Neuropsychological and Neuroanatomical Correlates of Event-Related Potentials in Patients with Alzheimer's Disease

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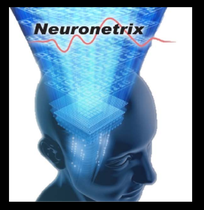

INTRODUCTION

Previous research has demonstrated the possibility of discriminating patients with Alzheimer's disease (AD) from healthy older adults using event-related potentials (ERPs) (see e.g., Vecchio & Maatta (2011).

Cecchi et al., (2015) showed using an active oddball paradigm that ERPs in patients with mild AD were significantly different from healthy older adult controls (ClinicalTrials.gov number NCT00938665). Differences could be seen across a number of ERP components - that included:

- N100 (amplitude) – associated with detecting acoustic change
- N200 (amplitude and latency) – which may reflect stimulus identification, discrimination and related attentional/executive processes
- P3b (classic P300; amplitude and latency) – thought to reflect attentional processes and the updating of working memory.

In this study we investigated the relationship between the oddball paradigm ERP measures and gray matter volume (GMV) and cortical thickness. A second study objective was to identify ERP measures that reflected disease staging determined by neuropsychological assessment and hippocampal atrophy.

METHODS

Participants: Out of a larger pool of 99 patients with mild AD, sixty-two patients (for whom 3 Tesla T1 weighted structural MRI scans were available with no movement or subsequent segmentation artefacts) were included in this analysis (29 males and 33 females; mean age 74.39, SD 7.50; mean education 14.16, SD 3.14; MMSE mean 23.18, SD 1.67, range 21-26).

Materials and Procedure: The patients were evaluated using a comprehensive neuropsychological assessment battery, an active auditory oddball ERP paradigm (see Cecchi et al., 2015 for full details), and were scanned using an MPRAGE or IR-SPGR MRI protocol.

The Oddball task stimuli included:

- Standard tones (1000Hz; probability = .75)
- Target tones (2000 Hz; probability = .15)
- Distractor tones (white noise; probability = .10)

There were 300-400 stimuli in total (presented binaurally at 70dB).

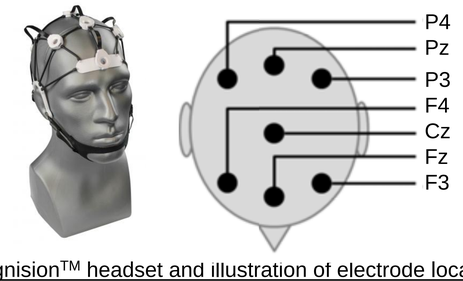

Figure 1. Cognision™ headset and illustration of electrode locations

The T1-weighted MRI scans were processed using the Computational Anatomy Toolbox, implemented within SPM12.

- Voxel-based morphometry was used to isolate GM and images were smoothed with an 8mm Gaussian filter.
- Cortical thickness measures were obtained using CAT12.
- Data was processed using correlation analysis for GMV and CT regions of interest (ROIs), and with multiple regression modelling to assess the relationship between the ERP measures and CT.

RESULTS

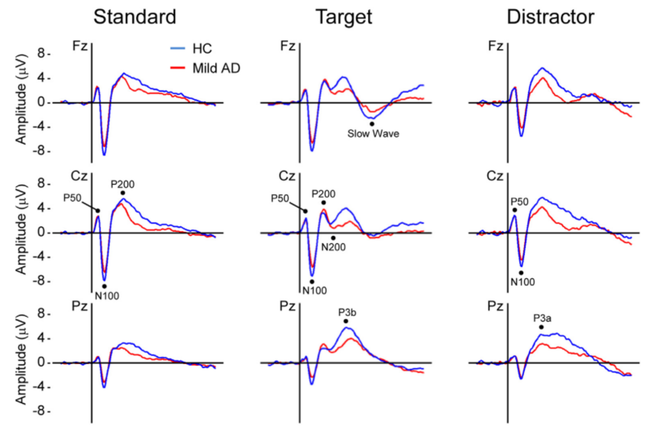

Figure 2. Grand average ERPs for the Standard, Target and Distractor stimuli in the full group of patients with AD (n=99) and healthy controls (n=100) (from Cecchi et al., 2015). ERP features of interest are illustrated.

Table 1. Significant correlations between oddball behavioural/ERP measures and CT measures

Measure/Component	Brain region (ROI analysis – DKT40JT atlas)
Accuracy oddball task	R rostral anterior cingulate cortex (ACC)***, L rostral ACC*, L insula***
N100 Standard amplitude	R supramarginal gyrus*
N100 Distractor amplitude	L caudal ACC*, R inferior parietal lobule*, L middle temporal cortex*, R parsopercularis, L posterior cingulate cortex (PCC)*, L precuneus*, L superior frontal gyrus*, R superior parietal lobule*, R supramarginal gyrus***, L insula*
Distractor P3a amplitude	L lingual gyrus*
Target P3b amplitude	R middle temporal gyrus*, L transverse temporal gyrus*, L fusiform gyrus*, L cuneus*, L lingual gyrus*

Note in the tables: R = right; L = left; * indicates p<0.05; ** indicates p<0.01; *** indicates p<0.001

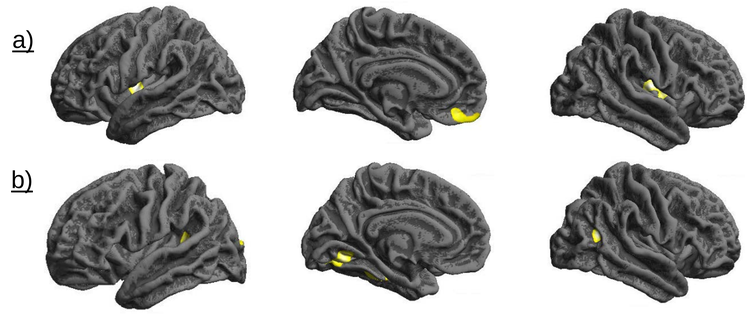

Figure 3. Whole-brain analyses: a) *Correlation between accuracy score on the oddball task and CT*; b) *Correlation between P3b Target amplitude and CT*

Table 2. Correlations between severity measures and oddball task measures

Marker of disease severity	ERP components
Alzheimer Disease Assessment Scale - Cognitive sub-scale (ADAS-Cog)	N100 Target latency*, P200 Standard latency*, P3a Distractor amplitude*, P3a Distractor latency*, P3a Distractor amplitude (average)*.
Left hippocampus (neuromorphometrics atlas)	P200 Standard Latency*
Right hippocampus (neuromorphometrics atlas)	N100 Distractor latency**, P200 Standard latency**, P200 Target Amplitude*, Slow-wave Target latency*.

CONCLUSION

These preliminary analyses demonstrate that increased accuracy on the oddball task was associated with greater CT within regions that comprise the salience network (the insular cortices) and the default mode network (the rostral ACC). Low performance on the task might therefore be associated with the spread of neuropathology to these networks.

Associations between ERP features (such as the N100 Distractor and Standard amplitudes) and CT were seen within the right supramarginal gyrus. Additionally, Target P3b amplitude was associated with CT within bilateral regions of the temporal cortex. Involvement of these regions (which have been implicated previously in fMRI studies of the oddball task) fit with the natural progression of AD.

In relation to disease severity - correlations were observed between the ADAS-cog and multiple ERP features. Hippocampal volume (in particular of the right hippocampus) was also linked to a range of ERP measures.

Given the simplicity of the oddball ERP test, these links to established measures of disease staging suggest a sub-selection of the ERP features might potentially be useful for patient monitoring.

REFERENCES:

- Cecchi, M., Moore, D. K., Sadowsky, C. H., Solomon, P. R., Doraiswamy, P. M., Smith, C. D., . . . Fadem, K. C. (2015). A clinical trial to validate event-related potential markers of Alzheimer's disease in outpatient settings. Alzheimers Dement (Amst), 1(4), 387-394. doi:10.1016/j.dadm.2015.08.004
- Vecchio, F., Maatta, S. (2011). The use of auditory event-related potentials in Alzheimer's disease diagnosis. Int J Alzheimers Dis 2011:1–7.