Modelling NMDA receptor activity in focal Epilepsy:

A Resting State study of EEG Effective Connectivity, towards a marker for epileptic seizures from unremarkable EEG traces.

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Introduction

The role of N-methyl-D-aspartate (NMDA) receptors in the pathophysiology of epilepsy and seizure generation has been established in pathological and animal models (1, 2, 3).

The role of NMDAR in modulating brain dynamics in patients with NMDAR autoimmune encephalitis has been studied using Dynamic Causal Modelling (DCM) for effective connectivity analysis (4, 5, 6). In study (4), researchers were able to use computational modelling to explain brain dynamics abnormal fluctuations in patients.

Aim

With this work, we aim to study regional hippocampal NMDA-dependent effective connectivity in patients with medial temporal lobe epilepsy (MTLE).

We used a similar DCM approach aiming to identify local NMDA-dependent effective connectivity alteration in clinically unremarkable resting state EEG recording.

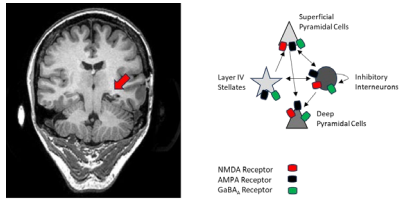

Figure 1. **Left**: example of a patient MRI scan. The red arrow indicates the sclerotic hippocampus. **Right**: Neural Mass model for intrinsic connectivity (adapted from 5).

Method

Resting state interictal EEG and MRI structural brain scans were collected from a cohort of 17 patients with diagnosis of epilepsy and unilateral hippocampal sclerosis.

The EEG data were pre-processed in 5-seconds epochs of source-localised electrophysiological activity arising from hippocampi.

MRI brain scans were used as the anatomical reference for patient-specific source localisation analysis.

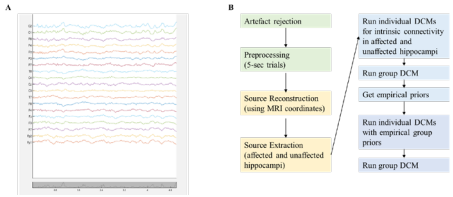

Figure 2. **A.** Example of resting state EEG trace (5 second epoch) in one participant. No epileptiform activity is present. **B**. Flowchart of our analysis pipeline.

We studied individual resting state microcircuitry in the affected (sclerotic) versus non-affected hippocampus using a neural mass model of regional network dynamics (5, 6).

We then used a group-level DCM analysis to validate the model and to obtain empirical priors on the parameters of the neural mass model.

Finally, we used the empirical priors to re-run an individual and group-level DCM analysis on sclerotic vs non-affected hippocampus.

Results

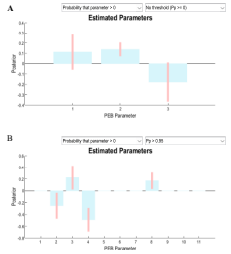

Figure 3. **A**. Estimated group DCM parameters with group empirical priors for AMPA (1), GABA (2) and NMDA (3) receptors changes. **B**. Estimated parameters (probabilities significance limit >0.95) for connections between SPP and SSC (2), II and SSC (3), self-connection for SPP (4) and self-connection for II (8).

Group-level DCM analysis for intrinsic connectivity could spot differences between sclerotic and unaffected hippocampus in clinically unremarkable resting state EEG.

The estimated model parameters for AMPA, GABA and NMDA receptors found a highly likely change in activity in GABA (probability 1) and NMDA (probability 0.94) in affected vs unaffected hippocampus (fig.3A).

Four connections were responsible, with high probability, for the local connectivity changes between affected and unaffected hippocampus (Fig.3B): excitatory between superficial pyramidal cells (SPP) and spiny stellate cells (SSC), and between inhibitory interneurons (II) and SSC; inhibitory self-connections in SSP populations, and self-connections in II populations.

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Conclusion

This work validates DCM as a valuable approach to investigate individual and group resting state EEG network dynamics.

DCM approaches successfully identifies local alterations of abnormal NMDAR and GABA activity in unremarkable EEG recording of patients with MTLE.

Our results suggest a highly probable role of NMDA and GABA receptors in local effective connectivity alterations.

Future work will aim to validate this methods in larger patient populations, and with control data from healthy volunteers.

Considering the specificity of the intrinsic hippocampal connectivity, future work might develop an ad hoc neural mass model.

If validated, this approach could be beneficial to investigate a variety of clinical populations where EEG traces are rarely clinically significant.

References

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