# Distinct ERP and EEG oscillatory mechanisms of memory dysfunction in Mild Cognitive Impairment (MCI)

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## Introduction

Episodic memory impairment is the prototypical features of amnestic MCI and early Alzheimer's Disease (AD). Three electrophysiological measures, the event-related potential (ERP) P600, suppression of oscillatory alpha (~10 Hz) activity, and cross-frequency coupling between theta and alpha/beta activity, have been found to be sensitive to the effect of word repetition and the efficiency of verbal learning and memory in healthy elderly and patients with MCI or prodromal Alzheimer's disease [5,6].

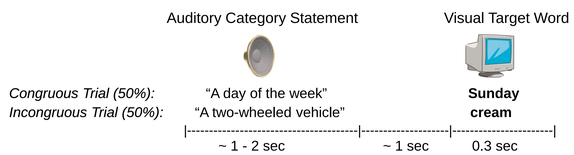
The present study was aimed to determine whether these three EEG/ERP measures are complementary predictors of verbal memory abilities as measured by standardized neuropsychological tests. Prior to testing this hypothesis, we investigated whether the P600 and alpha word-repetition effects, similar in timing and functional interpretation [2-7], are independent or reflect the same, or overlapping, underlying neural mechanisms.

## Participants

We examined the EEG recordings of 25 patients with amnestic MCI (mean age 73.2 years, range 55-84) and 11 healthy elderly controls (mean age 74.1 years, range 57-79). All were part of a previously published study[6] in which the patients were tested annually with a word repetition paradigm that has been found to reliably elicit the P600 brain potential. Fifteen of the 25 patients with MCI subsequently converted to AD within 3 years of their initial baseline EEG recordings (mean number of years 1.62 ± 0.7 years). For more specific information of participant demographics, and neurocognitive testing of participants please refer to Olichney et al. [6].

## Word Repetition Paradigm

EEG recordings were obtained during a cross-modal category judgment task as shown below. Two-thirds of the category-exemplar pairs (50% congruous, 50% incongruous) were repeated either once or twice between ~10-140 seconds later. Further details of the experiment paradigm have been published in previous reports [7].

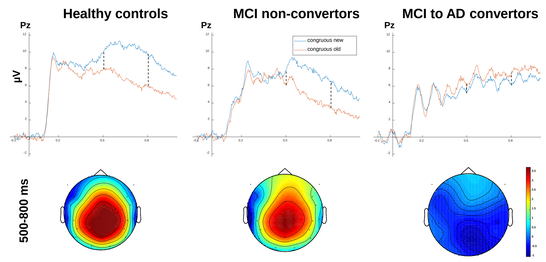



## EEG Analysis

19 to 32 channel EEG was recorded at 250 Hz, band passed .016 to 100 Hz, and re-referenced off-line to averaged mastoids. Epochs were time-locked to the onset of the target words. ERPs were averaged across congruous and incongruous conditions for new and repeated words using a prestimulus baseline of 0.1 s. Time-frequency representations (TFRs) of power were calculated for each trial using sliding Hanning tapers with varying time window of three cycles for each frequency. Word-induced changes in the power was assessed as proportional change from baseline (-0.5 to -0.1 s). Latencies of interest and selection of electrodes for statistical analyses were defined a-priori guided by previous literature [3,6].

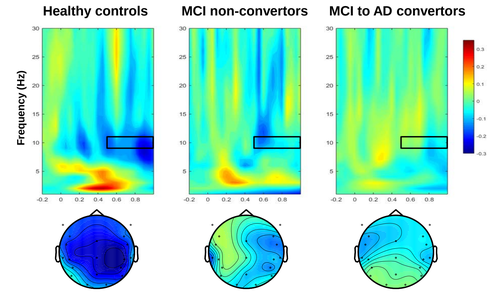
## Memory-related ERP/EEG Features

### P600 repetition effect:



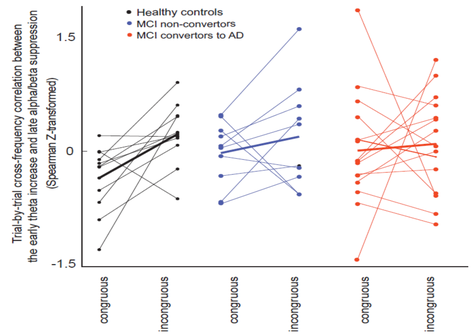

Grand averaged ERPs elicited by new and repeated congruous words at the midline-parietal electrode Pz. The P600 word repetition effect was measured as the difference in amplitude between congruous new and congruous old words 0.5 to 0.8 s after word onset (marked by the dotted lines). Repeated words elicited smaller P600 than new words in healthy controls ($t_{10}$ = 3.35, $p$ = .007) and MCI non-convertors ($t_9$ = 3.36, $p$ = .008), but not in MCI convertors ($t_{14}$ =-1.62, $p$ = .128).

### Alpha repetition effect:




B) Illustrates the difference in time-frequency spectra between new words and the third presentations of these words at electrode Pz. Alpha suppression effect was quantified as the difference in alpha activity . The alpha suppression diminished with repetition in healthy controls ($t_{10}$ = 6.16, $p$ < .001) and MCI non-convertors ($t_9$ = 2.46, $p$ = .036), but not in MCI convertors ($t_{14}$ =.61, $p$ = .552).

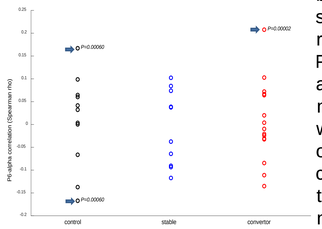
### Cross-frequency theta-alpha/beta coupling:




Trial-by-trial cross-frequency coupling between the theta increase (3-5 Hz, 0.4-0.5 s) at Pz and the alpha/beta (10-20 Hz) suppression at Fz following congruent versus incongruent words for the 3 groups.

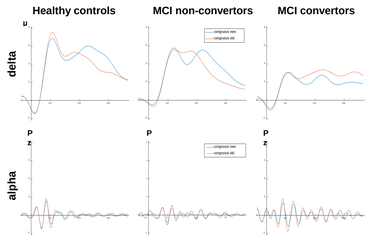
## The (lack of) relationship between P600 and alpha suppression

### Single-trial correlations:




Trial-by-trial correlations between P600 and alpha suppression using Spearman's rank-order test. Single-trial P600 was extracted using an automated denoising method[8]. The correlations were significant for only 3 out of 36 participants (Bonferroni corrected $\alpha$=0.0014), and these correlations were of modest strength (|$r$'s| < .21).

### Frequency band-specific ERPs




ERPs constructed from bandpass filtered single-trial data revealed that delta (1-4Hz) activity alone was correlated ($r$ =.94, $p$ < .001) with the traditional P600. ERPs in higher frequency bands, including alpha, did not contribute to the P600 effect (alpha: $r$ = .12, $p$ = .503).

## ERP/EEG models of verbal memory abilities

**CVLT list A, trial 1-5**

| Predictor variables | $R^2$ | Adjusted $R^2$ | Standardized $\beta$ | $P$ |
|---|---|---|---|---|
| Block 1 | .051 | -.038 | | |
| Age | | | .157 | .258 |
| Education | | | .242 | .097 |
| Gender (male) | | | -.061 | .667 |
| P600 repetition effect – congruous | .361 | .278 | .386 | .012* |
| θ-α/β coupling – congruous | .509 | .428 | -.471 | .002** |
| Alpha repetition effect | **.574** | .486 | -.272 | .045* |

**CVLT long delay free recall**

| Predictor variables | $R^2$ | Adjusted $R^2$ | Standardized $\beta$ | $P$ |
|---|---|---|---|---|
| Block 1 | .075 | -.012 | | |
| Age | | | .216 | .106 |
| Education | | | .300 | .034* |
| Gender (male) | | | -.134 | .323 |
| P600 repetition effect – congruous | .400 | .323 | .393 | .007** |
| θ-α/β coupling – congruous | .534 | .456 | -.452 | .002** |
| Alpha repetition effect | **.614** | .534 | -.303 | .021** |

**CVLT long delay cued recall**

| Predictor variables | $R^2$ | Adjusted $R^2$ | Standardized $\beta$ | $P$ |
|---|---|---|---|---|
| Block 1 | .030 | -.061 | | |
| Age | | | .265 | .044* |
| Education | | | .206 | .126 |
| Gender (male) | | | -.016 | .900 |
| P600 repetition effect – congruous | .404 | .327 | .427 | .003** |
| θ-α/β coupling – congruous | .540 | .464 | -.457 | .002** |
| Alpha repetition effect | **.633** | .558 | -.327 | .011* |

**CVLT short delay free recall**

| Predictor variables | $R^2$ | Adjusted $R^2$ | Standardized $\beta$ | $P$ |
|---|---|---|---|---|
| Block 1 | .036 | -.054 | | |
| Age | | | .189 | .194 |
| Education | | | .182 | .217 |
| Gender (male) | | | -.039 | .797 |
| θ-α/β coupling – congruous | .307 | .217 | -.580 | <.001** |
| Alpha repetition effect | .504 | .421 | -.444 | .002** |

**CVLT short delay cued recall**

| Predictor variables | $R^2$ | Adjusted $R^2$ | Standardized $\beta$ | $P$ |
|---|---|---|---|---|
| Block 1 | .031 | -.060 | | |
| Age | | | .296 | .059 |
| Education | | | .168 | .292 |
| Gender (male) | | | -.003 | .983 |
| P600 repetition effect – congruous | .318 | .230 | .477 | .003** |
| θ-α/β coupling – congruous | .451 | .359 | -.421 | .012* |

**CVLT discriminability**

| Predictor variables | $R^2$ | Adjusted $R^2$ | Standardized $\beta$ | $P$ |
|---|---|---|---|---|
| Block 1 | .095 | .010 | | |
| Age | | | .101 | .502 |
| Education | | | .157 | .318 |
| Gender (male) | | | -.131 | .403 |
| P600 repetition effect – congruous | .334 | .248 | .428 | .007** |
| θ-α/β coupling – congruous | .464 | .375 | -.418 | .011* |

Hierarchical linear regression models of California Verbal Learning Test (CVLT) scores using the three EEG/ERP measures as predictors, controlling for demographic factors of age, education, and gender. The three demographic factors were entered first in block, followed by stepwise regression that allowed each ERP/EEG measure to be independently entered (α-to-enter: $p \leq 0.05$) or removed (α-to-remove: $p \geq 0.1$) from the model. (* $p \leq 0.05$; ** $p \leq 0.01$)

## Conclusions

The lack of trial-by-trial relationship between P600 and alpha suppression suggests that these two word-repetition effects are dissociable, and thus unlikely to be generated by the same neural mechanisms.

The P600 word-repetition effect is most strongly correlated with delta activity, but not with higher frequency bands including alpha. Therefore it appears that the vast majority of the P600 word repetition effect is mediated by slow wave activity.

The three ERP/EEG features are independent measures of verbal memory. Combining all three provides the best model to account for variance (up to 63%) in CVLT scores, superior to any single measure alone.

Based on our current findings and the literature[2-7], it may be speculated that P600 is associated with the integration of a target word to its category context, whereas alpha suppression is related to word-level processing during sustained attention. The former is closely linked to cued recall and long-term memory, which requires associative encoding between a cue and a target word, while the latter is critical for successful free recall after a short delay.

The present study highlights the importance of combining ERP phase-locked and EEG non-phase-locked measures of brain activity in order to more comprehensively characterize the likely multiple mechanisms of memory failure in patients with MCI or prodromal AD.

## References

1. Ahmadi & Quian Quiroga, NeuroImage 2013; 2. Brouwer et al., Brain Research 2012; 3. Hanslmayr et al. Front Hum Neurosci 2012; 4. Klimesch Trends Cogn Sci 2012; 5. Mazzaheri et al. NeuroImage: Clinical 2018; 6. Olichney et al. Neurology 2008; 7. Olichney et al. Brain 2000.

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