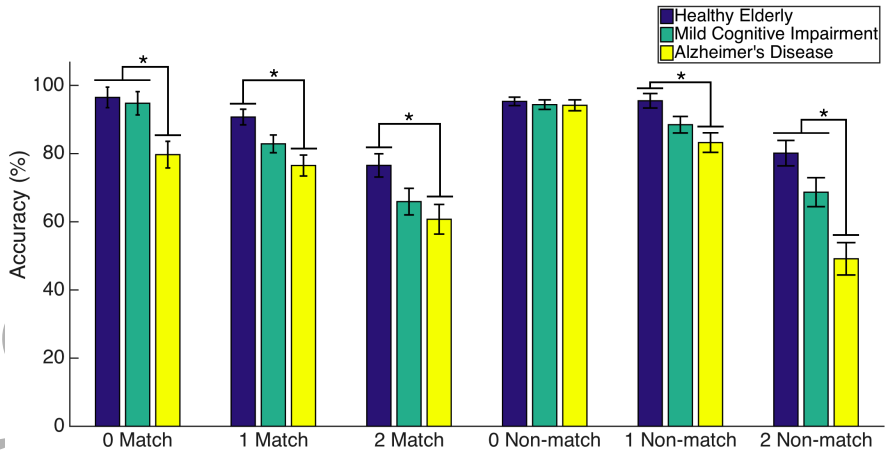

Figure 3: Average accuracy (in %, with error bars) in match/non-match discrimination for each group (HE, MCI and AD) and *N-back* ($N = 0, 1, 2$) task. Post-hoc multiple-comparisons where significant differences were found are marked with an asterisk.

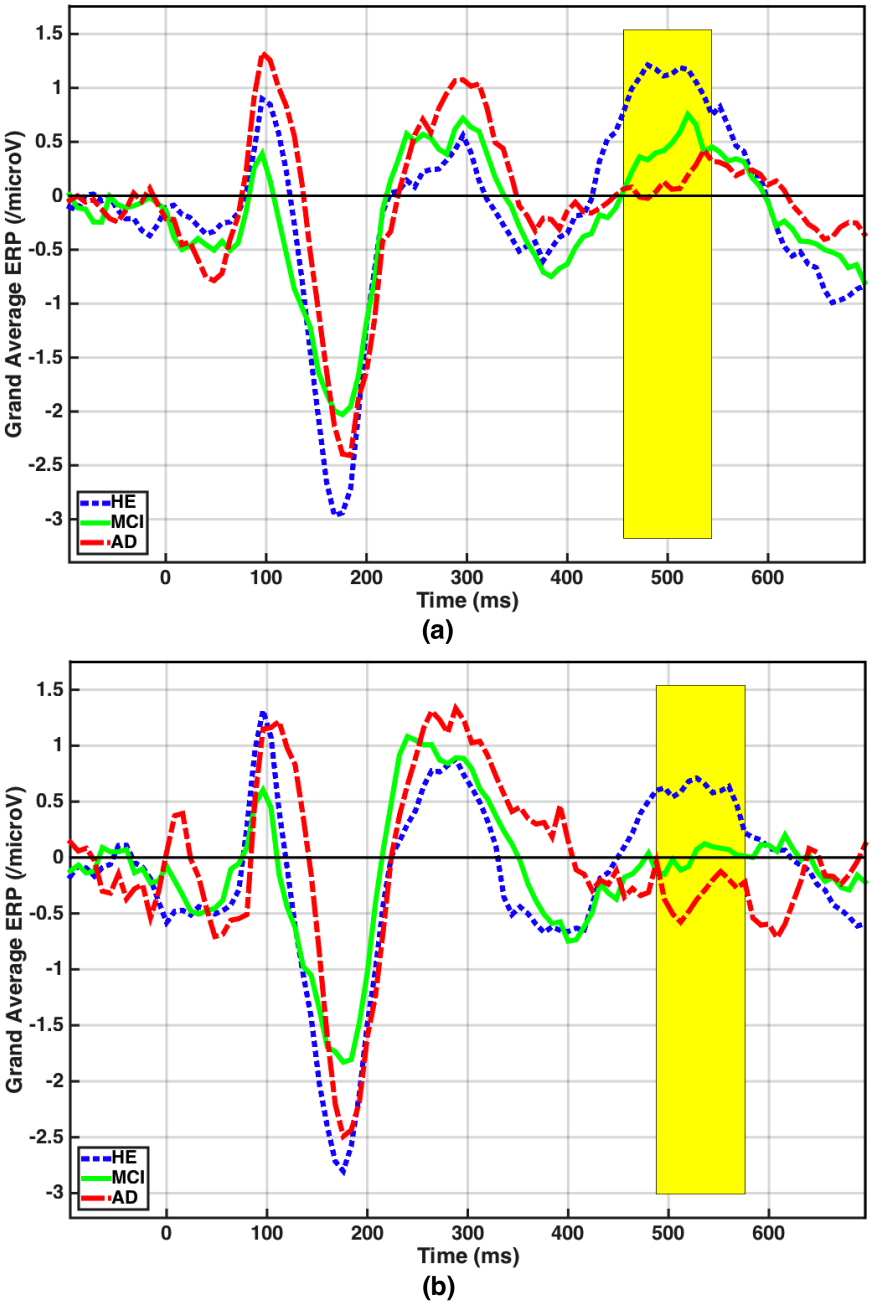

Figure 4: Grand average ERP at electrode P4. Intervals where significant $ERD\%$ differences are seen are highlighted in yellow and correspond to the HE vs. AD comparison (a) during execution of *0-back* non-match task and to the HE vs. MCI comparison (b) during execution of *1-back* non-match task.

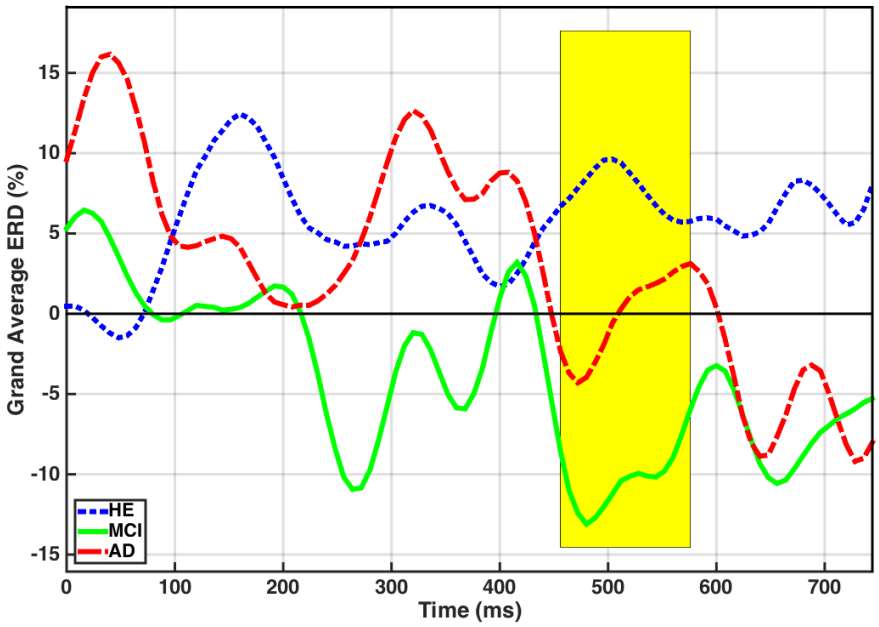

Figure 5: Grand average ERS/ERD patterns on frequency band gamma at electrode TP8. Intervals where significant $ERS\%$ differences were found are highlighted in yellow and correspond to the HE vs. MCI comparison during execution of *0-back* match task.

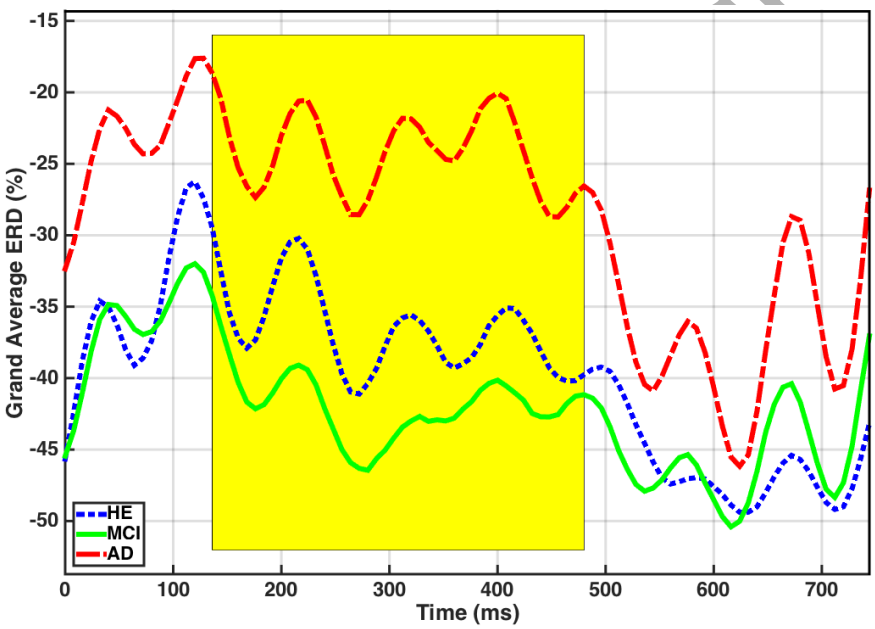

Figure 6: Grand average of ERS/ERD response on sub-band theta at left temporal scalp location T3. Intervals with *ERS%* differences between MCI and AD patients are highlighted in yellow and relate to the *0-back* non-match task.