Relationships between Depression Vulnerability and Brain Networks: A multimodal EEG fMRI study

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Introduction

Background:

- Major Depressive Disorder (MDD) is a significant health problem and creates substantial burden of disease economically and personally[1,2]. Understanding the underlying neuro pathophysiology of MDD is a critical goal.
- Considerable research has been devoted to examining MDD using two different functional neuroimaging modalities – EEG and fMRI, however, very little work has been devoted to examining their correspondence.
    - Alpha frequency oscillations of the human EEG generally and resting prefrontal EEG alpha asymmetry (FAA; relatively greater left-than-right alpha power) have been examined as promising risk factors for MDD as it is a stable trait[3] and is related to mood disorders, specifically history of depression[4].
    - Using fMRI, characterizable differences in 3 key resting state networks show differences associated with MDD state as well as history of and risk for MDD.

Approach:
Record simultaneous multimodal EEG and fMRI resting state (RS) data in efforts to examine the extent to which spatially-enhanced FAA relates to functional connectivity in resting state networks (RSNs).

Hypothesis:
Supported by meta-analysis of RS fMRI data[5], we expect to observe dysfunction within DMN, FPN, and salience RSNs associated with MDD. We also predict functional connectivity between these RSNs will be modulated via FAA and altered in individuals previously diagnosed with MDD.

Results: *Within* Network Functional Connectivity

History of Major Depressive Disorder

Dual regression analyses revealed that individuals with *no MDD history* exhibited greater within network connectivity than individuals *with MDD history* within the DMN, right FPN, left FPN, and salience components identified via ICA (Figure 1).

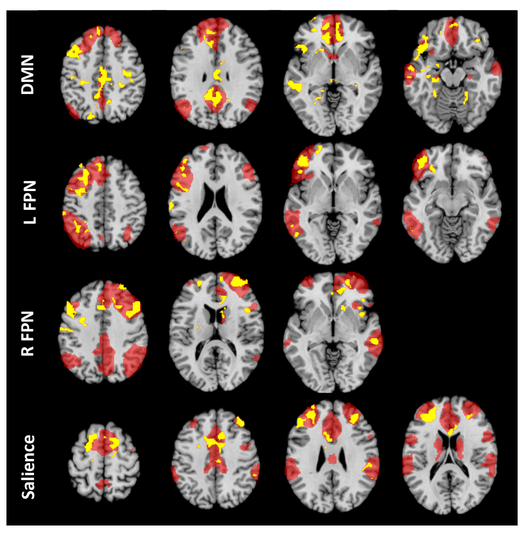

Figure 1: Increased Resting State functional connectivity in individuals with no history of MDD compared to individuals with MDD history (p<0.005).

Frontal Alpha Asymmetry

Dual regression analyses identified functional connectivity within the DMN, right and left FPN, and salience components was associated with *frontal alpha asymmetry* as measured via right and left F5/F6 homologous leads.

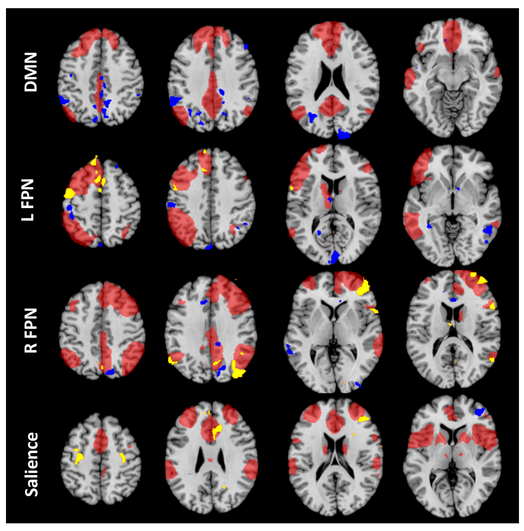

Figure 2: RS connectivity modulated via frontal alpha asymmetry. Yellow indicates positive association between FAA and RS connectivity, and blue indicates negative association between FAA and RS connectivity within the ICN (p>0.05)

Mid-Frontal Alpha Power

Mid-Frontal alpha was extracted across 8 sites centered on AFz (FP1, FPz, FP2, AF3, AF4, F1, FZ, F2), measuring EEG power over the dorsal nexus[9]. Within network effects associated with *mean alpha power* were observed in the DMN, and left FPN, while minimal effects were present in the right FPN and salience.

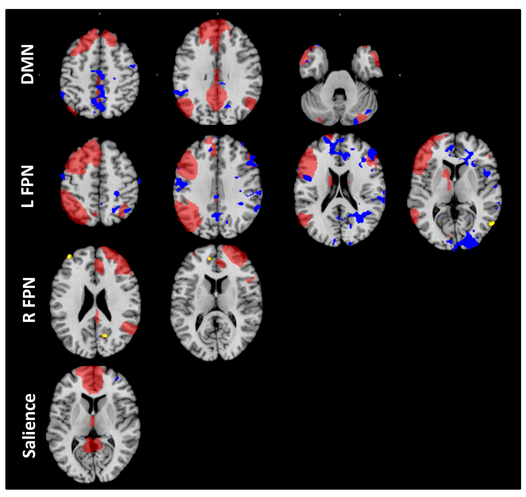

Figure 3: RS connectivity modulated via mid frontal alpha. Yellow indicates positive association between Alpha and RS connectivity, and blue indicates negative association between Alpha and RS connectivity within the ICN (p>0.05)

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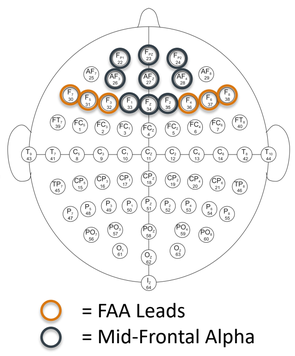
Methods

Participants:

- Hist - : 29 healthy adults (12 males, 17 females; Age: 19.0 +/- 1.1 yrs) with no history of MDD
- Hist +: 27 healthy adults (11 males, 16 females: Age: 19.0 +/- 1.7 yrs) not currently depressed, but had been previously diagnosed with MDD as defined by the DSM-5

EEG Data Collection and Analysis:

Multimodal 64-channel EEG and 3T RS fMRI was obtained from 56 adults during Eyes Open and Closed rest (alternating in pseudo random order for 2 min each). For all subjects, standard EEG data processing steps were applied, using 2.048 second epochs overlapping by 1.5 seconds. Data were current-source-density transformed to improve spatial specificity. Alpha was the average power in the 8- 13 HZ band. Frontal Alpha Asymmetry (FAA) was measured comparing left and right log transformed EEG alpha power (ln(right) – ln(left)) at homologous leads (F3&F4,F5&F6, F7&F8).



fMRI Data Collection and Analysis:

T1-weighted MPRAGE scans and 12 minutes of resting state functional EPI images using GRAPPA parallel imaging were collected. Standard fMRI preprocessing and independent components analysis (ICA) was carried out using FSL's MELODIC[6]. Single subject ICA was performed, followed by FSL FIX to remove spurious signals from the BOLD time series. A group ICA was generated on combined eyes open and closed RS fMRI data (198 time points of each eyes open and closed rest, d=10 components) followed by dual regression[7] to examine the relationship between resultant RSNs and resting EEG alpha power, FAA, or MDD history. Given our hypotheses, subsequent examination of ICNs focused on four ICNs corresponding to the DMN, right FPN, left FPN, and Salience networks.

Finally, to extract relationships between resultant ICNs, GLM analyses were performed by estimating connectivity between ICNs of interest using partial correlations in the FSLnets toolbox[8] (5,000 permutations).

Results: *Between* Network Functional Connectivity

Main Findings

Between ICN relationships were examined using the FSLnets toolbox[8].
Between network connectivity in individuals with *No MDD History* was greater compared to individuals *with MDD History* between the DMN and right FPN, the left FPN and right FPN, and the Salience and left FPN (Figure 4A). In addition, connectivity between all networks was more similar, with exception to the Salience and DMN, when mean frontal alpha power was increased (Figure 4C). No significant findings were associated with FAA.

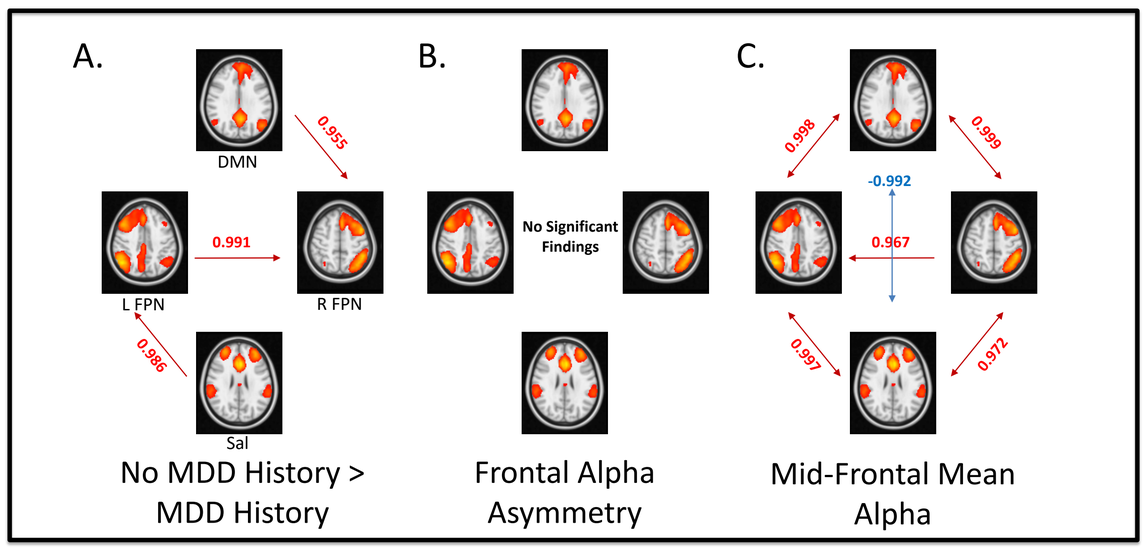


Figure 4: Altered between network resting state functional connectivity modulated by A) history of MDD, B) FAA (not significant) and C) Mean Frontal Alpha.
*Significance values shown correspond to 1-p.

Discussion

Our findings provide insight into functional connectivity differences within and between brain networks associated with MDD history, with alpha power, and alpha asymmetry - an important biomarker of risk for MDD.

- Studying connectivity modulations in functional brain networks associated with FAA and MDD support previous links associating MDD and FAA (inhibitory processing) with reduced FC among prefrontal brain networks. Furthermore, dual regression analyses confirm that RSN connectivity corresponds to FAA, particularly in the ventral lateral prefrontal cortices and anterior cingulate within the FPN components.
- Between network findings of greater within network connectivity associated with mean frontal alpha power may indicate that greater alpha power may be associated with a less controlled and less discrete state amongst brain networks. In other words, alpha may play a coordinating role that allows brain networks to function independently and exert task-specific control. Disruption of this function could reveal a critical risk factor for MDD.

Further extrication of such relationships may lead to the identification of biomarkers that may serve as an intermediate target for diagnosis, treatment or prevention in MDD.

Future Directions: We plan to employ additional network metrics, e.g. graph theory modularity, to further examine the the role Alpha power may play in coordinating brain network interactions.