Neuroanatomical and Neuropsychological Correlates of Resting State EEG Diagnostic Features in Patients with Alzheimer's Disease

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INTRODUCTION

In the search for accurate, low cost biomarkers for Alzheimer's disease (AD) and other dementias, quantitative electroencephalography (EEG) may offer a solution.

The data for the present study were collected as part of a seven site multicentre clinical trial (ClinicalTrials.gov number NCT00938665) that was focused on discriminating patients with Alzheimer's disease from normal healthy older adult controls. As part of the protocol both event-related (Cecchi et al., 2015) and resting state EEG (rsEEG) data were collected

Analysis of the rsEEG data flagged up 35 features that best discriminated the groups (Cassani et al., 2017). The current set of analyses utilise the rsEEG feature set from Cassani et al. (2017), in addition to the magnetic resonance imaging (MRI) and neuropsychological test data that were part of the protocol.

The primary objective of the current analysis, was to examine the relationships between the rsEEG feature set (that best discriminated patients with AD from controls) and neuroanatomy. The second objective was to identify which of the rsEEG measures best reflected disease staging.

METHODS

Participants: Out of a larger pool of 103 patients with mild AD, 99 patients with EEG were used to derive the diagnostic feature sets. Subsequent analyses were carried out on eighty-nine of those patients (for whom T1-weighted structural MRI scans were available with no movement or subsequent segmentation artefacts) (mean age 75.79 (SD 7.33; range 60-90), mean education 14.46 (SD 3.30; range 5-20) and mean MMSE score 23.33 (SD 1.81; range 21-26).

Materials and Procedure: The patients were evaluated using the comprehensive neuropsychological assessment battery employed in the Alzheimer Disease Neuroimaging Initiative, provided a 3 min eyes-open rsEEG (using the Cognision system – see Figure 1) and underwent magnetic resonance imaging to obtain a 3D T1-weighted scan.

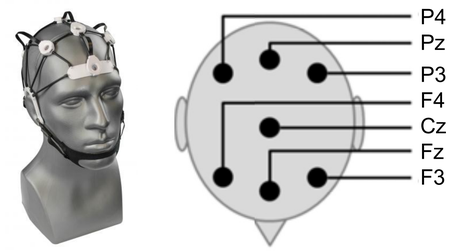

Figure 1. Cognision™ headset and illustration of electrode locations

The T1-weighted MRI scans were processed using Freesurfer using the default recon-all pipeline. Subcortical volumes were extracted as were ROI cortical thickness (CT) values using the Desikan-Killiany Atlas (aparc) .

The rsEEG data underwent a procedure of filtering (0.5-45Hz) and automatic artefact rejection using wavelet enhanced independent components analysis. Spectral, coherence and amplitude modulation measures were then computed.

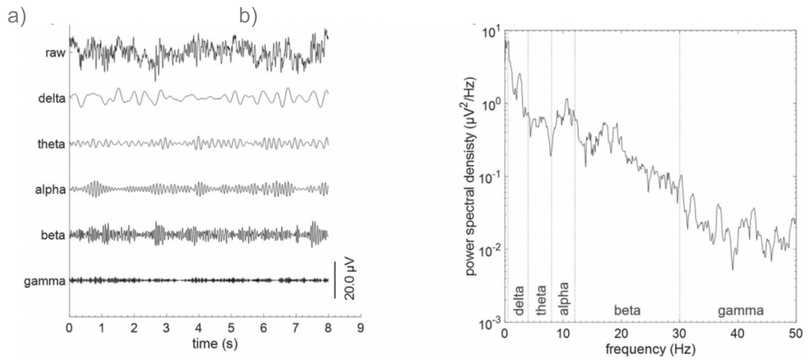

Figure 1. a) Example EEG data from a single electrode decomposed into standard frequencies by time. b) Spectral representation of that data in the frequency domain (from Cassani et al., 2017).

A support vector machine (SVM) classifier with cross-validation (10-fold and leave one subject out) was used used to select the 35 features that were most discriminatory. An independent dataset was also subjected to the same procedures (see Cassani et al., 2017 for details). This enabled the 9 features that were shared across datasets to be identified and selected.

Spearman's correlations were performed to assess the relationship between the 9 rsEEG features that most accurately discriminated the AD patients from controls (median values), the regions of interest (ROI) for cortical thickness (CT) (and subcortical volumes), and neuropsychological test results.

RESULTS

Table 1: Summary of the 9 rsEEG features that were shared across datasets and that were significantly different from controls.

Features	Electrode site
Delta	P4↑
Theta	Pz↑; Coherence (P3-P4)↓
Alpha	Cz↓, Fz↓; Alpha2 Fz↓
Beta	F3↓, Pz↓, P3↓

Table 1: Correlations between rsEEG features and Freesurfer ROIs.

Features	Freesurfer ROIs
Delta	Postiive correlations: L frontal pole*, rostral middle frontal*, inferior parietal* Negative correlations: R entorhinal*
Theta	Positive correlations: L choroid plexus*; L cerebellum**, R cerebellum*; brain stem* Negative correlations: L caudal anterior cingulate*, rostral anterior cingulate* (Coherence measure: L lateral occipital* and L lingual*).
Alpha, Alpha2	Positive Correlations: L hippocampus*
Beta	Positive correlations: L hippocampus*, L precuneus*, R precuneus* R entorhinal*, putamen*, rostral anterior cingulate*, paracentral*, supramarginal*, lingual*

R = right; L = left; * indicates p<0.05; ** indicates p<0.01

Table 2. Correlations with markers of disease severity.

Marker of disease severity	rsEEG features
Left hippocampus	Positive correlations – Alpha at Fz; Alpha 2 at Fz; Beta at F3.
Right entorhinal cortex	Negative correlation – Delta at P4; Positive correlation – Beta at F3.
Clinical Dementia Rating (CDR) score	No significant correlations with the 9 features shared across datasets. [Examining the full feature set (n=35) showed positive correlations with gamma spectral power at F3 and Fz (and a negative correlation with total power across the delta, theta, alpha, beta bands)].

CONCLUSION

The rsEEG discriminatory features that are consistent across datasets reflect previous research that shows ↑ delta and theta and ↓ alpha and beta power due to Alzheimer's disease (see e.g., Jeong, 2004).

Our preliminary analyses utilising the neuroanatomical measures highlighted that rsEEG abnormalities were associated with subcortical volume/cortical thickness within the left hippocampus, and the right entorhinal cortex. Other notable associated regions included the precuneus, supramarginal and inferior parietal cortex, in addition to the anterior cingulate and frontal pole/middle frontal cortex.

Although a small number of rsEEG features correlated with neuroanaomtical markers of disease severity, the rsEEG feature set was not derived on the basis of disease severity, but rather simple discrimination between AD and controls. In the future we will assess rsEEG features optimised for the prediction of disease severity classification.

Given the rich data offered by both rsEEG and by structural MRI, in the future we will investigate the combined potential for these techniques to classify dementia and disease severity.

REFERENCES: Cassani, R., Falk, T.H., Fraga, F.J., Cecchi, M., Moore, D.K., Anghinah, R. (2017). *Biomedica Signal Processing and Control, 33*. 261-271. http://dx.doi.org/10.1016/j.bspc.2016.12.009; Cecchi, M., Moore, D. K., Sadowsky, C. H., Solomon, P. R., Doraiswamy, P. M., Smith, C. D., . . . Fadem, K. C. (2015). *Alzheimers Dement (Amst), 1*(4), 387-394. doi:10.1016/j.dadm.2015.08.004; Jeong, J. (2004). *Clinical Neurophysiology, 115.* 1490-1505.