Personal Statement

The data used in the dissertation was gathered as a part a larger study in 2019 involving multiple types of neuroimaging scans. The data analysis plan was developed by Dr. O'Daly and myself. Guidance on LEiDA was given by PhD student Marie-Stephanie Cahart. Dr. Lythgoe provided insight into MRS data processing.

Tick the box to indicate your agreement: yes

Institute of Psychiatry, Psychology & Neuroscience

Neuroscience MSc

Exploring the Relationship Between Cingulate Glutamate Levels and Resting-State Brain Dynamics: A Multimodal Imaging Study

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INTRODUCTION

Glutamatergic signaling in the anterior cingulate cortex (ACC) has been implicated in the regulation of emotion, attention, and motivation and its dysregulation is linked to several psychiatric illnesses.[1]

The ACC has been known to be a key regulatory of network/state transition between two networks: the fronto-parietal executive network and the default mode network.[2]

Previous work exploring the link between neurotransmitter function and functional connectivity (FC) of cortical hubs, like the ACC, has assumed stable coupling between regions[2] over time, whereas in truth the such connectivity networks reflect an ongoing dynamical process.

There is a pressing need to understand whether individual differences in regional neurotransmitter levels are reflected in characteristic patterns of dynamic functional connectivity (dFC) of the ACC.

STUDY AIMS

To identify the patterns of dFC states both within the ACC, using a gross anatomical parcellation, and between the ACC and other regions that constitute the known resting-state networks, particularly those the ACC is known to interact with.

To investigate the link between individual differences in [Glutamate], through measurement of Glx ([glutamate] + [glutamine]) in the ACC and the dynamic coupling characteristics of that region.

HYPOTHESES

There will be several brain states identified in both within the ACC and between regions that shown synchrony with the ACC.

ACC [Glx] will demonstrate a significant correlation with state characteristics, characterized by LEiDA.

WORK CITED

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(6) Margulies, D. S., Kelly, A. M. C., Uddin, L. Q., Biswal, B. B., Castellanos, F. X., & Milham, M. P. (2007). Mapping the functional connectivity of anterior cingulate cortex. *NeuroImage*, *37*(2), 579–588.

(7) Provencher, S. W. (1993). Estimation of metabolite concentrations from localized in vivo proton NMR spectra. *Magnetic Resonance in Medicine*, *30*(6), 672–679.

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METHODS

Thirty healthy adults were scanned using the following sequences, multiband rsfMRI (T_E = 30 ms; T_R =750 ms; multi-band factor = 4; volumes = 652), T1 anatomical MRI (T_E= 3.02 ms; T_R= 7.3 ms; TI = 400 ms), and PRESS H^1 MRS (T_E = 30 ms; T_R =3000 ms).

MRS Voxel: 20 x 20 x 20 mm; centre placed 16 mm above the corpus callosum genu and perpendicular to the bicommissural line (Figure 1).

CONN toolbox[3] of SPM12[4] was used to pre-process the rsfMRI data. *Leading Eigenvector Dynamics Analysis* (LEiDA)[5] analyzed the dFC and characteristics of the rsfMRI data.

Two groups of ROIs were created; Between-ACC and Within-ACC. Between-ACC consisted of 32 known regions within common resting state networks. For Within-ACC, 32 spheres (3.5 mm radius) served as seeds (Figure 2).

Segmentation of T1 provided estimates of tissue classes in the MRS voxel. The concentrations of each chemical was determined with LCModel[7] which was further adjusted to control for partial volume using the following equation:

$$[M]_{Molar} = \frac{S_{M_{obs}}(f_{GM}d_{GM}R_{H2O_{GM}}+f_{WM}d_{WM}R_{H2O_{WM}}+f_{CSF}d_{CSF}R_{H2O_{CSF}})}{S_{H2O_{obs}}(1-f_{CSF})R_M}\frac{2}{N_M}[H_2O]_{molal}$$

Jamovi version 2.3[8] was used to perform statistical correlations between both Between-ACC and Within-ACC to ACC corrected [Glx].

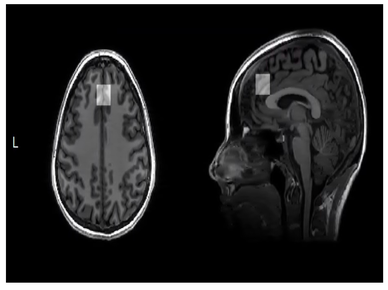

Figure 1: Voxel location from one participant

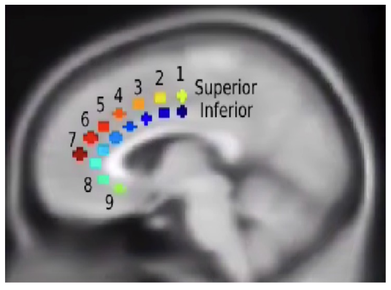

Figure 2: Location of Within-ACC seeds defined[6]

RESULTS

We found no significant correlations between [Glx] and either the probability of transition from a network including the ACC to either the DMN or the front-parietal executive network.

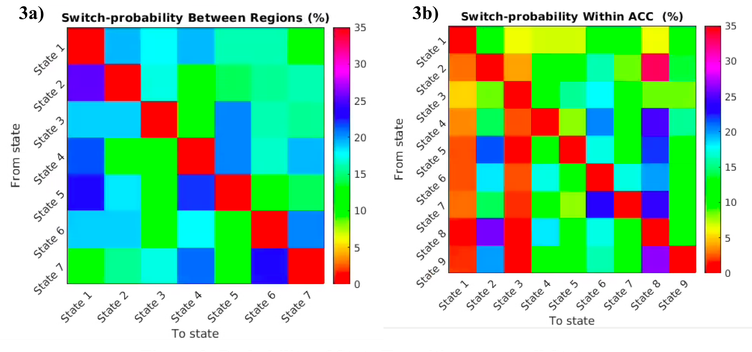

Figure 3: Probability of State Transition across all States; (a) Between-ACC; (b) Within-ACC

RESULTS

Across the thirty participants, the mean [Glx] was 10.97 mmol ± 1.22, but following correction for per water tissue volume, it was 9.18 mmol/L ± 1.09.

For Between-ACC and other cortical regions, two of seven identified states linked to ACC were consistent with the Somato-motor Network with a significant correlation of Probability of Occurrence of State 4 (p=0.037) with ACC [Glx] (Figure 5). However, this did not survive multiple comparisons correction.

Within the ACC, two of nine states were within the bounds of the MRS voxel. However, no significant correlation between state characteristics and ACC [Glx].

Exploring other states within the ACC, significant correlations of Probability of Occurrence in State 2 (p=0.049) and State 3 (p=0.022) were found, prior to multiple comparisons

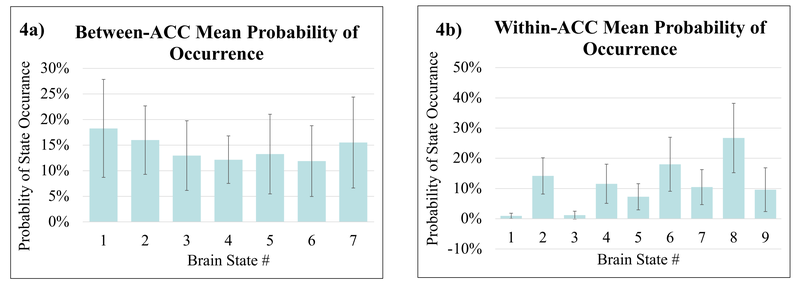

Figure 4: Mean Probability of Occurrence across all States; (a) Between-ACC; (b) Within-ACC; Error Bars are Standard Deviation.

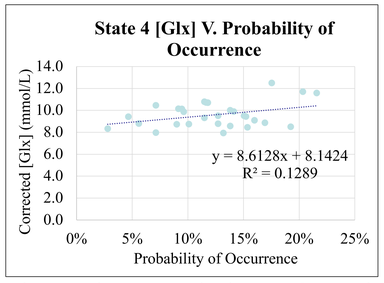

Figure 5: Linear Regression between Corrected [Glx] and Between-ACC State 4 Probability of Occurrence

CONCLUSION

First to demonstrate the possibility of using ACC parcellation methodology to observe dynamics within a single brain region, in addition to being the first study to document corrected [Glx] per water tissue volume in the ACC using a 3T scanner.

Differing from our hypotheses, we did not observe correlations between both Between-ACC and Within-ACC and varying [Glx] in the ACC.

A limitation was that the protocol the rsfMRI and MRS scans were not taken simultaneously, but rather sequentially.

Further research is needed to investigate other metabolites in the ACC and dFC.

Additionally, using this approach to study those with a psychiatric diagnosis may yield useful insights in the future.