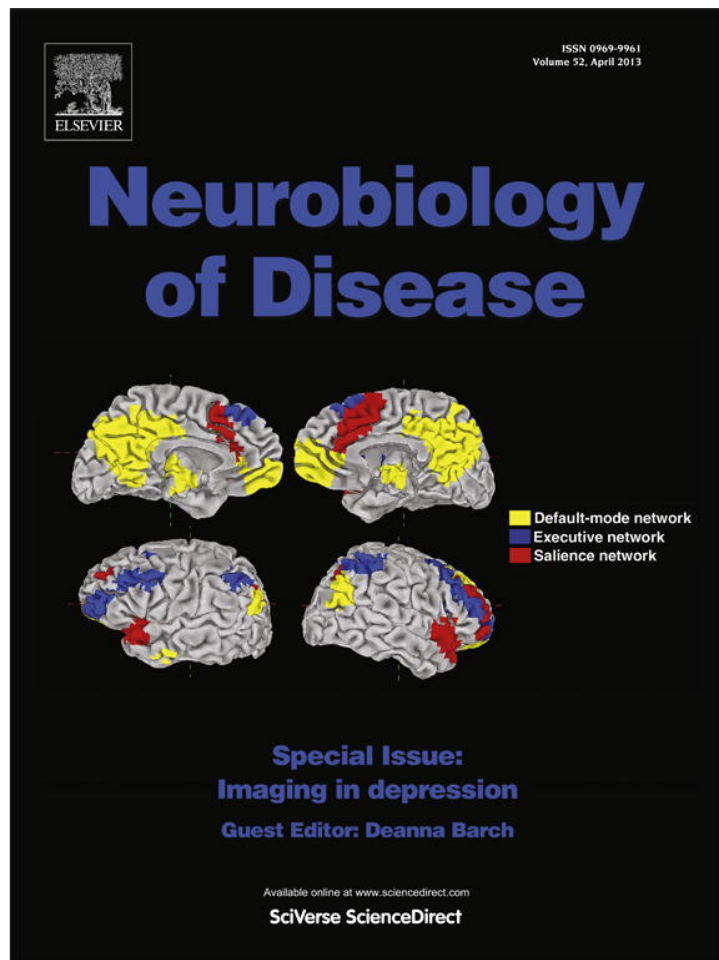


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Review

Neural systems approaches to understanding major depressive disorder: An intrinsic functional organization perspective[☆]J. Paul Hamilton, Michael C. Chen, Ian H. Gotlib^{*}

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ABSTRACT

Recent research detailing the intrinsic functional organization of the brain provides a unique and useful framework to gain a better understanding of the neural bases of Major Depressive Disorder (MDD). In this review, we first present a brief history of neuroimaging research that has increased our understanding of the functional macro-architecture of the brain. From this macro-architectural perspective, we examine the extant body of functional neuroimaging research assessing MDD with a specific emphasis on the contributions of default-mode, executive, and salience networks in this debilitating disorder. Next, we describe recent investigations conducted in our laboratory in which we explicitly adopt a neural-system perspective in examining the relations among these networks in MDD. Finally, we offer directions for future research that we believe will facilitate the development of more detailed and integrative models of neural dysfunction in depression.

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Introduction

Major Depressive Disorder (MDD) is among the most prevalent of all psychiatric disorders and is associated with enormous personal and societal costs (2009). Recent estimates indicate that almost 20% of the American population, or more than 30 million adults, will experience a clinically significant episode of depression during their

lifetime. MDD is also a recurrent disorder: three-quarters of depressed persons have more than one depressive episode, and almost two-thirds of people who have ever had been clinically depressed will be in an episode in any given year over the rest of their lives (Boland and Keller, 2009). At its core, MDD is arguably a disorder of emotion regulation; in addition, however, investigators have consistently documented the occurrence of repetitive, perseverative, negative thinking in depression, as well as biases in attention to and memory for negative information that appear to underlie the increased responsiveness to negative stimuli in MDD (see Gotlib and Joermann, 2010, for a review of this literature).

Over the past two decades, investigators have examined patterns of neural activation that are associated with these emotional and cognitive aspects of MDD. Thus, researchers have assessed neural

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responding in depressed individuals to a variety of positively and negatively valenced emotional stimuli and to cognitive challenges, and have documented anomalous responding in MDD in a range of frontal, temporal, cerebellar, and subcortical regions (see Fitzgerald et al., 2008, for a review of this literature). While this work has been important in advancing our understanding of neural aspects of MDD, we still lack a cogent, comprehensive, and therapeutically useful model of brain function and dysfunction in this disorder. In this context, it is important to note that massive interconnectivity among neural ensembles in the brain ensures that neural events seldom occur in isolation; consequently, attempting to understand depression from a neural-network perspective may yield an incremental advancement to existing neural models of MDD. Although investigators engaged in neuroimaging in depression have long noted the potential benefits of exploring MDD at the neural-systems level (e.g., Drevets et al., 1992), it is only recently that brain imaging acquisition and analysis techniques, as well as our understanding of the architecture of the brain, have advanced sufficiently to make network-level explorations and conceptualizations of MDD feasible.

By far, the majority of neuroimaging studies of MDD use paradigms that involve affective or cognitive tasks. Certainly, the results of these studies have informed network-level conceptualizations of depression, such as the formulation that altered cortico-limbic connectivity is a central feature of MDD (Siegle et al., 2007). It is important to recognize, however, that the brain regions and networks that underlie responses to affective and cognitive challenges in the laboratory may not be the same regions that are involved in the generation or maintenance of spontaneously occurring affect or rumination in MDD. Moreover, given that depression is fundamentally a disorder of mood, it is likely that neural processes that occur over the course of minutes or hours, as opposed to seconds, are more relevant to our understanding of MDD. Increasingly, therefore, researchers are investigating neural functioning in MDD over relatively long periods in the absence of externally presented tasks or stimuli. Investigators conducting these 'resting-state' studies typically use either functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) to examine brain activity or connectivity during rest while participants are not performing specific tasks. Importantly, these studies have identified a set of dissociable intrinsic functional networks that exhibit correlated activity across brain regions. We propose that investigating MDD from the perspective afforded by these functionally unified networks can yield a more elegant and useful neural conceptualization of depression; indeed, investigators are increasingly studying these networks in the context of MDD (e.g., Sheline et al., 2009). In this review we focus on these intrinsic networks, the normal cognitive and affective functions with which these networks are associated, and the dysfunction in these networks that may be related to MDD.

Evolving conceptions of the intrinsic functional organization of the brain

An early discovery from fMRI investigations of the brain was that functionally homogeneous neural regions showed correlated activity even when they were not actively prompted. Biswal et al. (1995) first demonstrated this in an fMRI study of motor regions. Using the activation maps derived from a bilateral finger-tapping task, Biswal et al. planted a region-of-interest 'seed' in left motor cortex and queried the time courses of all other voxels during rest to identify other regions in which activation was correlated with activity in this seed region. This analysis showed that, in addition to nearby voxels, the contralateral motor cortex and midline cortical regions were also correlated with the seeded left motor cortex. Thus, in this resting-state analysis, it was the *correlation* of the time courses, rather than the *magnitude* of a response, that determined network connectivity. The functional connectivity map that resulted from this analysis was spatially similar to the map of regions that were activated by the bilateral

finger-tapping task. Biswal et al. interpreted their data as reflecting actual physiological neural connectivity, rather than connectivity in response to an anticipated or imagined motor task.

Subsequent research has expanded on Biswal et al.'s (1995) conceptualization of an implicit functional organization in the brain. In a meta-analysis of PET studies of visual processing in humans, Shulman et al. (1997) investigated regions in which metabolic activity decreased during an active task. These regions were found to include the posterior cingulate cortex (PCC), bilateral parietal cortex, medial prefrontal cortex (mPFC), and medial temporal lobe (MTL) regions. These decreases in activity, which showed remarkably little spatial variation despite a wide range of extrinsic tasks, prompted investigators to begin to study a consistent, spatially organized baseline state of metabolic functioning. Perhaps most notably, Raichle et al. (2001) examined metabolic demands during eyes-closed rest and described a 'default-mode' pattern of metabolic activity in the brain that included PCC, bilateral parietal cortex, and mPFC. By using PET to examine blood flow and oxygen consumption, Raichle et al. were able to determine an absolute level of metabolic activity during rest, rather than a relative level of activity during the transition from rest to activity. Thus, the "default-mode network" (DMN) identified by Raichle et al. reflects an ongoing metabolic demand of these regions, a physiological baseline rather than the relative baseline of BOLD fMRI signals (Raichle and Snyder, 2007).

Investigators have begun to examine factors that may explain the functional connectivity of the brain regions that comprise the DMN. One likely candidate is monosynaptic white-matter connectivity among these regions; another potential factor is common connectivity with a third structure. In testing these possibilities, Greicius et al. (2009) conducted a study examining both functional and structural connectivity by using blood oxygenation level-dependent (BOLD) signal and diffusion tensor imaging (DTI), respectively, to visualize connectivity. To obtain seed regions for DTI, Greicius et al. used probabilistic independent component analysis (ICA) to analyze fMRI data. ICA decomposes the whole-brain data into independent spatiotemporal components, including the DMN (Beckmann et al., 2005). Using DMN regions, including the PCC, mPFC, and MTL, as seed regions, Greicius et al. identified white-matter tracts that directly connected PCC to mPFC and PCC to MTL, but not to structures outside the DMN. Thus, the temporal correlation of activity in these regions at rest is likely due, at least in part, to tracts that link DMN regions directly.

In an important extension of formulations of macro-architectural organization of the brain, Fox et al. (2005) posited that components of the so-called intrinsic functional organization of the brain – the DMN, described above, and the task positive network (TPN; a network of structures that increase in activation during performance of attention-demanding tasks) – have a competitive, anti-correlated relation with each other. Fox et al. noted that, during performance of cognitive tasks, structures comprising the TPN (dorsolateral prefrontal, lateral parietal, and anterior insular cortices) were characterized robustly by increases in activation, whereas structures comprising the DMN showed reliable decreases in activity. Importantly, Fox et al. documented this same negative relation between DMN and TPN during resting-state fMRI scans: fluctuations in activation in one network were associated with inverse activation fluctuations in the other network.

Working to develop a better characterization of the organization of the TPN, Seeley et al. (2007) used resting-state fMRI functional connectivity analysis to demonstrate that the TPN is actually composed of two dissociable networks: an executive network (EN) and a salience network (SN). In specifying the functions of these networks and further demonstrating their dissociability, Seeley et al. showed that the extent of recruitment of nodes in the EN, comprising dorsolateral prefrontal and lateral parietal cortices, correlated positively and selectively with executive task performance, whereas connectivity in

the SN, comprising the anterior insula, amygdala, and dorsal anterior cingulate cortex (ACC), correlated positively with ratings of state anxiety.

Conceptualizing depression from a neural network perspective

In the following sections we focus on the roles of the DMN, EN, and SN in MDD (see Fig. 1 for a whole-brain map showing the loci of each network). It is important to note that these networks are derived from imaging studies of healthy participants; consequently, they encompass normal functional networks based on anatomic connectivity, rather than a network based on interconnected regions that have been implicated in MDD. Yet, we think that these three networks are particularly relevant to understanding the neural bases of MDD in part because their putative functions map well onto significant and specific aspects of depressive symptomatology, including rumination (DMN), emotional disinhibition (EN), and emotional over-reactivity (SN). Investigators are increasingly examining how dysfunction in these typical, or “normal”, networks is associated with symptoms of depression, and we review this growing body of evidence below.

The default-mode network in depression

Given the conceptual fit between the self-reflective processes supported by the DMN and self-directed patterns of ruminative thought that play a pivotal role in the maintenance of MDD (Nolen-Hoeksema et al., 1993), clinical neuroscientists have made a considerable effort to understand the role of the DMN in MDD. Consistent with researchers' expectations concerning DMN function in MDD, Sheline et al. (2009) found that depressed persons did not demonstrate the typical pattern of deactivation in several components of the DMN during presumably self-relevant active and passive processing of negative stimuli. In a subsequent study assessing more directly the neural substrates of ruminative responding in depression, (Cooney et al., 2010) found increased activation in several DMN structures, including the MPFC, posterior cingulate cortex, and parahippocampus during ruminative self-focus in MDD.

In addition to demonstrations of abnormal DMN responding in MDD, researchers have also found that depressed and nondepressed individuals differ in the spatial extent of the DMN. Specifically, using ICA, which permits investigators to identify different intrinsic brain networks by their unique neural signatures, Greicius et al. (2007) found greater contributions to the DMN in depressed than in nondepressed participants from the thalamus and ventral ACC, a structure implicated reliably in self-generated feelings of sadness (Damasio et al., 2000; Mayberg et al., 1999). Further, Greicius et al. found that the extent of recruitment of the ventral ACC was positively

correlated with the duration of participants' current depressive episodes in the MDD group. In a subsequent study, we (Hamilton et al., 2011a) used Granger causality analysis to investigate patterns of neural cause and effect among components of the DMN in depression. We found that activation in the hippocampus, a primary regulator of the hypothalamic–pituitary–adrenal stress response, initiates apparently maladaptive over-responding in the ventral ACC in depressed individuals. In addition, we found mutually excitatory activation between the ventral ACC and the mPFC that was, itself, positively correlated with levels of maladaptive, depressive rumination in MDD.

To further examine the role of the DMN in MDD, we pooled the data from fMRI studies published through January 2011 in which investigators had conducted standard, whole-brain analyses comparing the neural responses of depressed and healthy persons to positive stimuli (e.g., happy faces, rewards, favorite music) and/or negative stimuli (e.g., sad words, punishments, sad pictures). We then calculated the proportion of reported differences that were in the DMN, based on maps from Greicius et al. (2003), as a function of group and valence of stimuli. In addition, we conducted a similar analysis using the data comparing depressed to control groups with respect to resting-state regional cerebral blood flow (rCBF) as measured with PET or single photon emission computed tomography (SPECT). These analyses incorporated the data from 24 fMRI (Abler et al., 2007; Bar et al., 2007; Canli et al., 2004; Cooney et al., 2010; Frodl et al., 2009; Fu et al., 2004, 2007, 2008; Gotlib et al., 2005; Herwig et al., 2010; Keedwell et al., 2005; Knutson et al., 2008; Kumari et al., 2003; Lawrence et al., 2004; Mitterschiffthaler et al., 2003, 2008; Osuch et al., 2009; Pizzagalli et al., 2009; Scheuerecker et al., 2010; Strigo et al., 2008; Surguladze et al., 2005; Townsend et al., 2010; Wang et al., 2008; Yang, 2004) and 14 PET/SPECT studies (Aihara et al., 2007; Bench et al., 1992; Brody et al., 2001a; Drevets et al., 1992; Germain et al., 2007; Kennedy et al., 2001; Kimbrell et al., 2002; Kohn et al., 2007; Krausz et al., 2007; Mayberg et al., 2005; Perico et al., 2005; Saxena et al., 2001; Skaf et al., 2002; Videbech et al., 2001); see Table 1. As we present in Fig. 2, under conditions of task responding, depressed participants show less DMN activation than do healthy participants in response to both negative and positive stimuli. Importantly, however, this pattern is reversed for resting-state rCBF studies, with a greater proportion of incidences of DMN activation noted in MDD. This pattern of findings suggests that neural substrates of self-relational processing in MDD are not activated as much by conditions of affective probes as by allowing spontaneous thought. In addition, and reflecting the challenges faced by studies that rely on eliciting ruminative responses which, by definition, are unwanted, (Johnson et al., 2009) found increased DMN activation in MDD only during non-self-referential thinking; they found,

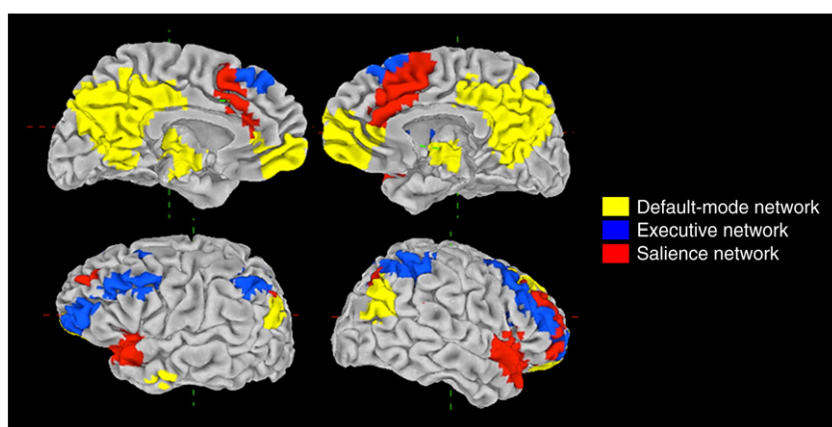


Fig. 1. Intrinsic functional networks of primary interest in the study of depression.

Table 1

Studies measuring regional cerebral bloodflow differences (blue) and response to affective challenge (orange) in depressed and healthy persons.

Included rCBF studies	Method	Included fMRI studies	Affective challenge
Aihara et al. (2007)	PET – [18F]–FDG	Abler et al. (2007)	Anticipation and viewing of negative, neutral, and positive pictures
Bench et al. (1992)	PET – [15O]–H ₂ O	Bär et al. (2007)	Experiencing variable intensity thermal pain
Brody et al. (2001)	PET – [18F]–FDG	Canli et al. (2004)	Performing lexical decision task for neutral, happy, sad, and threat words
Drevets et al. (1992)	PET – [15O]–H ₂ O	Cooney et al. (2010)	Thinking about personal traits, abstract ideas, and physical objects
Germain et al. (2007)	PET – [18F]–FDG	Frodl et al. (2009)	Emotion (explicit) or gender (implicit) matching of negative faces to target; shape matching control
Kennedy et al. (2001)	PET – [18F]–FDG	Fu et al. (2004)	Gender identification of variable intensity sad faces
Kimbrell et al. (2002)	PET – [18F]–FDG	Fu et al. (2007)	Gender identification of variable intensity happy faces
Kohn et al. (2007)	SPECT – 99mTc–ECD	Fu et al. (2008)	Gender identification of variable intensity sad faces
Krausz et al. (2007)	SPECT – 99mTc–ECD	Gotlib et al. (2005)	Viewing of happy, sad and neutral faces
Mayberg et al. (2005)	PET – [15O]–H ₂ O	Herwig et al. (2010)	Viewing of negative and neutral pictures
Perico et al. (2005)	SPECT – 99mTc–ECD	Keedwell et al. (2005)	Remembering happy, sad, and neutral experiences
Saxena et al. (2001)	PET – [18F]–FDG	Knutson et al. (2008)	Anticipation and receipt of monetary gains, losses, and neutral outcomes
Skaf et al. (2002)	SPECT – 99mTc–ECD	Kumari et al. (2003)	Viewing positive, negative and neutral picture-caption pairs
Videbech et al. (2001)	PET – [15O]–H ₂ O	Lawrence et al. (2004)	Viewing high and low intensity happy, sad, and fear faces; neutral-face control
		Mitterschiffthaler et al. (2003)	Viewing positive and neutral images
		Mitterschiffthaler et al. (2008)	Identifying colors of sad and neutral words
		Osuch et al. (2009)	Listening to endorsed favorite and neutral music
		Pizzagalli et al. (2009)	Anticipation and receipt of monetary gains, losses, and neutral outcomes
		Scheuerecker et al. (2010)	Emotion (explicit) or gender (implicit) matching of negative faces to target; shape matching control
		Strigo et al. (2008)	Anticipation and receipt of painful and non-painful thermal stimuli
		Surguladze et al. (2005)	Viewing of variable intensity happy and sad faces
		Townsend et al. (2010)	Matching of negative faces to emotion face or word target; shape matching control
		Wang et al. (2008)	Oddball target detection with sad or neutral picture as background
		Yang (2004)	Viewing erotic and neutral film clips

further, that the degree of DMN activation during non-self-referential thinking was associated with individual differences in trait rumination.

The executive network in depression

The foundational role of dysregulated emotional responding in MDD has motivated several investigations of structures that subserve cognitive control in MDD; these investigations have focused most prominently on DLPFC dysfunction. In general, these investigations have found decreased DLPFC functioning in MDD both at rest (e.g., Bench et al., 1992; Mayberg et al., 2005) and in response to negative stimuli (e.g., Pizzagalli et al., 2009; Strigo et al., 2008) see, however, Frodl et al. (2009). Interestingly, attenuated DLPFC responding in MDD to positive stimuli has been reported much less frequently, suggesting that DLPFC under-responding in MDD is specific to negative stimuli. While this body of findings with respect to DLPFC dysfunction in MDD is intriguing, it leaves unaddressed important questions regarding both the role of DLPFC dysfunction in the pathophysiology

of MDD and the relation of DLPFC deactivation at rest to DLPFC under-responding in depression.

Given that most functional neuroimaging studies of MDD are conducted with individuals who are in a depressive episode during scanning, it is not possible to determine from their results whether functional neural anomalies are necessary for depressive pathology, or alternatively, whether aberrations arise as a consequence of having developed depression. In this context, our understanding of the role of DLPFC under-activation in MDD has benefitted from work examining the effects of using transcranial magnetic stimulation (TMS), a technique that involves rapidly oscillating magnetic fields to modulate regional neural response on the cortical surface, to exogenously increase DLPFC activation in depressed persons. Consistent with the formulation that DLPFC under-activation plays a critical role in depressive pathology, meta-analyses have reported intermediate (O'Reardon et al., 2007) to strong (Gross et al., 2007) effects of using TMS to increase DLPFC activation in order to ameliorate depressive symptoms.

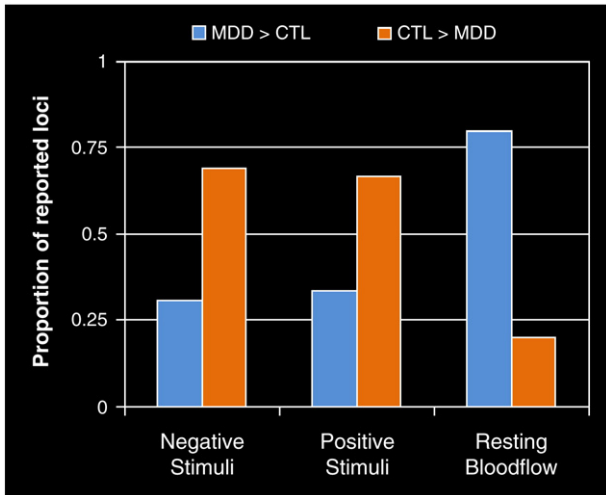


Fig. 2. Proportions of reported group-difference loci falling in the default-mode network in functional neuroimaging studies of depression.

Cognitive theories of MDD posit a cyclical relation between negative affective responding and depressed mood, in which negative affective biases promote depressed mood which, in turn, exacerbates negative emotional responding, which further increases negative biases. In this context, we might ask a similar question at the neural level regarding the relation between DLPFC under-response to negative stimuli and decreased DLPFC activation at rest in MDD. More specifically, is the part of the DLPFC that is most reliably under-active at rest the same region that is under-responsive to negative stimuli? To begin to address this question, we projected the data from fMRI investigations of neural response to negative stimuli in MDD and resting-state rCBF studies of MDD onto a common template and assessed the degree of overlap between findings from response and resting-state studies (see our description of this meta-analysis in the previous section for more details). Interestingly, the loci of the most reliable neural response and resting-state DLPFC findings in MDD did not overlap; in fact, as we present in Fig. 3, while both regions fell within the boundaries of the EN as specified by Seeley et al. (2007), the part of the DLPFC that shows reliable under-responding to negative stimuli in MDD is contralateral and posterior relative to the part of the DLPFC that is under-activated at rest in depression. These findings support a formulation in which tonic (resting state) and phasic (affective response) neural functional anomalies in MDD are undergirded by separate components of a functionally coherent network. In developing a more precise neural model of MDD, it is critical in future that investigators examining the EN in this disorder focus on the distinct functions supported by these disparate regions of the DLPFC.

The salience network in depression

The putative role of the SN in being aware of, and orienting and responding to, biologically relevant stimuli suggests a clear mapping of the functions of this network to negative response biases in MDD. Indeed, heightened response in the amygdala, anterior insula, and dorsal ACC has been documented in MDD across a wide range of negative conditions. For example, investigators have found greater activation in depressed than in nondepressed persons in the amygdala during anticipation of aversive pictures (Abler et al., 2007) and of receiving thermal pain (Strigo et al., 2008), in the anterior insula in anticipation of monetary loss (Pizzagalli et al., 2009) and of receiving thermal pain (Strigo et al., 2008), and in the dorsal ACC during viewing of sad faces (Fu et al., 2004) and words (Mitterschiffthaler et al., 2008). It is noteworthy that, consistent with its putative role in vigilance and threat detection (Whalen, 2007), the amygdala has been implicated in over-response during anticipation of noxious stimuli in depression. In contrast, the insula has been found to be over-active in MDD during the receipt, as opposed to the anticipation, of negative stimuli, a finding consistent with formulations that this structure subserves emotional awareness (Craig, 2009). Importantly, and reflecting network-level disturbance of the SN in MDD, the amygdala and insula have been found to be simultaneously over-responsive to affective challenge in depression (Suslow et al., 2010). The fact the few investigators have found SN over-response to positive stimuli in MDD suggests that, as in the EN, heightened SN response in MDD is specific to negative stimuli.

An important difference between dysfunction in the SN and dysfunction in the DMN and EN in MDD is that whereas all primary nodes of the SN are affected in MDD, individual components of the EN and DMN (primarily the parietal components) have not been found to exhibit aberrant activation in MDD. The relative coherence of the SN response in MDD warrants additional inquiry, specifically with respect whether a common neurobiological mechanism might promote heightened SN response in this disorder. We propose that one such mechanism involves functional anomalies in the pulvinar nucleus of the thalamus in MDD. We offer this proposal because several investigators have reported heightened baseline activation of the pulvinar in PET studies of MDD (Aihara et al., 2007; Brody et al., 2001b; Drevets and Raichle, 1992; Germain et al., 2007; Saxena et al., 2001), and because of two important properties of the pulvinar. First, the pulvinar has been shown to have monosynaptic connectivity with primary components of the SN, including projections to the amygdala (Jones and Burton, 1976), as well as bidirectional connectivity with the insula and dorsal ACC (Mufson and Mesulam, 1984; Pessoa and Adolphs, 2010). Second, the pulvinar has been found to play a central role in emotion attention, that is, in allocating attentional resources to biologically important stimuli. This role is suggested by evidence that the pulvinar is necessary for feature binding (Ward et al., 2002), which is a key function of attention in integrating the contributions of distinct cell ensembles that code for different perceptual features (Treisman, 1999). This formulation is supported by the results of a recent fMRI study examining

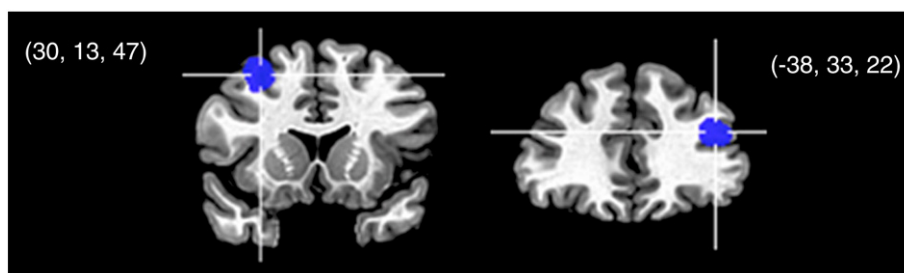


Fig. 3. Loci of reliable between-groups differences in the executive network for studies of resting blood flow (right) and neural response to negative stimuli (left) in depression.

pulvinar responding to stimuli that were either affective or neutral, and either detected or undetected (Padmala et al., 2010). Consistent with the formulation described above, Padmala et al. found pulvinar response *only* to detected affective stimuli. Given this role of the pulvinar nucleus in emotional attention and awareness, in addition to its connectivity with the amygdala, insula, and dorsal ACC, we propose that increased baseline pulvinar activation acts to potentiate SN response to negative stimuli in MDD.

New directions: cross-network interactions in depression

Contemporary neural models of MDD, such as Mayberg's (1997) reciprocal limbic-cortical dysregulation model, emphasize dysfunctional interactions between neural networks, as opposed to unisubstructural or uni-network functional anomalies, as critical in contributing to depressive pathology. Given this emphasis, as well as the putative functions of the default-mode and task-positive networks in supporting passive and self-reflective, and active and externally focused processes, respectively, we investigated the relation between DMN and TPN, and their association with maladaptive and adaptive styles of rumination, in MDD (Hamilton et al., 2011b). Specifically, we used a unique metric to estimate DMN dominance over TPN: the number of fMRI acquisitions for which DMN activity exceeded TPN activity during a resting-state fMRI scan. We then calculated correlations between our metric of DMN dominance over TPN and depressive (maladaptive) and reflective (adaptive) subscales of the Ruminative Responses Scale (Nolen-Hoeksema et al., 1993). We found in depressed, but not in healthy, individuals that greater DMN dominance was associated with higher levels of depressive rumination and lower levels of reflective rumination. In a follow-up analysis, we examined the relations in activation between the right anterior insula, a component of the SN, and TPN and DMN. The right anterior insula has been implicated causally in switching between modes of relative DMN and TPN dominance (Sridharan et al., 2008) and in interoceptive error detection (Paulus and Stein, 2006). In this analysis, we estimated response of the right anterior insula at the time of initiations of ascent in DMN and in TPN activity in depressed and healthy individuals. Whereas in the depressed participants we found increased right insula activation at the onset of increases in TPN activation, in the healthy control participants we found increased insula response at the onset of increases in DMN activity. These findings are consistent with the formulation that the DMN supports the representation of negative, self-related information in depression, and that the right insula, when prompted by heightened levels of DMN activity in MDD, initiates potentially adaptive engagement of the TPN.

Importantly, such multi-network conceptualizations of psychopathology as this increasingly are being presented and utilized in clinical neuroscience (Menon, 2011). Supporting this approach, Dannlowski et al. (2009) and others have described anomalous functional connectivity between the amygdala and the DLPFC in MDD. Given that these two structures are implicated in the functioning of the SN and EN networks, respectively, altered connectivity between these structures may reflect disrupted interactions between the SN and EN networks. Sheline et al. (2010) recently presented the data relevant to understanding how, at a neural level, there might be simultaneous dysfunction in the default mode, salience, and executive networks in MDD. Using resting-state fMRI, Sheline et al. found a dorsomedial prefrontal region (which they call 'the dorsal nexus') that showed abnormally elevated connectivity to SN, DMN, and EN networks in depressed individuals. Such integrative work as this will be instrumental in achieving more elegant and therapeutically useful neural-network models of MDD.

Future directions

Our review of functional neuroimaging studies of MDD indicates that understanding depression from the perspective afforded by

research examining the intrinsic functional organization of the brain could represent a significant contribution to neural theory of this disorder. Our understanding of resting-state networks, both within and between individuals, has advanced significantly over the past decade. With this increased knowledge, however, we have also had to recognize and acknowledge important methodological issues (Cole et al., 2010). While methods used to identify resting-state networks have often involved seed regions or individual-level ICA, these analyses generally do not take into account small but significant variation across individuals in DMN and other networks. Researchers have also identified significant variability in the spatiotemporal characteristics of these networks (Chang and Glover, 2010); indeed, networks like the DMN may actually consist of smaller sub-networks that underlie different aspects of cognitive functions (Leech et al., 2011). Despite these caveats, however, careful application of group-level analyses will likely lead to stronger, more accurate, and more systematic characterizations of network dysfunction not only in MDD, but in other psychiatric disorders as well.

While network-level conceptions of neural dysfunction in MDD provide an elegant, integrative framework through which to understand this disorder, they also raise important questions. Are there factors that might unite and integrate the network-level findings we have presented here in the context of a more cohesive framework? For example, we identified robustly increased SN response and decreased EN response to negative stimuli in MDD. While this pattern of findings suggests both over-response and under-regulation of emotional systems in depression, it is not clear what neural factors might unite these findings. A potential mechanism for integrating these apparently disparate effects is the documented decrease in the availability of striatal dopamine in MDD (Meyer et al., 2006) along cortico-striatal-thalamic pathways that connect ventral to dorsal cortical processing regions. This is but one possible mechanism; future research that uses multimodal imaging methods, including combined fMRI and PET, will be important in elucidating the neural and molecular links among different brain networks that are disrupted in major depression.

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