QIMR Berghofer Medical Research Institute

Metro South Health

Brain signatures of chronic gut inflammation

Caitlin V. Hall*[1,2,3], Graham Radford-Smith[4], Emma Savage[1], Luca Cocchi[1,3], Rosalyn J. Moran[2].

Introduction

Gut inflammation is thought to modify brain activity and behaviour via modulation of the gut-brain axis[1,2]. However, how relapsing and remitting exposure to peripheral inflammation over the natural history of inflammatory bowel disease (IBD) contributes to altered brain dynamics is poorly understood.

Research objectives

In this study, we investigated whether Crohn's Disease (CD) and Ulcerative Colitis (UC) – inflammatory bowel diseases (IBD) characterised by long-standing and repeated exposure to systemic inflammation - were associated with alterations to spontaneous brain state dynamics.

Methods

For this study, 40 CD, 30 UC, and 28 healthy participants completed a (I) general health and clinical questionnaire; (II) neurocognitive assessment; (III) resting state EEG recording; and (IV) a stool sample collected at home.

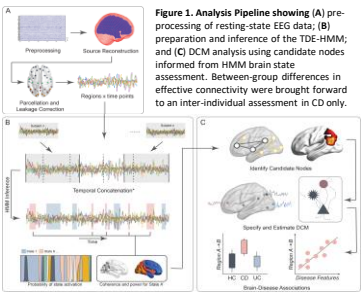

Figure 1. Analysis Pipeline showing (**A**) pre-processing of resting-state EEG data; (**B**) preparation and inference of the TDE-HMM; and (**C**) DCM analysis using candidate nodes informed from HMM brain state assessment. Between-group differences in effective connectivity were brought forward to an inter-individual assessment in CD only.

We fit the Time-Delay Embedded Hidden Markov Model (TDE-HMM) to resting-state EEG data (**Fig. 1A**) which describes brain dynamics as a sequence of transient and distinct patterns of power and phase-coupling (**Fig. 1B**)[3]. We further investigated these brain dynamics at a sub-network resolution, showing differential patterns of effective connectivity that are specific to CD (**Fig. 1C**).

Results

Results from the TDE-HMM brain state assessment showed that resting-state EEG data was best described by six transient and recurring brain states, each with unique spatiotemporal profiles. The spatial maps of power and coherence networks were averaged across a wideband frequency range (1-30 Hz) (**Fig. 2**).

Taken together, temporal dynamics estimated from the HMM suggest that: (a) CD and UC individuals spent less time in, and are less likely to transition to the *visual* state; (b) UC are more likely to transition to, and may spend more time in the *prefrontal* state (although not reaching significance); and (c) individuals with CD reside for longer in, and spent less time between consecutive visits to the *DMN-parietal* state.

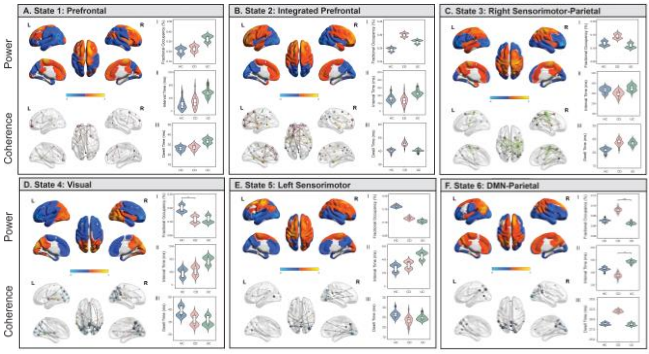

Fig 2. Brain states identified using Hidden Markov Modelling represent networks of power and spectral coherence. (**A**) Left panel shows wideband (1-30 Hz) power maps and coherence networks displayed for each state. (**A.I-III**) Comparison of temporal statistics between healthy controls (HC), Crohn's Disease (CD) and Ulcerative Colitis (UC) individuals for each state, after adjusting for age and sex. Permutation tests were performed to assess the null hypothesis of equality in temporal measures between groups. * denotes $p < 0.05$; ** denotes $p < 0.005$.

Sub-network (DCM) Assessment

To identify the key drivers of these differences, we performed a refined sub-network dynamic causal modelling (DCM) analysis on communication between specific nodes within the *visual* and *DMN-parietal* states **(Fig. 3A).**

Using the time series from each candidate region, we performed a dynamic causal model (DCM) for cross-spectral densities (CSD), which estimates the effective (directed) connectivity between network nodes (**Fig. 3B**). Results showed significantly stronger connectivity from the left insula to mPFC compared to HC and UC **(Fig. 3C-D).** Using a multiple regression, we provide preliminary support to suggest that chronic hyper-signalling between these regions co-occurs with disease duration in CD (**Fig. 3E**).

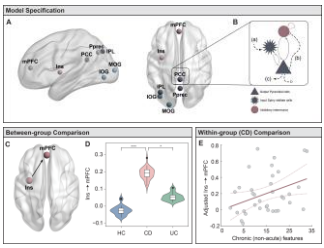

Fig 3. Targeted analyses of effective brain connectivity (Dynamic Causal Modelling, DCM). (A-B) Candidate regions were selected from the HMM brain states for a DCM analysis. (**C-D**) Results from a one-way MANCOVA, showing significantly stronger effective connectivity from the left insula to the mPFC in CD individuals. (**E**) Multiple regression in CD group testing whether disease duration or behavioural symptoms predict the strength of left insula to mPFC connectivity. * denotes $p < 0.05$; *** denotes $p < 0.0005$.

Conclusion

Using an ecologically valid model, we demonstrate that IBD individuals exhibit alterations in brain states and patterns of effective connectivity supporting computations within internal, interoceptive mental states.

References

1. Bell, J. A. *et al.* Repeated exposure to systemic inflammation and risk of new depressive symptoms among older adults. *Translational Psychiatry* **7**, e1208-e1208, doi:10.1038/tp.2017.155 (2017).
2. Schrepf, A. *et al.* A multi-modal MRI study of the central response to inflammation in rheumatoid arthritis. *Nature Communications* **9**, 2243, doi:10.1038/s41467-018-04648-0 (2018).
3. Vidaurre, D. *et al.* Spontaneous cortical activity transiently organises into frequency specific phase-coupling networks. *Nature Communications* **9**, 2987, doi:10.1038/s41467-018-05316-z (2018).
4. Pascal, V. *et al.* A microbial signature for Crohn's disease. *Gut* **66**, 813-822 (2017).

Affiliations

[1]Clinical Brain Networks Group, QIMR Berghofer Medical Research Institute, Brisbane, Australia.
[2]Department of Neuroimaging, Institute of Psychiatry, Psychology & Neuroscience, Kings College London, London, UK.
[3]School of Biomedical Sciences, Faculty of Medicine, University of Queensland, Brisbane, Australia.
[4]Gut Health Research Group, QIMR Berghofer Medical Research Institute, Brisbane, Australia.

2021 Embracing diversity in healthcare
Princess Alexandra Hospital Health Symposium
24–27 August 2021

Queensland Government

QIMR Berghofer Medical Research Institute

King's College London

The University Of Queensland Australia