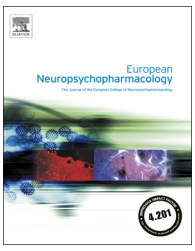
European Neuropsychopharmacology (2014) 24, 1784–1792



www.elsevier.com/locate/euroneuro

Alterations in effective connectivity anchored on the insula in major depressive disorder

Sarina J. Iwabuchi[a], Daihui Peng[b,**], Yiru Fang[b], Kaida Jiang[b], Elizabeth B. Liddle[a], Peter F. Liddle[a], Lena Palaniyappan[a,c,*]

[a]*Translational Neuroimaging, Division of Psychiatry, Institute of Mental Health, University of Nottingham, Room-09 C Floor, Triumph Road, Nottingham, NG7 2TU England, UK*
[b]*Division of mood disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, China*
[c]*Nottinghamshire Healthcare NHS Trust, Nottingham, UK*

Received 18 March 2014; received in revised form 26 July 2014; accepted 10 August 2014

KEYWORDS
Effective connectivity;
Insula;
Depression;
Granger causality;
Resting fMRI

Abstract
Recent work has identified disruption of several brain networks involving limbic and cortical regions that contribute to the generation of diverse symptoms of major depressive disorder (MDD). Of particular interest are the networks anchored on the right anterior insula, which binds the cortical and limbic regions to enable key functions that integrate bottom-up and top-down information in emotional and cognitive processing. Emotional appraisal has been linked to a presumed hierarchy of processing, from sensory percepts to affective states. But it is unclear whether the network level dysfunction seen in depression relates to a breakdown of this presumed hierarchical processing system from sensory to higher cognitive regions, mediated by core limbic regions (e.g. insula). In 16 patients with current MDD, and 16 healthy controls, we investigated differences in directional influences between anterior insula and the rest of the brain using resting-state functional magnetic resonance imaging (fMRI) and Granger-causal analysis (GCA), using anterior insula as a seed region. Results showed a failure of reciprocal influence between insula and higher frontal regions (dorsomedial prefrontal cortex) in addition to a weakening of influences from sensory regions (pulvinar and visual cortex) to the insula. This suggests dysfunction of both sensory and putative self-processing regulatory loops centered around the insula in MDD. For the first time, we demonstrate a network-level processing defect

Abbreviations: AAL, Automated Anatomical Labeling; ACC, anterior cingulated cortex; BOLD, blood-oxygen level dependent; CBT, Cognitive Behavioral Therapy; DMPFC, dorsomedial prefrontal cortex; DPARSF, Data Processing Assistant for resting-state fMRI; DSM, Diagnostic and Statistical Manual for Mental Disorders; EPI, echo-planar imaging; FOV, field of view; FWE, Family-wise Error; FWHM, full-width, half-maximum; GCA, Granger causality analysis; HAMA, Hamilton Anxiety Scale; HRF, haemodynamic response function; HDRS, Hamilton Depression Rating Scale; MNI, Montreal Neurological Institute; rAI, right anterior insula; SFG, superior frontal gyrus; SPM, Statistical Parametric Mapping; TE, echo time; TMS, transcranial magnetic stimulation; TR, repetition time

*Corresponding author at: Translational Neuroimaging, Division of Psychiatry, Institute of Mental Health, University of Nottingham, Room-09 C Floor, Triumph Road, Nottingham, NG7 2TU England, UK.
**Co-corresponding author.
E-mail address: lena.palaniyappan@nottingham.ac.uk (L. Palaniyappan).

http://dx.doi.org/10.1016/j.euroneuro.2014.08.005

extending from sensory to frontal regions through insula in depression. Within limitations of inferences drawn from GCA of resting fMRI, we offer a novel framework to advance targeted network modulation approaches to treat depression.

1. Introduction

With a lifetime prevalence of approximately 1 in 10 individuals, Major Depressive Disorder (MDD) is the most costly of brain disorders (Sobocki et al., 2006) and has been highlighted as the 2nd most disabling condition for its impact on quality of life (Murray and Lopez, 1997) with a high degree of association with suicide rates (Cavanagh et al., 2003). In the last decade, important progress has been made in understanding the neural basis of depression, and key brain networks have been identified to play a role in generating the diverse symptoms of depression.

A prominent neural network model for MDD proposed by Mayberg et al. (1999) suggests that depression is characterized by a disruption in the limbic–cortical network. Using PET, it has been shown that in healthy individuals, activity is decreased in the limbic and paralimbic structures over the cortical, while in depression, this pattern is reversed with overactivity of limbic regions and decreases in dorsal cortical regions (Mayberg et al., 1999). To offer support for this model, Hamilton et al. (2011a) have recently documented increased excitation within the limbic and paralimbic structures (e.g. the hippocampus), and increased inhibition of cortical structures (e.g. dorsomedial prefrontal cortex (DMPFC) and cuneus/posterior cingulate) by the commonly implicated ventral anterior cingulate cortex (vACC). A region in the DMPFC, termed the 'dorsal nexus', has also shown to possess abnormally increased connectivity with the three major networks (i.e. cognitive control, affective, default mode) in MDD (Sheline et al., 2010). This 'hot-wiring' pattern results in widespread information processing imbalance across the brain, which is thought to underlie the complex symptoms and cognitive deficits observed in MDD.

An additional structure that has garnered increased attention as a key contributor to the pathophysiology of MDD is the anterior insula. The anterior insula shares extensive and widespread anatomical connections to cortical and limbic regions and plays a crucial role in the coordination between the cognitive control and default mode network (Menon and Uddin, 2010). The rich connectivity of the anterior insula to both sensory processing regions (visual, auditory cortices and thalamus) and the so-called self-processing multimodal regions (prefrontal and anterior temporal) suggests a unique role for anterior insula in the ordered or hierarchical information processing, presumed to include bottom-up (sensory to multimodal) and top-down (multimodal to sensory) reciprocal influences. Given the insula's posited role in functions related to emotional processing, in addition to its connections to limbic regions, it seems reasonable that the diverse symptoms of MDD may be associated with impaired functioning of this region. Indeed, the functional activity and connectivity of the insula have been shown to be perturbed in several studies of patients with depression (Busatto, 2013; Hamilton et al., 2012, 2011b; Sliz and Hayley, 2012; Sprengelmeyer et al., 2011). For example, the activity of the right fronto-insular network was attenuated in patients with depression, and this was associated with greater levels of maladaptive rumination (Hamilton et al., 2011b). Studies of regional homogeneity, which measures local connectivity, have also shown reductions in the right insula, which correlated positively with anxiety and hopelessness (Yao et al., 2009). Similar patterns were also observed in first-degree relatives of MDD patients, suggesting that insular dysfunction represents a crucial vulnerability marker for depression (Liu et al., 2010).

Functional changes have also been reported in the insula following various treatments for MDD. Regional cerebral blood flow of the insula was reduced following repetitive transcranial magnetic stimulation (rTMS) treatment, which also correlated with treatment efficacy (Kito et al., 2011). Other studies have also revealed reductions in insula activity with antidepressant treatment (Delaveau et al., 2011; Fitzgerald et al., 2008). In a recent PET study, the right anterior insula (rAI) was localized as a crucial region for differentiating MDD patients who are responsive to CBT or antidepressants (McGrath et al., 2013). Hypometabolism of the rAI predicted response to CBT, while hypermetabolism predicted a patient to respond to antidepressants. Therefore, the insula offers great promise as a target region for treatment of MDD, where its modulation will have widespread effects on the connectivity of networks that are disrupted in MDD. Studying the directed influence (effective connectivity) of the insula on other structures implicated in depression is crucial for our understanding of the neural circuitry of depression.

We therefore sought to investigate the effect of depression on the effective connectivity of the rAI with the rest of the brain. We employed Granger causality analysis (GCA) on resting-state functional magnetic resonance imaging (fMRI) data to investigate whether positive or negative influences of the rAI on the rest of the brain differ in patients with current major depression. We anticipated a reduction in the connectivity of the fronto-insula network in MDD patients, as well as more widespread abnormalities in connectivity between the rAI and limbic and cortical regions. It is important to note that while Granger-causality allows directional inferences to be made on the basis of temporal precedence observed within the limits of the sparse resolution offered by fMRI, the inferences do not provide conclusive evidence on underlying neural state shifts.

2. Experimental procedures

2.1. Participants

Sixteen patients and 16 healthy controls were recruited from Shanghai Mental Health Centre and Shanghai Huashan Hospital. The MDD group consisted of 9 females and 7 males, aged 26–45 years