Multivariate clinical phenotype - brain structure association in autoimmune limbic encephalitis

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Introduction

- Autoimmune limbic encephalitis (ALE) is the most common type of autoimmune Encephalitis.
- Subacute memory disturbance, temporal lobe seizures, and psychiatric symptoms are clinical hallmarks of the disease[1].
- However, little is known on relation between brain structural changes, measured with magnetic resonance imaging (MRI) and clinical features such as memory functioning, anterior temporal epileptiform discharges and slowing (shown by electroencephalography, EEG) and blood-cerebrospinal fluid (CSF)-barrier function.
- The study of complex relations requires multivariate approaches with a machine learning framework. Here, we sought to identify multidimensional associations between brain structural changes and clinical measurements in ALE by applying a regularized canonical correlation approach (RCCA)[2] to a multicentric sample of ALE patients.

Methods

1) Datasets:
The sample included imaging and clinical data of 122 patients with ALE (age (mean ± SD): 50.4 ± 16.6 years; 62 females) based on current diagnostic criteria[3].

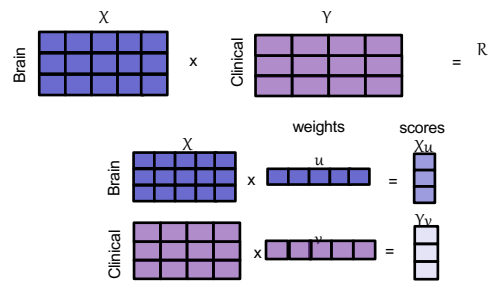
- **Clinical data:**

Clinical measurements included evidence of visual and verbal memory deficits, electroencephalography (EEG) scoring for uni- or bilateral anterior temporal interictal epileptiform discharges and/or slowing and ictal events as well as diffuse slowing, absence or presence of autoantibodies (AABs)in Serum–CSF against intracellular or cell surface neural antigens, the diagnostic likelihood of ALE[3] and preceding immunotherapies[1].

- **Imaging data and preprocessing:**

T1-weighted MRI scans were acquired on 1.5 or 3.0 tesla scanners. MRI scans were preprocessed with CAT12.5 and mean gray matter volume (GMV) was computed for 200 cortical (Schaefer atlas[4]) and 32 subcortical (Melbourne subcortical atlas[5]) parcels.

2) Regularized canonical correlation approach[2] :
The parcel-wise GMV and the aforementioned clinical measurements were entered into a RCCA with a hyperparameter tuning and cross-validation framework.

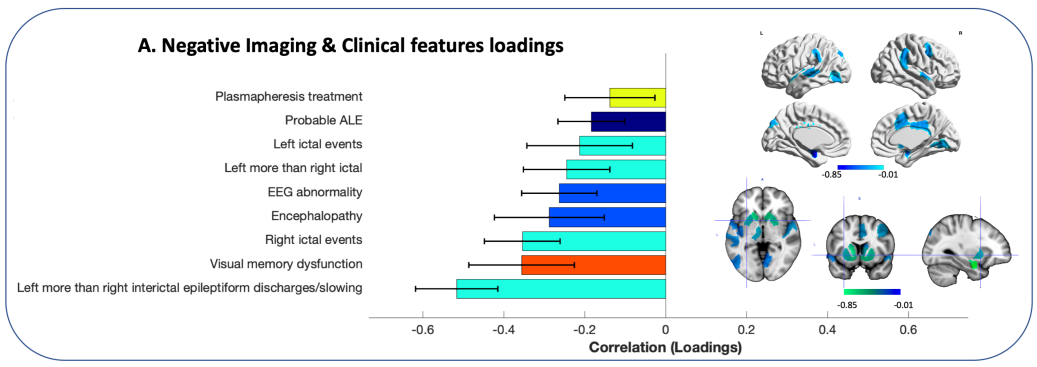


- X and Y: subjects are in rows, measures are in columns
- RCCA finds the weights which maximizing the covariance, R, between X and Y.
- Brain loadings: correlation (X, X_u)
- Clinical loadings: correlation (Y,Y_v)
- RCCA was applied independently in each cohort.
- Age, age-squared, sex, education, total intracranial volume (TIV) and cube-root of TIV were regressed out all variables.
- Random training-validation split were performed 100 times and statistical significance was assessed with 1000 permutations[2]. The results were averaged across significant splits and only variables whose loading sign remain constant across these splits are reported.

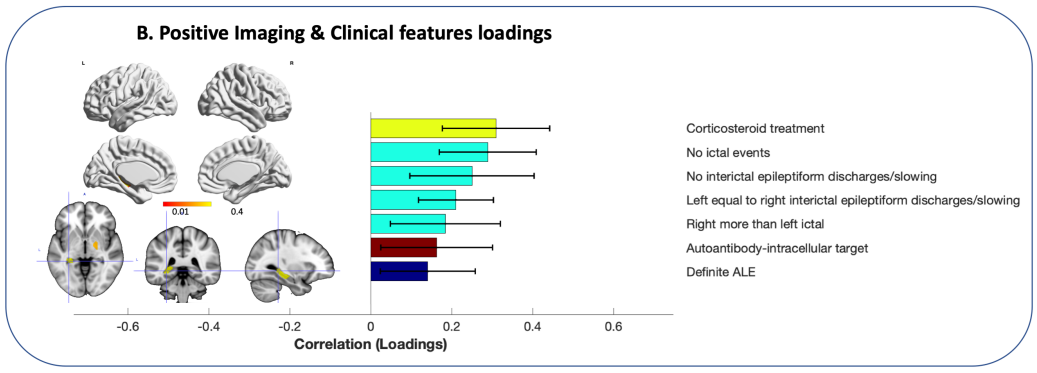
Results

One significant latent dimension robustly relating brain structure to clinical variables was identified across multiple runs ($r_{correlation}$range =0.35-0.62, p<0.05).

- Results suggest that patients with definite ALE[3], absence of interictal and ictal EEG changes, AABs against intracellular neural antigens and pretreatment with corticosteroids showed reduced GMV in the amygdala, posterior cingulate cortex, temporo-parietal junction, superior temporal gyrus and visual association areas (Fig A).



- On the other hand, patients with probable ALE[3], visual memory dysfunction, bilateral anterior temporal interictal epileptiform activity and/or slowing, unilateral or bilateral anterior temporal ictal events and diffuse slowing i.e. encephalopathy on EEG, and pretreatment using plasmapheresis showed decreased posterior hippocampal GMV (Fig B).



Discussion

- Employing a multivariate framework with cross-validation scheme in a large sample of ALE patients reveals that the heterogeneity in brain and clinical profiles can be summarized along a latent dimension differentiating anterior vs. posterior medial temporal lobe structural patterns[6].
- Our results suggest that patients with probable ALE[3], memory dysfunction and neuronal network dysfunction and hyperexcitability affecting the anterior temporal lobe (and beyond) on EEG tend[7] to show GMV decrease primarily in the posterior hippocampus.
- In contrast, patients with definite ALE[3] and absence of interictal and ictal EEG changes show GMV decrease primarily in the amygdala[8], but also in several regions engaged in socio-affective and object recognition processing consistent with previous own findings[9].
- These findings support the notion that in ALE, gray matter alteration is tightly associated with neuronal network dysfunction and hyperexcitability.

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