# EVENT-RELATED SYNCHRONISATION RESPONSES TO N-BACK MEMORY TASKS DISCRIMINATE BETWEEN HEALTHY AGEING, MILD COGNITIVE IMPAIRMENT, AND MILD ALZHEIMER'S DISEASE

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# ABSTRACT

In this study we investigate whether or not event-related (de)synchronisation (ERD/ERS) can be used to differentiate between 27 healthy elderly, 21 subjects diagnosed with amnestic mild cognitive impairment (aMCI) and 16 mild Alzheimer's disease (AD) patients. Using 32-channel EEG recordings, we measured ERD responses to a three-level visual N-back task (N = 0, 1, 2) on the well-known delta, theta, alpha, beta and gamma bands. Our findings revealed that healthy elderly (HE) elicited consistently greater beta and alpha ERD responses than MCI and AD patients at many scalp electrodes, most of them located at fronto-central and temporal-parietal areas. Additionally, significant ERD differences were found on the gamma band in the MCI vs. AD comparison. Based on these findings, we conclude that ERD responses to a working memory (N-back) task could be useful for early MCI diagnosis or for improved AD diagnosis, and also for assessing the likelihood of MCI progression to AD.

*Index Terms*— working memory, event-related (de)synchronisation, mild cognitive impairment, Alzheimer's disease

## 1. INTRODUCTION

Amnestic mild cognitive impairment (aMCI) has been shown to be an important risk factor in the development of Alzheimer's disease (AD) [1]. Recent statistics show that about 50% of all people who reported aMCI symptoms to a doctor will develop AD within four years, with an average annual conversion rate of 12% [2]. Over the last few years, neuroimaging has gained significant grounds in helping characterize MCI and AD, using resting-awake experimental protocols to investigate the so-called "default mode network" (DMN) [3] as well as other protocols designed to capture task-related brain activity[4]. Functional magnetic resonance imaging (fMRI), for instance, has shown that hippocampal atrophy is a reliable indicator of aMCI and its conversion to AD [5]. Hippocampal atrophy, however, represents a relative late stage of neural dysfunction, one where cell loss has already manifested. In contrast, salient measures extracted from the electroencephalogram (EEG) which reflects the electrical activity of neural tissue may be better suited to reveal functional impairment long before actual tissue loss occurs, thus opening doors for very early diagnostics. Indeed, EEG sub-band analysis and crossfrequency interactions have revealed discriminative patterns between healthy controls, MCI, and AD patients in restingawake EEG data [6]. Similarly, EEG amplitude modulation analysis has been shown to be useful in characterizing AD progression from mild to moderate stages [7, 8].

While resting-awake protocols have shown to be useful in diagnostics, this study explores the use of EEG analysis during an executive function test, as deficits in such tasks have been shown to be prevalent in MCI [9]. To this end, event-related potential (ERP) analysis has been explored [10, 11], 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 with resting-awake EEG [12]. In this paper, we overcome this full-band analysis limitation by using an alternate analysis technique called sub-band event-related (de)synchronization (ERD/ERS) [13], in response to working memory *N*-back tasks [14].

### 2. MATERIALS AND METHODS

#### 2.1. Participants

Sixty four volunteers were enrolled in the study. Of these participants, 27 were healthy elderly (HE), 21 were diagnosed with mild cognitive impairment (MCI) and 16 with probable Alzheimer's disease (AD). Patients (participants with MCI and AD) were recruited and diagnosed at the Memory Clinic of the Sir Mortimer B. Davis-Jewish General Hospital (JGH), in Montreal, which is a tertiary care referral center of McGill University. Healthy elderly controls (HE) were recruited from research participation databases at Concordia University and

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the Memory Clinic at the JGH. Ethics approval was obtained from Concordia University as well as the Jewish General Hospital. All 64 recruited participants provided written consent.

Healthy elderly (HE) were selected after undergoing a review of its overall cognitive function, made through the Montreal Cognitive Assessment test - MoCA [15], which is a cognitive screening tool sensitive to detect MCI. Subjects were excluded from the HE group if they score under 26 on this measure. Mild cognitive impairment diagnosis was made according to agreed-upon criteria [16], which included a subjective report about the cognitive decline (made by the individual or his/her family): it should be gradual and lasting at least six months. In addition, objective verification of cognitive impairment was performed by neuropsychological tests (i.e., 1.5 SD of appropriate standards for age) to assure the absence of significant impairment in activities of daily life and failure to meet the ADRDA-NINCDS criteria for dementia [17], as determined by the assessing physician in the Memory Clinic. All patients were diagnosed as amnestic MCI, demonstrating a deficiency in episodic memory measures. Diagnosis of AD was based on ADRDA-NINCDS criteria for probable AD [17], which includes a established progressive cognitive decline and the absence of any other condition capable of producing a dementia syndrome. Only participants who were competent to sign the consent form, without assistance, were included in the AD group. Thus, all patients with AD who participated in the study had a mild degree of the disease.

#### 2.2. N-back task description

All subjects were submitted to a three-level visual *N*-back task (N = 0, 1, 2) [18]. *N*-back are working memory (WM) tasks with increasing levels of memory load, where the participant has to indicate with a button press whether the current visual stimulus displayed on a screen (here, a digit from one to nine), is the same or different from (a) a digit they have been asked to remember (0-back), (b) the digit they saw in the previous trial (1-back) or (c) the digit they saw 2 trials previously (2-back). Any given trial is termed a "match" or a "non-match" trial, based on whether or not it matches the digit presented *N* trials previously (or the target digit in the 0-back case), respectively.

Single digits (1-9) were presented sequentially on a computer screen in white letters on a black background (Arial font point 150). Three levels of *N*-back task were completed in ascending WM load (0-back, 1-back, 2-back). Each condition consisted of 100 trials, 40% of which were match trials (match vs. non-match stimuli were distributed pseudorandomly). Each digit was presented an equal number of times, in a pseudo-random order (limited by the demands of our 40/60 ratio for match/non-match). The stimuli were presented during 600 ms, with an inter-stimulus interval of 1,400 ms. Participants responded by pressing the left or right button on a keyboard with the index finger of each hand.

#### 2.3. EEG signals recording and pre-processing

Electroencephalography signals were recorded using a 32channel Neuroscan device with 500 Hz sampling rate and following the international 10-20 placement system; the 32 Ag/AgCl electrodes were mounted in an elastic Easycap and impedance was kept below 8 k $\Omega$ . The reference electrode was placed in the left earlobe during EEG recording, but for offline analysis all signals were re-referenced to the average of the left and right ear electrodes. From the 32 channels available, two were reserved for monitoring vertical (blinks) and horizontal (saccades) eyeball movements, and a third was attached to the right earlobe and used as an additional reference, as mentioned before, thus resulting in 29 useful EEG channels. Recorded data were then lowpass filtered (57 Hz), downsampled to 125 Hz, and further highpass filtered (1.2 Hz) to eliminate drifting effects. Next, eye blinks, saccades, heart beats and other muscular as well as electrode artifacts were removed using the Independent Component Analysis tool of the EEGLAB software[19]. To allow for frequencyspecific EEG analysis, the full-band EEG signals were then decomposed into four well-known sub-bands, namely: theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz) and gamma (30 - 45 Hz). Sub-band signals were then segmented into 2seconds epochs ranging from -500 ms to 1500 ms, where 0 ms indicates the instant when the visual stimulus was presented to participants.

#### 2.4. Signal processing for ERD/ERS quantification

Event-related cortical synchronization (ERS) and desynchronization (ERD) relate to the increase (or decrease) in firing synchrony of neurons involved in frequency-specific eventrelated processes, respectively. According to Pfurtscheller, "ERD characterizes cortical areas involved in task-relevant processing and ERS marks cortical areas in an idling state" [20]. In order to quantify ERS/ERD patterns, a procedure similar to the one described in [20] was performed. First, for each of the four sub-band signals, the sample amplitudes were squared to obtain energy signals, which were then passed through a 100ms-length moving average filter to generate the smoothed bandpass energy signals E(t). After filter delay correction, the pre-stimulus reference (average energy from -500 to 0 ms) of the smoothed bandpass energy signals (termed R) were computed. Lastly, the percentage power decrease (%ERD) or increase (%ERS) were computed as

$$\% ERD(t) = 100 \times \frac{E(t) - R}{P},\tag{1}$$

where P indicates average energy of the entire epoch (i.e., from -500 to 1500 ms). So, when % ERD(t) is negative it means power decrease, otherwise it means the power has increased as compared to the baseline. The main difference between Eq. 1 and the one used in [20] lies in the normalizing factor, where we use P in lieu of R. In our experiments, we found that this normalization procedure was more robust to inter-subject EEG signal power variations. Throughout our analyses, the so-called "cumulative ERS/ERDs" were used and computed as the sum of the ERS/ERD signal samples % ERD(t) over 150 ms intervals with 75 ms overlapp, from 75 ms to 1300 ms post-stimulus. This variable was used instead of directly comparing the % ERD(t) signal samples in order to reduce both data variability and size. The notation ERD% will be used from now on to denote those "cumulative ERS/ERDs".

#### 2.5. Statistical Analysis

Statistical significance was established at 5% level for all tests. As the ERD/ERS patterns usually do not follow a normal probability distribution, the non-parametric Kruskal-Wallis test was applied followed by Bonferroni post-hoc tests for multiple comparisons correction. In order to properly assess statistically significant differences between groups, multiple comparisons were performed over all five EEG channels belonging to the Region of Interest (ROI). For each sub-band and 150 ms interval, we defined as ROI the top-five scalp locations where ERD% "distances" between groups were the greater ones, according to a variation of the Mahalanobis distance for univariate and non-parametric statistical testing, which we developed specifically for this study and is given by

$$D(G_1, G_2) = \frac{|Med(G_1) - Med(G_2)|}{\sqrt{\sigma_1 \sigma_2}},$$
 (2)

where  $Med(G_1)$  and  $Med(G_2)$  are the ERD% medians of groups 1 and 2, respectively, while  $\sigma_1$  and  $\sigma_2$  are the corresponding standard deviations. Herein, groups 1 or 2 denote whichever two groups (HE, MCI or AD) being compared.

#### 3. RESULTS

To avoid misjudgment issues, we only analyzed the ERD/ERS responses where the participant provided the correct answers for both match and non-match trials. Table 1 lists all significant differences found in the "match" (M) and "non-match" (N) trials for the HE vs. MCI, HE vs. AD and MCI vs. AD post-hoc comparisons, when participants performed the threelevel N-back task. Most differences were encountered in the HE vs. MCI comparison, the majority of them on beta subband in the M1-back and N0-back conditions and some on alpha band in the M2-back trials. Interestingly, no differences in ERD% for any comparisons occurred when participants were making the 0-back matched decisions. Regarding the HE vs. AD comparison, in turn, three ERD% differences were found: one on the alpha sub-band, at electrode C3, other on gamma band at scalp location F4 (both in M2-back trials) and the last one was found on gamma at Fz (N1-back task). As for findings related to the MCI vs. AD comparison, we



Fig. 1. ERS/ERD grand average on gamma at Fz (*N0-back* task). The interval with significant ERD% difference between MCI and AD is highlighted in yellow.



Fig. 2. Grand average of the % ERD(t) response on alpha band at TP7 (*M2-back* task, HE vs. MCI comparison).

relied only in "non-match" trials (*N0-back*), where just two differences were found, and both on gamma band at Fz. Finally, no significant differences in all post-hoc comparisons were found for delta and theta bands across the 3-level task situations, for both match and non-match trials.

In Fig. 1 we show a representative grand average (across all subjects) ERS/ERD pattern observed on the gamma subband at frontal electrode Fz, where significant ERD% differences (highlighted in yellow) were observed for the MCI vs. AD post-hoc comparison (*0-back* non-match task). Fig. 2, at temporal-parietal electrode TP7, shows a significant HE vs. MCI difference on the alpha sub-band when participants were performing the 2-back match task.

_	Task	Sub-band	Interval (ms)	Electrode	${\rm HE} ERS\%$	MCI $ERS\%$	AD $ERS\%$
-	M1-back	beta	150-300	CP3	-62.0	-19.7	
			225-375	P3	-58.0	-30.0	
			450-600	TP8	-51.0	-18.8	
			450-600	P4	-65.0	-28.1	
		gamma	375-525	FZ	3.0	-22.7	
	M2-back	alpha	150-300	TP7	-40.8	24.4	
			225-375	T5	-68.9	-12.7	
			225-375	C3	-70.9		-22.0
		gamma	525-675	F4	8.7		-31.4
	N0-back	beta	375-525	C4	-57.2	-34.8	
			750-900	C4	-20.4	1.7	
			825-975	CP4	-15.6	5.3	
			825-975	C4	-20.6	6.9	
		gamma	75-225	FZ		-0.3	-16.9
			150-300	FZ		0.3	-23.1
	N1-back	gamma	150-300	FZ	-2.9		-22.5
	N2-back	beta	975-1125	TP8	-21.8	22.7	

**Table 1**. Frequency sub-bands, time intervals and electrode locations where we found ERS% differences (negative percentages indicate ERD) in the post-hoc group comparisons for matched (M) and non-matched (N) conditions with participants performing the 0,1,2-back task levels.

#### 4. DISCUSSION

It has been shown in the literature that alpha band rhythm over broad scalp regions presents desynchronization (ERD) in judgement and memory tasks [21]. More recently, some studies found out that ERDs on different frequency bands are induced in some attention and memory tasks, thus leading us to believe that such ERDs could be related to a broader range of cognitive processes[22, 23]. Our results (Table 1) corroborate such findings. Furthermore, it has also been previously reported that an increase in task complexity and/or attention results in greater ERD magnitudes [24], an effect also observed in this study, thus further confirming the relationship between ERD and cognitive load. In this work, consistent event-related desynchronization was observed on alpha and mainly on beta, across several N-back task levels/types and scalp regions. More specifically, both the MCI and AD groups showed a consistent lowering (i.e., less negativity) of ERD%relative to the HE group at many scalp electrodes, chiefly at fronto-central and temporal-parietal areas.

Although more tests over larger databases are needed to further validate our findings, we conclude that ERS/ERD responses to working memory (visual *N-back*) tasks could be useful not only for early MCI diagnosis or for improved AD diagnosis, but also for assessing the likelihood of MCI progression to AD.

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