A brain network model for depression: From symptom understanding to disease intervention

Baojuan Li[1,2], Karl Friston[3], Maria Mody[2], Huaning Wang[4], Dewen Hu[5], Hongbing Lu[1]

[1]School of Biomedical Engineering, Fourth Military Medical University, Xi'an, Shaanxi, China

[2]Department of Radiology, Athinoula A Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA

[3]The Wellcome Trust Centre for Neuroimaging, University College London, Queen Square, London WC1N 3BG UK

[4]Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi, China

[5]College of Mechatronic Engineering and Automation. National University of Defense Technology. Changsha, Hunan, 410073, P.R.China

Address for Correspondence

Hongbing Lu

School of Biomedical Engineering, Fourth Military Medical University, Xi'an, Shaanxi, China

Tel (86) 029 84774837; Fax (86) 029 84774837

Email: luhb@fmmu.edu.cn

Keywords: depression, functional connectivity, effective connectivity, default mode network, affective network, affective network.

Number of words in the abstract:

Number of words in the article body:

Number of figures: 2

Number of tables: 0

Short title: neurobiological basis of depression

Abstract

Understanding the neural substrates of depression is crucial for diagnosis and treatment. Here, we review recent studies of functional and effective connectivity in depression, in terms of functional integration in the brain. Findings from these studies, including our own, point to the involvement of at least four networks in patients with depression. Elevated connectivity of a ventral limbic affective network appears to be associated with excessive negative mood (dysphoria) in the patients; decreased connectivity of a frontal-striatal reward network has been suggested to account for loss of interest, motivation, and pleasure (anhedonia); enhanced default mode network connectivity seems to be associated with depressive rumination; and diminished connectivity of a dorsal cognitive control network is thought to underlie cognitive deficits especially ineffective top-down control of negative thoughts and emotions in depressed patients. Moreover, the restoration of connectivity of these networks-and corresponding symptom improvement-following antidepressant treatment (including medication, psychotherapy, and brain stimulation techniques) serves as evidence for the crucial role of these networks in the pathophysiology of depression.

Introduction

Over the years, depression has contributed to an increasing psychiatric burden on society; however, effective diagnosis, treatment and prevention of the disorder have remained elusive. The main challenge appears to be our limited understanding of the primary underlying mechanisms of depression. Recently, there has been a growing optimism that functional neuroimaging may help us answer key questions about the pathophysiology of disorder. For example, which brain systems are associated with affective and cognitive dysfunction in depression? How do distributed regions interact to produce the symptoms of depression? What is the neural mechanism underlying remission following antidepressant treatment? Why is the relapse rate so high in remitted depressed patients? Advances in neuroimaging techniques and brain connectivity analysis are now making it possible to address these questions, thereby tackling one of the greatest mysteries of the human mind.

A growing literature supports the notion that the symptoms of depression are associated with widespread network dysconnectivity; rather than the aberrant responses of individual brain regions. Here, we review recent advances in functional magnetic resonance imaging (fMRI) studies that have tried to elucidate the neurobiological underpinnings of depression, from the perspective of functional integration. Depression – frequently seen as withdrawal from the prosocial environment – is characterized by excessive self-focus, aberrant emotional and

affective processing, and diminished cognitive control. To this end, we pay special attention to three core networks that have been implicated in these processes: the default mode network (DMN), the affective network (AN), and the cognitive control network (CCN), respectively. First, we briefly review brain connectivity. Detailed descriptions of the different methods we will refer to can be found in [1-8].

1. A brief summary of brain connectivity analysis methods

Characterizations of brain connectivity include structural connectivity, functional connectivity and effective connectivity. For the most part, structural connectivity analysis relies on techniques such as diffusion magnetic resonance imaging (dMRI) and tractography,, which report the integrity of white matter fiber tracts. The remaining distinction between functional and effective connectivity is important to understand [1-3]. The former refers to (undirected) correlations between the activities of two brain regions, while the latter refers to (directed and usually reciprocal) causal influences among brain regions within a network.

Specifically, functional connectivity corresponds to the temporal correlations (or statistical dependencies) among regional brain responses [2, 3]. It is a simple characterization of brain connectivity and can be measured directly from fMRI data using different methods. The easiest way to measure functional connectivity is to use a seed-based method. Usually, one extracts the mean time series of a region of interest

(ROI) and computes the correlation between the time series of the ROI and all other voxels (or regions) in the brain. The ensuing (thresholded) correlation map represents functional connectivity between the ROI and all other voxels (or regions). Lately, researchers have started to map whole-brain functional connectivity using fMRI. Usually, the brain is segmented into many (about 100) regions according to a template (e.g. the automated anatomical labeling atlas, AAL). Whole-brain functional connectivity can then be summarized with a correlation matrix. Finally, independent component analysis (ICA) is widely used to derive coherent patterns or modes of activity from neuroimaging data that correspond to functionally connected brain networks. This sort of characterization decomposes the correlation (or covariance) matrix into a series of spatial modes that are correlated or independent over regions or time. This represents a useful and compact summary of distributed brain activity.

Unlike functional connectivity, effective connectivity infers directed (i.e., causal) interactions within a brain network. Effective connectivity is defined as the influence one neural system exerts on another [1, 3]. In the past decade, different approaches to measuring effective connectivity such as psychophysiological interaction (PPI) analysis, structural equation modeling (SEM), Granger causality modeling (GCM) and dynamic causal modeling (DCM) have been developed. GCM tries to infer directed connectivity from observed BOLD signals using autoregressive models [4]. Strictly speaking, GCM measures directed functional connectivity because it operates on observed haemodynamic (BOLD) responses. In contrast, DCM treats the brain as a

dynamic system of (unobserved or hidden) neuronal states, which are driven by experimental inputs or endogenous fluctuations to produce BOLD responses [5, 6]. DCM estimates neural interactions using state-space models based on (deterministic or random) differential equations. These equations describe neural dynamics and are supplemented with hemodynamic equations to transform regional neuronal activity to the observed BOLD response [5]. Both empirical and simulated data suggest DCM may be more robust than GCM, when estimating directed connectivity [9, 10].

2. Impaired cortical networks in depression

In this section, we examine three core networks affected in depression, the pattern of disruption within each – as related to the symptoms of depression – and their response to various treatments.

2.1 Default mode network

The default mode network (DMN) [11] consists of a specific set of regions including the midline cortical regions within the posterior cingulate cortex (PCC), precuneus, medial prefrontal cortex (mPFC) and lateral parietal regions, such as the inferior parietal cortex [11, 12]. These regions exhibit high metabolic activity at rest and during passive sensory processing tasks, while being deactivated during performance of goal-directed cognitive tasks [11, 13]. The DMN has been associated with self-referential processes [14, 15] and may be separable into anterior (ventromedial PFC) and posterior (PCC) components [16]. It has also been implicated in studies of depression. For example, we found that the DMN was among the most discriminating

networks classifying patients from healthy controls [17]

2.1.1 Altered connectivity of the default mode network in depression

Elevated functional connectivity of the DMN has been consistently reported in individuals with depression. Greicius et al. (2007) conducted one of the first studies to investigate resting-state functional connectivity of the DMN in MDD patients. Using independent component analysis (ICA), the authors found increased DMN connectivity in depressed subjects compared to healthy controls [18]. Gaffrey et al. investigated how a history of preschool depression may affect the developmental trajectory of the DMN. Using the PCC as a seed region, they examined the functional connectivity between the PCC and other brain regions. Children with a history of preschool depression exhibited increased PCC functional connectivity in the subgenual and anterior cingulate cortices [19]. Elevated DMN functional connectivity in depressed patients was also detected when subjects were instructed to engage in externally-focused thought [20]. Additionally, adolescents with MDD exhibited persistent and elevated DMN connectivity, both at rest and during an emotion identification task [21]. Elevated DMN functional connectivity thus appears to be a robust marker of MDD that is evident even in remitted depression: Zamoscik and colleagues found remitted depressed patients exhibit greater PCC connectivity with the parahippocampal gyri (PHG) during (sad) mood induction. In fact, stronger PCC-PHG connectivity – associated with more episodes of depression – and higher levels of rumination and sadness predicted depressive symptoms at follow-up [22].

MDD patients are known to exhibit hyperconnectivity of the DMN during task performance even in a recovered-state [23]. A few studies, however, found reduced connectivity or no significant alterations in functional connectivity of the DMN [24, 25].

2.1.2 Symptoms, treatments and the DMN subnetworks in depression

Previous brain connectivity studies on depression have also suggested that the DMN may consist of interacting sub-networks. Zhu et al. (2012) reported elevated functional connectivity in the anterior division of the DMN in MDD patients to be positively correlated with rumination score. Interestingly, they also found attenuated functional connectivity in the posterior division of the DMN in the patients to be negatively correlated with autobiographical memory scores [26]. In our study, using group ICA to investigate resting-state functional connectivity in MDD, we found evidence for two dissociable subnetworks in the DMN: an anterior subnetwork which had the highest amplitude in the mPFC, and a posterior subnetwork, which had the highest amplitude in the bilateral precuneus [27]. Unlike Zhu and colleagues, Sambataro et al. (2013) found increased functional connectivity within posterior, ventral and core DMN subsystems in patients with MDD. They also reported altered interactions between DMN subsystems in patients [28]. Marchetti and colleagues argued that an imbalance between the task positive and task negative components of the DMN may present as a risk factor for recurrent depression [29], thereby proposing a potential neurobiological model of functional dysconnectivity for depression.

As noted earlier, there is some evidence for a positive correlation between DMN connectivity and rumination score in MDD patients. In a study by Berman et al., resting state functional connectivity, between the posterior cingulate and the subgenual cingulate, correlated positively with rumination scores both in depressed and healthy subjects. However, when the depressed patients were engaged in a short-term memory task, the correlation between posterior cingulate-subgenual cingulate functional connectivity and rumination scores was not significant [30]. Moreover, although mood changed significantly from unconstrained resting-states to induced-ruminative states, healthy controls were able to maintain brain connectivity while MDD patients exhibited elevated DMN connectivity [31].

Pharmacological treatment studies of depression have found antidepressants to normalize the increased DMN functional connectivity in subjects with dysthymic disorder, a mild but long-term form of depression [32]. Even in healthy controls, antidepressant drug treatment was found to reduce DMN connectivity within two weeks [33]. Studies of depression have reported decreased activation and restored functional connectivity of the DMN in the patients following antidepressant treatment [34-37]. Some studies have also found differences in DMN functional connectivity between those who responded to the treatment and treatment-resistant participants [38]. Specifically, abnormalities in the frontal cortex have been found to persist in remitted subjects [27, 36, 39]. In our previous work, we investigated changes in DMN

functional connectivity after 12 weeks of antidepressant treatment in MDD patients. Although depressed subjects exhibited increased functional connectivity in both anterior and posterior sub-networks, aberrant connectivity of the posterior sub-network was normalized with the remission of symptoms. In contrast, elevated functional connectivity of the anterior sub-network persisted in remitted subjects. This indicates that antidepressants may not modulate the functional connectivity of the mPFC [27]. This may have been due to the specific effects of antidepressants as seen in other studies [39]. In order to achieve enduring remission, one may need to combine antidepressants with cognitive behavior therapy, which has been shown to modulate mPFC connectivity [40]. These results suggest that persistent abnormalities in the mPFC in remitted subjects may also serve as a risk factor for relapse of depression: Farb et al. investigated this hypothesis in recurrent unipolar depression. They found that activity of the mPFC in remitted patients predicted relapse of the disease [41].

2.2 The affective network and depression

Emerging neuroimaging findings suggest an involvement of the affective network (AN) in the pathophysiology of depression [42]. This network comprises the orbitofrontal cortex (OFC), the affective division of the anterior cingulate cortex (ACC), and limbic regions including the amygdala, hippocampus, nucleus accumbens, hypothalamus and insula [43] [44]. Crucially, the AN has been associated with emotional processing and regulation. Previous studies have found hyperactivation of

the amygdala and subgenual ACC, associated with dysfunctional emotional processing in depressed patients. In summary, functional neuroimaging points to aberrant connectivity within the AN, which may underlie emotion dysregulation, a hallmark of depression.

2.2.1 Negative emotions and components of the affective network

several studies have reported an attentional bias for sad faces in individuals with depression, when presented with sad and happy faces [45, 46]; whereas healthy controls show a positive bias toward happy faces [46]. Related to these findings, decreased amygdala connectivity was found in MDD patients during implicit processing of sad faces [47]. In addition, depressed patients also show increased memory sensitivity for negative information associated with increased amygdala-hippocampus and amygdala-caudate-putamen connectivity [48]. Tao et al. found that a brain 'hate circuit' that encompasses the superior frontal gyrus, insula and putamen was uncoupled in depression [49]. In a study of MDD, Admon et al (2014) found an increased susceptibility to negative stimuli in remitted patients compared to controls. The increases in cortisol and anxiety levels were higher in the remitted MDD individuals than the controls in a stress task. It is worth noting that only remitted subjects showed elevated caudate-amygdala and caudate-hippocampus connectivity, when responding to negative stimuli [50].

Anhedonia, a loss of pleasure, interest, or motivation is also a highly prevalent

symptom of depression [51] . Studies have found that – compared to healthy controls – depressed patients show reduced magnitude and duration of positive responses [52] and that this inability to sustain positive affect is associated with reduced fronto-striatal connectivity [53]. In a separate study, Admon and colleagues used PPI analyses to reveal decreased connectivity between the caudate and dACC in MDD patients in response to monetary gains [54].

Studies of affective processing indicate a role for the orbitofrontal cortex (OFC) in emotional regulation in healthy subjects [55]. As such, the abnormal functional connectivity of this region in depression may explain the increased salience of negative stimuli and decreased salience of positive stimuli in depressed patients [56]. Frodl et al. reported decreased OFC connectivity in dorsal ACC, precuneus, and cerebellum and increased OFC connectivity in the dorsolateral prefrontal cortex (DLPFC), inferior frontal operculum, and motor areas in patients with MDD during a face-matching task [57]. Using structural equation modeling, Carballedo et al found lower bilateral effective connectivity from the amygdala to OFC in major depression [58]. Interestingly, remitted MDD patients showed reversed frontotemporal effective connectivity in a DCM study of emotional face processing. Specifically, happy faces modulated bidirectional OFC-amygdala and OFC-fusiform gyrus connectivity in depressed subjects. The same pattern of modulation was observed when healthy controls viewed sad faces [59]. Taken together, these results speak to a significant role for the OFC in the affective network.

Recent efforts to integrate functional and structural neuroimaging are shedding light on the neurobiology of depression. In a recent study, de Kwassteniet and colleagues found that depression subjects exhibited greater subgenual ACC (sgACC) functional connectivity in the amygdala bilaterally and in right hippocampus; the increased connectivity being positively correlated with depression severity. Further analysis revealed that the functional abnormalities were associated with white matter integrity of the uncinate fasciculus, which connects the sgACC to the amygdala and hippocampus. Specifically, sgACC functional connectivity was more negatively correlated with uncinate fasciculus FA in MDD patients [60]. These results are in keeping with those of Davey and colleagues (2012) who found increased resting-state connectivity of both the subgenual and pregenual regions of the rostral cingulate cortex with the frontal cortex [61].

In addition to be being widely reported in depressed adults, functional dysconnections of the affective network have also been found in early-childhood-onset MDD [62] and in adolescents with depression [63]. MDD adolescents exhibited attenuated amygdala-hippocampal/brainstem functional connectivity and elevated amygdala-precuneus functional connectivity at rest [64]. Hyperconnectivity between the sgACC and amygdala has also been consistently found in depressed adolescents both at rest [65] and during processing of negative stimuli [66]. Altered striatal functional connectivity has also been associated with MDD severity in depressed

adolescents [67]. Importantly, increase in connectivity between the amygdala and subgenual ACC in adolescents has been found to be associated with the onset of first-episode depression [68]. Taken together, these results support the importance of the subgenual ACC in the neurobiology of depression.

2.2.2 Treatment

A variety of treatments have targeted the affective network in depression. Improvements in positive affect following antidepressant treatment have been associated with increased fronto-striatal connectivity [69]. Results of repetitive transcranial magnetic stimulation (rTMS) appear to vary depending on the severity of pre-treatment anhedonia symptoms and connectivity of the reward network, thereby yielding responders and non-responders [70]. On a related note, pre-treatment functional connectivity of the OFC and insula has been shown to predict response to psychotherapy [71]. Deep brain stimulation（DBS）has been shown to be effective in treatment-resistant depression [72] – the therapeutic effects appearing to be mediated by subgenual ACC connections to the OFC and limbic system [73].

2.3 The cognitive control network and depression: Atypical connectivity

In patients with depression, impaired emotion processing is often accompanied by cognitive impairments [74] [75]. These impairments can persist even after remission of affective symptoms. Related to these impairments, another brain network has been

implicated in the pathophysiology of depression, the so-called cognitive control network (CCN). This network mainly consists of functionally connected brain regions including the dorsolateral prefrontal cortex (DLPFC), the cognitive subdivision of ACC and the parietal cortex [76-79]. The CCN is thought to be an executive or control system, responsible for regulating thoughts and actions in accordance with internal goals [80, 81] . Neuroimaging studies have identified coactivation of the CCN during performance of different cognitive tasks. A failure of effective cognitive control over emotional processing is one of the central characteristics of depression [82, 83]. Neuroimaging studies seeking to elucidate the neural substrates of depression have identified prominent impairments of the CCN in depression.

Dysconnectivity of regions involved in the CCN has been reported in patients with depression during performance of tasks involving working memory [84], Stroop effects[85], executive-control [86] and affective interference [87], as well as during rest [43, 88, 89]. However, the findings have been divergent. Vasic et al. (2009) observed increased functional connectivity in the left DLPFC during a working memory task in MDD [84]. Sheline et al. (2010), using the bilateral DLPFC as a seed region, reported increased resting-state functional connectivity in the bilateral dorsomedial prefrontal cortex (DMPFC) in depressed subjects [43]. However, Aizenstein et al. (2009) reported reduced DLPFC-dACC functional connectivity on an executive-control task in patients with late-life depression (LLD) [86]. Children with a parental history of depression are known to be at high risk to develop this disorder.

In a recent study, Clasen and the colleagues reported decreased resting-state functional connectivity within the CCN in depression-naive adolescent females with a parental history of depression. In addition, severity of the parents' depression was associated with deficits in functional connectivity of the CCN in their children [90]. Neuroimaging studies thus support a link between impairments in the CCN and depression vulnerability even in healthy patients.

2.3.1 Abnormal executive control and the CCN in depression

Evidence over the years suggests that abnormal top-down cortical regulation of the limbic systems may also contribute to inefficient emotion regulation in depressed patients. In an early study, Anand and colleagues found that while regions in the affective network showed increased activation, functional connectivity between the anterior cingulate cortex (ACC) and limbic regions was decreased both at rest and during exposure to different stimuli (neutral, positive, and negative pictures) in depressed subjects. This finding may reflect an ineffective regulatory effect of the ACC on the hyperactivation of the limbic system [91]. Additionally, reduced functional connectivity between amygdala and the PFC found in depressed subjects both at rest and in response to fearful faces [92, 93], appears to further support a poor top-down emotional regulation view of depression. In a resting-state study of mood regulation in refractory and non-refractory major depression, Lui et al. (2011) found decreased functional connectivity in bilateral prefrontal-limbic-thalamic areas in both patient groups [94].

Studies of directed functional and effective connectivity have further confirmed a diminished top-down cortical control of the limbic systems in depressed patients. A recent study compared activity and effective connectivity in postpartum healthy and depressed mothers; when subjects responded to negative emotional faces [95]. Using Granger causality mapping, the authors studied the top-down regulation of the amygdala by the dorsomedial prefrontal cortex. They found a significant effective connection from the left dorsomedial prefrontal cortex to the left amygdala in healthy controls, but this connection was absent in depressed subjects [95]. In a separate study using PPI analysis, Erk and colleagues observed reduced amygdala-DLPFC connectivity in depressed patients during active emotion regulation [96]. In contrast, Schlosser et al. (2008) found increased effective connectivity with DCM, from the dorsal cognitive division of the ACC to the rostral affective division in patients with MDD during a Stroop imaging task [85]. However, a GCM study showed that only MDD subjects with a history of early life trauma (ELT) presented reduced mPFC–amygdala connectivity. In non-ELT exposed patients, mPFC inhibition of the amygdala was intact [97]. Amygdala-prefrontal effective connectivity has also been shown to distinguish bipolar disorder from major depressive disorder [98].

2.3.2 Remediation of cognitive control in depression

Given the central role of the CCN in the neurobiology of depression, its response to antidepressant treatments have been studied frequently, revealing increased functional

connectivity between anterior cingulate cortex and limbic regions in unipolar depressed patients [99]. In addition, pre-treatment functional connectivity within the CCN has been found to predict the outcome of antidepressant treatment in depressed subjects, with low CCN functional connectivity being associated with low remission rate [89]. Increased ACC-DLPFC and ACC-PCC functional connectivity has been reported in patients with depression following ECT [100]. Furthermore, two resting-state networks centered in the dorsomedial prefrontal cortex and ACC have been found to predict the outcome of ECT in treatment-resistant patients [101], providing further evidence of the importance of the role of brain circuits and functional integration in the understanding of depression.

Recent studies have demonstrated that the clinical efficacy of transcranial magnetic stimulation (TMS) – a noninvasive therapy alternative for refractory depression approved by the US Food and Drug Administration – appears to be associated with functional connectivity between brain regions implicated in the neurobiology of depression [102, 103]. In particular, higher connectivity between the frontal cortex and subgenual cingulate predicted better treatment outcome with repetitive TMS (rTMS) [104]. Treatment of depression with rTMS has generally targeted the left DLPFC, which has been reported to show hypometabolism in patients with depression [105]. In a recent study comparing functional connectivity between different DLPFC TMS targets and the subgenual cingulate cortex, Fox et al (2012) found that all the DLPFC TMS targets showed significantly negative functional connectivity with the

subgenual cingulate cortex; however, targets that demonstrated stronger anti-correlation were found to be more effective [102]. Fox and colleagues further reported that such differences in functional connectivity may be applied to identify individualized TMS targets [106].

3. Connectivity between different brain networks: some concluding thoughts

The findings above present an emerging picture of three aberrant networks in depression; namely, abnormal connectivity *within* the DMN, AN and CCN. However, the interactions *between* these different networks may be disrupted as well [107-110]. Recent meta-analysis studies have revealed increased functional connectivity between the AN (subgenual prefrontal cortex) [109] and the CCN [108, 109] with the DMN in MDD. In fact, Sheline et al. (2010) found a bilateral region in the dorsomedial prefrontal cortex, which they termed the dorsal nexus, consistently showing increased functional connectivity with each of the three networks implicated in depression [43]. Later, Perrin and the colleagues (2012) reported reduced connectivity of the dorsal nexus and an improvement in symptoms in depressed patients following treatment with electroconvulsive therapy [111]. There is further evidence showing that TMS targeting the DLPFC (a component of the CCN) modulated functional connectivity of the DMN [112]. These findings suggest that depression may not only be associated with interactions between different brain regions, but also interactions between distributed brain networks. Future studies may try to integrate the three core networks

(DMN, AN and CCN) and their contributions towards developing an extended model of depression for improved diagnosis, treatment and prevention of the disorder.

In conclusion, we have reviewed an overwhelming amount of evidence based upon studies of functional and effective connectivity that implicate three key modes or intrinsic brain networks in depression. The functional anatomy of these modes fits comfortably with the psychopathology of depression; namely, depressive rumination, a failure of emotion regulation and difficulties with top-down or executive control. The fact that the implicit functional dysconnection shows systematic changes with therapeutic interventions lends further support to the notion that depression may a functional disintegration or dysconnection within and between these intrinsic brain networks. One might hope that future studies will reveal the synaptic basis of the implicit disintegration of distributed activity in these specific systems – and how they relate to modulatory mechanisms that contextualize neuronal coupling and computations in the depressed brain.

Acknowledgments

We acknowledge the support of National Natural Science Foundation of China (81301199), and NLM Family Foundation (BL and MM). KJF is funded by a Wellcome Trust Principal Research Fellowship (Ref: 088130/Z/09/Z).

References

1. Friston, K.J., C.D. Frith, and R.S.J. Frackowiak, *Time-dependent changes in effective connectivity measured with PET.* Hum Brain Mapp, 1993. **1**: p. 69-80.
2. Friston, K.J., et al., *Functional connectivity: the principal-component analysis of large (PET) data sets.* J Cereb Blood Flow Metab, 1993. **13**(1): p. 5-14.
3. Friston, K.J., *Functional and Effective Connectivity in Neuroimaging: A Synthesis.* Hum Brain Mapping, 1994. **2**: p. 56-78.
4. Goebel, R., et al., *Investigating directed cortical interactions in time-resolved fMRI data using vector autoregressive modeling and Granger causality mapping.* Magn Reson Imaging, 2003. **21**(10): p. 1251-61.
5. Friston, K.J., L. Harrison, and W. Penny, *Dynamic causal modelling.* Neuroimage, 2003. **19**(4): p. 1273-302.
6. Li, B., et al., *Generalised filtering and stochastic DCM for fMRI.* Neuroimage, 2011. **58**(2): p. 442-57.
7. van den Heuvel, M.P. and H.E. Hulshoff Pol, *Exploring the brain network: a review on resting-state fMRI functional connectivity.* Eur Neuropsychopharmacol, 2010. **20**(8): p. 519-34.
8. He, Y. and A. Evans, *Graph theoretical modeling of brain connectivity.* Curr Opin Neurol, 2010. **23**(4): p. 341-50.
9. David, O., et al., *Identifying neural drivers with functional MRI: an electrophysiological validation.* PLoS Biol, 2008. **6**(12): p. 2683-97.
10. Friston, K.J., et al., *Granger causality revisited.* Neuroimage, 2014. **101**: p. 796-808.
11. Raichle, M.E., et al., *A default mode of brain function.* Proc Natl Acad Sci U S A, 2001. **98**(2): p. 676-82.
12. Shulman, G.L., et al., *Common Blood Flow Changes across Visual Tasks: II. Decreases in Cerebral Cortex.* J Cogn Neurosci, 1997. **9**(5): p. 648-63.
13. Greicius, M.D., et al., *Functional connectivity in the resting brain: a network analysis of the default mode hypothesis.* Proc Natl Acad Sci U S A, 2003. **100**(1): p. 253-8.
14. Broyd, S.J., et al., *Default-mode brain dysfunction in mental disorders: a systematic review.* Neurosci Biobehav Rev, 2009. **33**(3): p. 279-96.
15. Gusnard, D.A., et al., *Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function.* Proc Natl Acad Sci U S A, 2001. **98**(7): p. 4259-64.
16. Uddin, L.Q., et al., *Functional connectivity of default mode network components: correlation, anticorrelation, and causality.* Hum Brain Mapp, 2009. **30**(2): p. 625-37.
17. Zeng, L.L., et al., *Identifying major depression using whole-brain functional connectivity: a multivariate pattern analysis.* Brain, 2012. **135**(Pt 5): p. 1498-507.
18. Greicius, M.D., et al., *Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus.* Biol Psychiatry, 2007. **62**(5): p. 429-37.
19. Gaffrey, M.S., et al., *Default mode network connectivity in children with a history of preschool onset depression.* J Child Psychol Psychiatry, 2012. **53**(9): p. 964-72.
20. Belleau, E.L., L.E. Taubitz, and C.L. Larson, *Imbalance of default mode and regulatory networks during externally focused processing in depression.* Soc Cogn Affect Neurosci, 2014.

21. Ho, T.C., et al., *Emotion-Dependent Functional Connectivity of the Default Mode Network in Adolescent Depression.* Biol Psychiatry, 2014.
22. Zamoscik, V., et al., *Increased involvement of the parahippocampal gyri in a sad mood predicts future depressive symptoms.* Soc Cogn Affect Neurosci, 2014.
23. Nixon, N.L., et al., *Biological vulnerability to depression: linked structural and functional brain network findings.* Br J Psychiatry, 2014. **204**: p. 283-9.
24. Sexton, C.E., et al., *Magnetic resonance imaging in late-life depression: multimodal examination of network disruption.* Arch Gen Psychiatry, 2012. **69**(7): p. 680-9.
25. Chase, H.W., et al., *Disrupted posterior cingulate-amygdala connectivity in postpartum depressed women as measured with resting BOLD fMRI.* Soc Cogn Affect Neurosci, 2014. **9**(8): p. 1069-75.
26. Zhu, X., et al., *Evidence of a dissociation pattern in resting-state default mode network connectivity in first-episode, treatment-naive major depression patients.* Biol Psychiatry, 2012. **71**(7): p. 611-7.
27. Li, B., et al., *A treatment-resistant default mode subnetwork in major depression.* Biol Psychiatry, 2013. **74**(1): p. 48-54.
28. Sambataro, F., et al., *Revisiting default mode network function in major depression: evidence for disrupted subsystem connectivity.* Psychol Med, 2013: p. 1-11.
29. Marchetti, I., et al., *The default mode network and recurrent depression: a neurobiological model of cognitive risk factors.* Neuropsychol Rev, 2012. **22**(3): p. 229-51.
30. Berman, M.G., et al., *Depression, rumination and the default network.* Soc Cogn Affect Neurosci, 2011. **6**(5): p. 548-55.
31. Berman, M.G., et al., *Does resting-state connectivity reflect depressive rumination? A tale of two analyses.* Neuroimage, 2014. **103**: p. 267-79.
32. Posner, J., et al., *Antidepressants normalize the default mode network in patients with dysthymia.* JAMA Psychiatry, 2013. **70**(4): p. 373-82.
33. van Wingen, G.A., et al., *Short-term antidepressant administration reduces default mode and task-positive network connectivity in healthy individuals during rest.* Neuroimage, 2013. **88C**: p. 47-53.
34. Delaveau, P., et al., *Brain effects of antidepressants in major depression: a meta-analysis of emotional processing studies.* J Affect Disord, 2011. **130**(1-2): p. 66-74.
35. Fang, J., et al., *Transcutaneous Vagus Nerve Stimulation Modulates Default Mode Network in Major Depressive Disorder.* Biol Psychiatry, 2015.
36. Wu, M., et al., *Default-mode network connectivity and white matter burden in late-life depression.* Psychiatry Res, 2011. **194**(1): p. 39-46.
37. Wang, L., et al., *The effects of antidepressant treatment on resting-state functional brain networks in patients with major depressive disorder.* Hum Brain Mapp, 2015. **36**(2): p. 768-78.
38. Andreescu, C., et al., *Resting state functional connectivity and treatment response in late-life depression.* Psychiatry Res, 2013. **214**(3): p. 313-21.
39. Lemogne, C., et al., *Self-referential processing and the prefrontal cortex over the course of depression: a pilot study.* J Affect Disord, 2010. **124**(1-2): p. 196-201.
40. Goldapple, K., et al., *Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy.* Arch Gen Psychiatry, 2004. **61**(1): p. 34-41.

41. Farb, N.A., et al., *Mood-linked responses in medial prefrontal cortex predict relapse in patients with recurrent unipolar depression.* Biol Psychiatry, 2011. **70**(4): p. 366-72.
42. Sudheimer, K., et al., *Decreased hypothalamic functional connectivity with subgenual cortex in psychotic major depression.* Neuropsychopharmacology, 2015. **40**(4): p. 849-60.
43. Sheline, Y.I., et al., *Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus.* Proc Natl Acad Sci U S A, 2010. **107**(24): p. 11020-5.
44. McCarthy, H., et al., *Attention network hypoconnectivity with default and affective network hyperconnectivity in adults diagnosed with attention-deficit/hyperactivity disorder in childhood.* JAMA Psychiatry, 2013. **70**(12): p. 1329-37.
45. Gotlib, I.H., et al., *Attentional biases for negative interpersonal stimuli in clinical depression.* J Abnorm Psychol, 2004. **113**(1): p. 121-35.
46. Joormann, J. and I.H. Gotlib, *Selective attention to emotional faces following recovery from depression.* J Abnorm Psychol, 2007. **116**(1): p. 80-5.
47. Chen, C.H., et al., *Functional coupling of the amygdala in depressed patients treated with antidepressant medication.* Neuropsychopharmacology, 2008. **33**(8): p. 1909-18.
48. Hamilton, J.P. and I.H. Gotlib, *Neural substrates of increased memory sensitivity for negative stimuli in major depression.* Biol Psychiatry, 2008. **63**(12): p. 1155-62.
49. Tao, H., et al., *Depression uncouples brain hate circuit.* Mol Psychiatry, 2013. **18**(1): p. 101-11.
50. Admon, R., et al., *Striatal Hypersensitivity During Stress in Remitted Individuals with Recurrent Depression.* Biol Psychiatry, 2014.
51. Nutt, D., et al., *The other face of depression, reduced positive affect: the role of catecholamines in causation and cure.* J Psychopharmacol, 2007. **21**(5): p. 461-71.
52. Horner, M.S., et al., *C'mon get happy: reduced magnitude and duration of response during a positive-affect induction in depression.* Depress Anxiety, 2014. **31**(11): p. 952-60.
53. Heller, A.S., et al., *Reduced capacity to sustain positive emotion in major depression reflects diminished maintenance of fronto-striatal brain activation.* Proc Natl Acad Sci U S A, 2009. **106**(52): p. 22445-50.
54. Admon, R., et al., *Dissociable cortico-striatal connectivity abnormalities in major depression in response to monetary gains and penalties.* Psychol Med, 2014: p. 1-11.
55. Phillips, M.L., et al., *Neurobiology of emotion perception I: The neural basis of normal emotion perception.* Biol Psychiatry, 2003. **54**(5): p. 504-14.
56. Disner, S.G., et al., *Neural mechanisms of the cognitive model of depression.* Nat Rev Neurosci, 2011. **12**(8): p. 467-77.
57. Frodl, T., et al., *Functional connectivity bias of the orbitofrontal cortex in drug-free patients with major depression.* Biol Psychiatry, 2010. **67**(2): p. 161-7.
58. Carballedo, A., et al., *Functional connectivity of emotional processing in depression.* J Affect Disord, 2011. **134**(1-3): p. 272-9.
59. Goulden, N., et al., *Reversed frontotemporal connectivity during emotional face processing in remitted depression.* Biol Psychiatry, 2012. **72**(7): p. 604-11.
60. de Kwaasteniet, B., et al., *Relation between structural and functional connectivity in major depressive disorder.* Biol Psychiatry, 2013. **74**(1): p. 40-7.
61. Davey, C.G., et al., *Regionally specific alterations in functional connectivity of the anterior cingulate cortex in major depressive disorder.* Psychol Med, 2012. **42**(10): p. 2071-81.
62. Luking, K.R., et al., *Functional connectivity of the amygdala in early-childhood-onset*

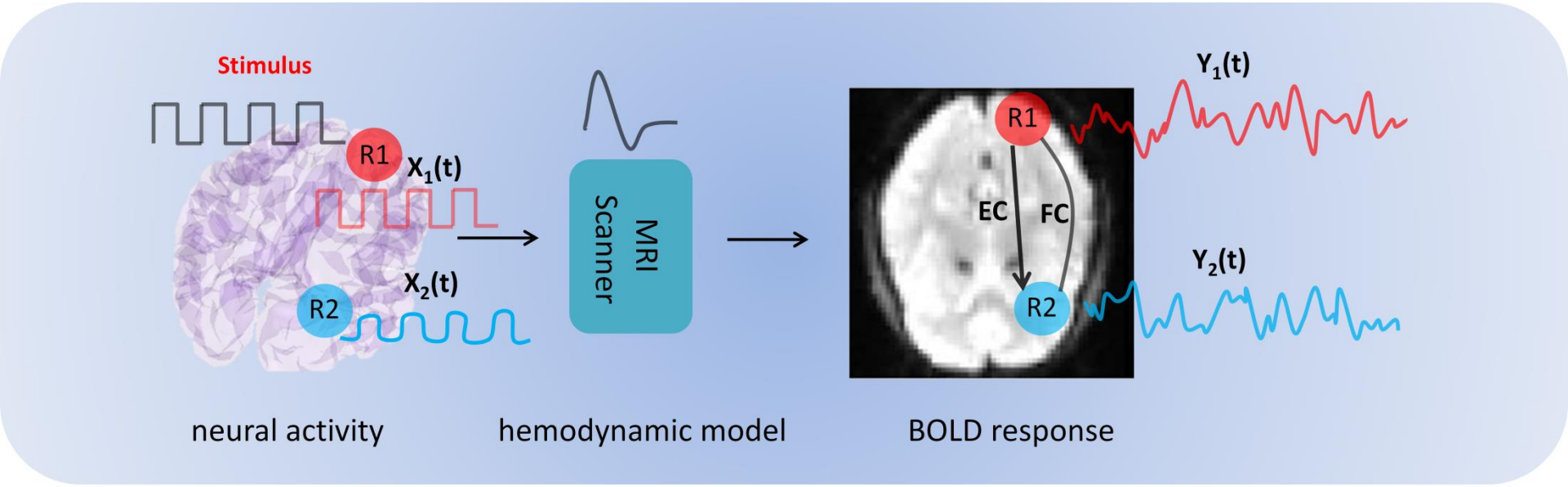
depression. J Am Acad Child Adolesc Psychiatry, 2011. **50**(10): p. 1027-41 e3.
63. Pannekoek, J.N., et al., *Aberrant resting-state functional connectivity in limbic and salience networks in treatment--naive clinically depressed adolescents.* J Child Psychol Psychiatry, 2014. **55**(12): p. 1317-27.
64. Cullen, K.R., et al., *Abnormal amygdala resting-state functional connectivity in adolescent depression.* JAMA Psychiatry, 2014. **71**(10): p. 1138-47.
65. Connolly, C.G., et al., *Resting-state functional connectivity of subgenual anterior cingulate cortex in depressed adolescents.* Biol Psychiatry, 2013. **74**(12): p. 898-907.
66. Ho, T.C., et al., *Functional connectivity of negative emotional processing in adolescent depression.* J Affect Disord, 2014. **155**: p. 65-74.
67. Gabbay, V., et al., *Striatum-based circuitry of adolescent depression and anhedonia.* J Am Acad Child Adolesc Psychiatry, 2013. **52**(6): p. 628-41 e13.
68. Davey, C.G., et al., *Functional brain-imaging correlates of negative affectivity and the onset of first-episode depression.* Psychol Med, 2015. **45**(5): p. 1001-9.
69. Heller, A.S., et al., *Relationships between changes in sustained fronto-striatal connectivity and positive affect in major depression resulting from antidepressant treatment.* Am J Psychiatry, 2013. **170**(2): p. 197-206.
70. Downar, J., et al., *Anhedonia and reward-circuit connectivity distinguish nonresponders from responders to dorsomedial prefrontal repetitive transcranial magnetic stimulation in major depression.* Biol Psychiatry, 2014. **76**(3): p. 176-85.
71. Crowther, A., et al., *Resting-state connectivity predictors of response to psychotherapy in major depressive disorder.* Neuropsychopharmacology, 2015. **40**(7): p. 1659-73.
72. Mayberg, H.S., et al., *Deep brain stimulation for treatment-resistant depression.* Neuron, 2005. **45**(5): p. 651-60.
73. Johansen-Berg, H., et al., *Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression.* Cereb Cortex, 2008. **18**(6): p. 1374-83.
74. Oral, E., et al., *Cognitive functions and serum levels of brain-derived neurotrophic factor in patients with major depressive disorder.* Brain Res Bull, 2012. **88**(5): p. 454-9.
75. Snyder, H.R., *Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review.* Psychol Bull, 2013. **139**(1): p. 81-132.
76. Cole, M.W. and W. Schneider, *The cognitive control network: Integrated cortical regions with dissociable functions.* Neuroimage, 2007. **37**(1): p. 343-60.
77. Dosenbach, N.U., et al., *Distinct brain networks for adaptive and stable task control in humans.* Proc Natl Acad Sci U S A, 2007. **104**(26): p. 11073-8.
78. Vincent, J.L., et al., *Evidence for a frontoparietal control system revealed by intrinsic functional connectivity.* J Neurophysiol, 2008. **100**(6): p. 3328-42.
79. Niendam, T.A., et al., *Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions.* Cogn Affect Behav Neurosci, 2012. **12**(2): p. 241-68.
80. Braver, T.S., *The variable nature of cognitive control: a dual mechanisms framework.* Trends Cogn Sci, 2012. **16**(2): p. 106-13.
81. De Baene, W. and M. Brass, *Switch probability context (in)sensitivity within the cognitive control network.* Neuroimage, 2013. **77**: p. 207-14.

82. Wolkenstein, L. and C. Plewnia, *Amelioration of cognitive control in depression by transcranial direct current stimulation.* Biol Psychiatry, 2013. **73**(7): p. 646-51.
83. Goeleven, E., et al., *Deficient inhibition of emotional information in depression.* J Affect Disord, 2006. **93**(1-3): p. 149-57.
84. Vasic, N., et al., *Aberrant functional connectivity of dorsolateral prefrontal and cingulate networks in patients with major depression during working memory processing.* Psychol Med, 2009. **39**(6): p. 977-87.
85. Schlosser, R.G., et al., *Fronto-cingulate effective connectivity in major depression: a study with fMRI and dynamic causal modeling.* Neuroimage, 2008. **43**(3): p. 645-55.
86. Aizenstein, H.J., et al., *Altered functioning of the executive control circuit in late-life depression: episodic and persistent phenomena.* Am J Geriatr Psychiatry, 2009. **17**(1): p. 30-42.
87. Kaiser, R.H., et al., *Distracted and down: neural mechanisms of affective interference in subclinical depression.* Soc Cogn Affect Neurosci, 2014.
88. Kerestes, R., et al., *Specific functional connectivity alterations of the dorsal striatum in young people with depression.* Neuroimage Clin, 2015. **7**: p. 266-72.
89. Alexopoulos, G.S., et al., *Functional connectivity in the cognitive control network and the default mode network in late-life depression.* J Affect Disord, 2012. **139**(1): p. 56-65.
90. Clasen, P.C., et al., *Cognitive control network connectivity in adolescent women with and without a parental history of depression.* Dev Cogn Neurosci, 2014. **7**: p. 13-22.
91. Anand, A., et al., *Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study.* Biol Psychiatry, 2005. **57**(10): p. 1079-88.
92. Tang, Y., et al., *Decreased functional connectivity between the amygdala and the left ventral prefrontal cortex in treatment-naive patients with major depressive disorder: a resting-state functional magnetic resonance imaging study.* Psychol Med, 2013. **43**(9): p. 1921-7.
93. Kong, L., et al., *Functional connectivity between the amygdala and prefrontal cortex in medication-naive individuals with major depressive disorder.* J Psychiatry Neurosci, 2013. **38**(6): p. 417-22.
94. Lui, S., et al., *Resting-state functional connectivity in treatment-resistant depression.* Am J Psychiatry, 2011. **168**(6): p. 642-8.
95. Moses-Kolko, E.L., et al., *Abnormally reduced dorsomedial prefrontal cortical activity and effective connectivity with amygdala in response to negative emotional faces in postpartum depression.* Am J Psychiatry, 2010. **167**(11): p. 1373-80.
96. Erk, S., et al., *Acute and sustained effects of cognitive emotion regulation in major depression.* J Neurosci, 2010. **30**(47): p. 15726-34.
97. Grant, M.M., et al., *Early life trauma and directional brain connectivity within major depression.* Hum Brain Mapp, 2014. **35**(9): p. 4815-26.
98. Almeida, J.R., et al., *Abnormal amygdala-prefrontal effective connectivity to happy faces differentiates bipolar from major depression.* Biol Psychiatry, 2009. **66**(5): p. 451-9.
99. Anand, A., et al., *Antidepressant effect on connectivity of the mood-regulating circuit: an FMRI study.* Neuropsychopharmacology, 2005. **30**(7): p. 1334-44.
100. Beall, E.B., et al., *Effects of electroconvulsive therapy on brain functional activation and connectivity in depression.* J ECT, 2012. **28**(4): p. 234-41.
101. van Waarde, J.A., et al., *A functional MRI marker may predict the outcome of*

electroconvulsive therapy in severe and treatment-resistant depression. Mol Psychiatry, 2015. **20**(5): p. 609-14.

102. Fox, M.D., et al., *Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate.* Biol Psychiatry, 2012. **72**(7): p. 595-603.
103. Baeken, C., et al., *Accelerated HF-rTMS in treatment-resistant unipolar depression: Insights from subgenual anterior cingulate functional connectivity.* World J Biol Psychiatry, 2014. **15**(4): p. 286-97.
104. Salomons, T.V., et al., *Resting-state cortico-thalamic-striatal connectivity predicts response to dorsomedial prefrontal rTMS in major depressive disorder.* Neuropsychopharmacology, 2014. **39**(2): p. 488-98.
105. Hallett, M., *Transcranial magnetic stimulation: a primer.* Neuron, 2007. **55**(2): p. 187-99.
106. Fox, M.D., H. Liu, and A. Pascual-Leone, *Identification of reproducible individualized targets for treatment of depression with TMS based on intrinsic connectivity.* Neuroimage, 2013. **66**: p. 151-60.
107. Lemogne, C., et al., *In search of the depressive self: extended medial prefrontal network during self-referential processing in major depression.* Soc Cogn Affect Neurosci, 2009. **4**(3): p. 305-12.
108. Kaiser, R.H., et al., *Large-Scale Network Dysfunction in Major Depressive Disorder: A Meta-analysis of Resting-State Functional Connectivity.* JAMA Psychiatry, 2015.
109. Hamilton, J.P., et al., *Depressive Rumination, the Default-Mode Network, and the Dark Matter of Clinical Neuroscience.* Biol Psychiatry, 2015.
110. Hamilton, J.P., et al., *Investigating neural primacy in Major Depressive Disorder: multivariate Granger causality analysis of resting-state fMRI time-series data.* Mol Psychiatry, 2011. **16**(7): p. 763-72.
111. Perrin, J.S., et al., *Electroconvulsive therapy reduces frontal cortical connectivity in severe depressive disorder.* Proc Natl Acad Sci U S A, 2012. **109**(14): p. 5464-8.
112. Liston, C., et al., *Default mode network mechanisms of transcranial magnetic stimulation in depression.* Biol Psychiatry, 2014. **76**(7): p. 517-26.

FIG 1



Functional connectivity analyses:
- usually undirected correlations between $Y_1(t)$ and $Y_2(t)$

Granger causality modelling:
- Directed functional connectivity between $Y_1(t)$ and $Y_2(t)$

Dynamic causal modelling:
- Directed effective connectivity between $X_1(t)$ and $Y_2(t)$

FIG 2

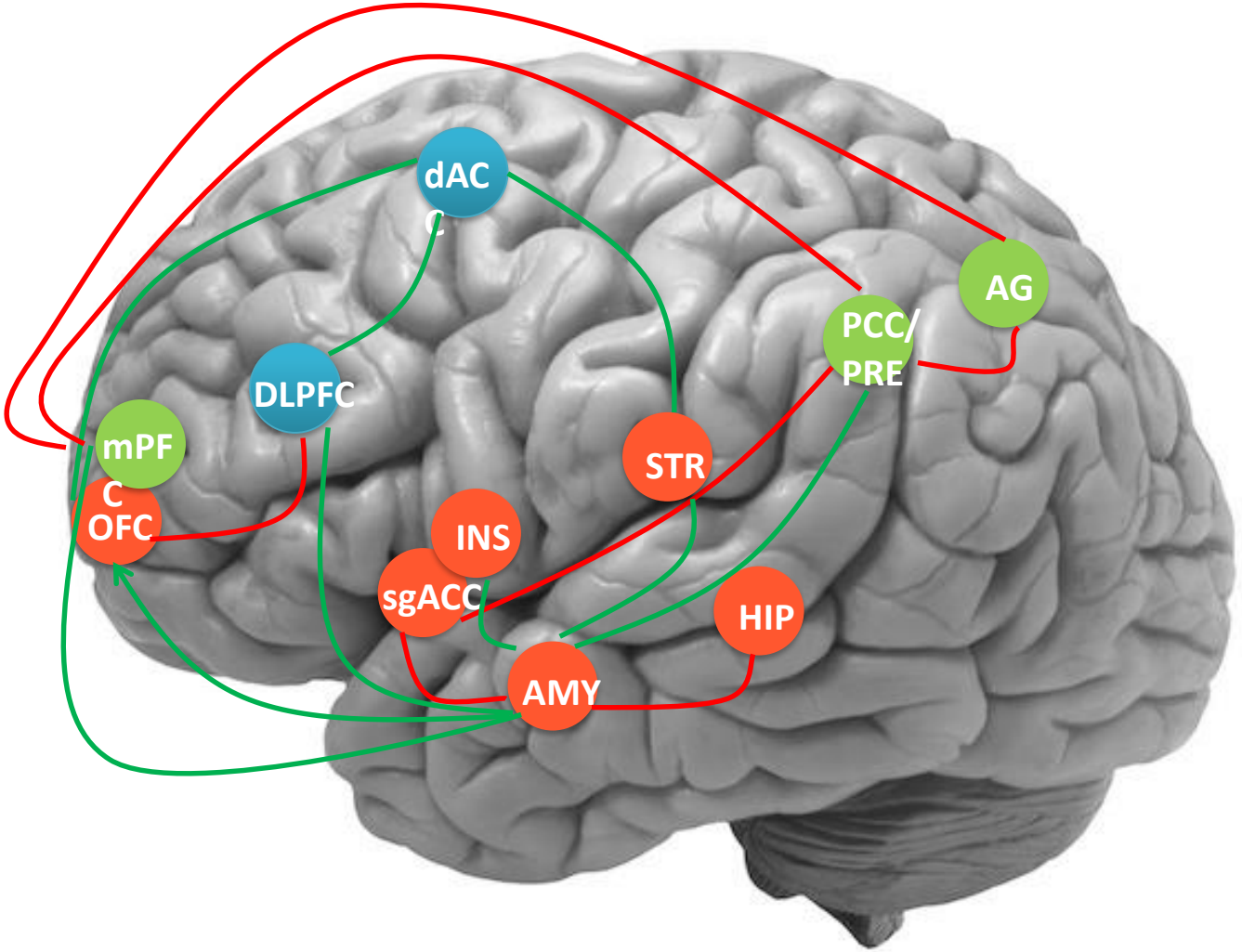


FIG 3