

A Framework for Causal Connectivity Analysis of fMRI in Patient Populations: An application to Major Depression and Early Life stress

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Introduction

Differential pathophysiology within major depression (MDD) based on early life stress history is associated with two distinct phenotypes; (I) a hyper-responsive subtype characterized by exaggerated amygdala reactivity and decreased anterior cingulate (BA 32/24) volume among trauma-exposed MDD and (II) a hypo-responsive subtype associated with attenuated limbic reactivity and unaffected cingulate volume among never trauma-exposed MDD [1, 2]. Translational models of stress [3] as well as imaging findings in non-clinical human studies [4] have demonstrated key roles for medial and lateral prefrontal cortex (PFC) (e.g., anterior cingulate and dorsal lateral PFC) in modulation of limbic response to stress. The current study investigated whether differential amygdala reactivity within MDD based on early life stress history was associated with failure of inhibition from medial or lateral PFC.

Method

Twenty un-medicated patients with MDD and 19 healthy controls performed a gender identification variant of the Eriksen flanker task of selective attention [5]. The task was designed to identify the influence of valence on the efficiency of selective attention by emotion (positive, negative, and neutral) and level of task difficulty (non-conflict, congruent and incongruent). The participants were asked to respond as quickly and accurately with a button press to identify gender centralized target faces. fMRI data were acquired on a 3T Philips Intera Achieva scanner with a TR of 3000ms. The mean time series were extracted from 11 different activated regions of interest (ROIs) for all participants. The underlying neuronal response for these times series were obtained by normalizing them and deconvolving the hemodynamic response using a cubature Kalman filter [6]. This was then input into a dynamic multivariate autoregressive model (dmVAR) [7, 8] to obtain the connectivity matrices which were then populated into different samples (negative and neutral valence of non-conflict difficulty), separately for patients and controls. T-tests were performed between the samples and paths significantly greater during negative valence condition as compared to neutral valence were

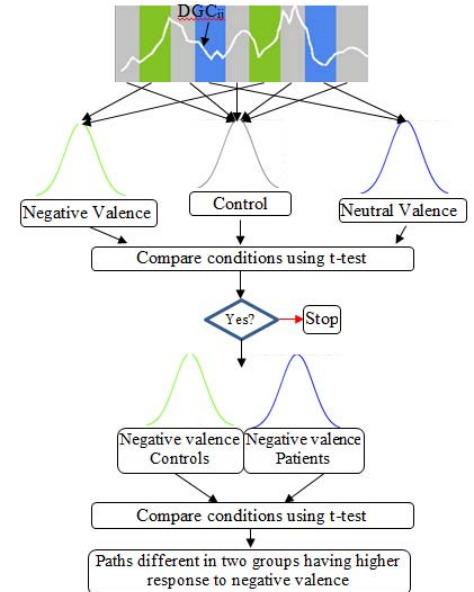


Figure 1 Schematic of Connectivity Analysis & Statistical Inference

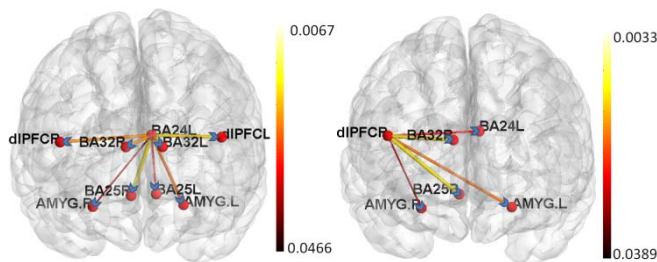


Figure 2: Paths which are significantly greater in MDD patients.

Figure 3: Paths which are significantly greater in controls

identified. Among these paths, those that were significantly different between controls and MDD patients were obtained ($p < 0.05$). A schematic of the analysis procedure is illustrated in Fig.1. These set of paths were then examined to see if they were significantly correlated with childhood trauma scores.

Results

Figs.2 and 3 show the paths which were significantly greater in MDD and controls, respectively, and at the same time also greater during negative valence condition. Paths originated from left Brodmann area 24 (BA24L) were significantly greater in MDD, whereas outputs from right dorsolateral PFC (dlPFC R) were greater in controls. Fig. 4 shows the scatter plot for correlation ($R = -0.8218$, $p < 0.05$) of the path BA24L to left Amygdala (amygL) with scores for emotional abuse. Similarly Fig.5 represents scatter plot of correlation ($R = -0.7129$, $p < 0.05$) between the same path and the physical abuse scores.

Discussion

The current investigation revealed between group differences in directional connectivity in response to aversive stimuli among MDD and HC. Specifically, inputs to amygdala from lateral PFC was higher in HC and from medial PFC was higher in MDD. Negative correlation of the path from medial PFC to amygdala with early life trauma in MDD supports the view that differential amygdala reactivity within MDD based on early life stress history is associated with failure of top-down inhibition

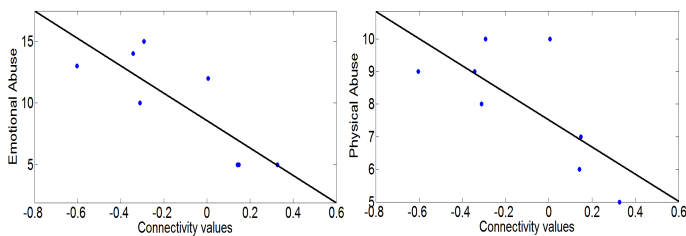


Figure 4: Correlation between path BA24L to Left Amygdala, and emotional abuse

Figure 5: Correlation between path BA24L to Left Amygdala, and physical abuse.

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