Review

Biological Psychiatry

Depressive Rumination, the Default-Mode Network, and the Dark Matter of Clinical Neuroscience

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ABSTRACT

The intuitive association between self-focused rumination in major depressive disorder (MDD) and the self-referential operations performed by the brain's default-mode network (DMN) has prompted interest in examining the role of the DMN in MDD. In this article, we present meta-analytic findings showing reliably increased functional connectivity between the DMN and subgenual prefrontal cortex (sgPFC)—connectivity that often predicts levels of depressive rumination. We also present meta-analytic findings that, while there is reliably increased regional cerebral blood flow in sgPFC in MDD, no such abnormality has been reliably observed in nodes of the DMN. We then detail a model that integrates the body of research presented. In this model, we propose that increased functional connectivity between sgPFC and the DMN in MDD represents an integration of the self-referential processes supported by the DMN with the affectively laden, behavioral withdrawal processes associated with sgPFC—an integration that produces a functional neural ensemble well suited for depressive rumination and that, in MDD, abnormally taxes only sgPFC and not the DMN. This synthesis explains a broad array of existing data concerning the neural substrates of depressive rumination and provides an explicit account of functional abnormalities in sgPFC in MDD.

Keywords: Default-mode network, Intrinsic functional connectivity, Major depressive disorder, Medial-dorsal thalamus, Rumination, Subgenual prefrontal cortex

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Ruminative responding in major depressive disorder (MDD) is defined as a recurrent, self-reflective, and uncontrollable focus on depressed mood and its causes and consequences (1–3). Higher levels of rumination have been found to predict both more severe depressive symptoms in depressed individuals (4) and the onset of depressive symptomatology in nondepressed people (5). Although ruminative responding is not considered a criterion symptom of depression in DSM-5 or ICD-10, measures of rumination nonetheless consistently [and often, perfectly, e.g., (6)] differentiate depressed from never-depressed individuals. Indeed, theorists have posited that rumination is a central aspect of the phenomenology of MDD (7).

Over the past decade, investigators have elucidated the intrinsic functional connectivity (IFC) of the brain, an endeavor that has proven useful in understanding brain functioning at a systems level (see Supplement 1 for a brief history of work on the brain's IFC). Combining findings from the brain mapping literature and correlations reported between network activity and measures of overt behavior, researchers have identified at least seven networks with distinct patterns of connectivity and functions (8). The perspective afforded by emerging knowledge of the IFC of the brain has provided clinical neuroscientists with a means of conceptualizing the neural substrates of psychopathology (9–11). Among the identified neural networks, the default-mode network (DMN) has received the most attention in the context of the clinical neuroscience of depression, largely because the self-referent processes attributed to the DMN (12) provide an intuitive basis for the neural conceptualization of rumination in MDD. In the following review, we describe the current status of the growing but enigmatic neuroimaging literature involving DMN functioning in MDD—both with respect to where DMN abnormalities are found and where they are not found. We then present a neural model of rumination in MDD that integrates and explains this literature.

PROPERTIES OF THE DMN

In working to elucidate the role of the DMN in supporting ruminative processes in MDD, it is important to understand the nature of the operations carried out within the ventromedial prefrontal cortex (vmPFC) and posterior cingulate cortex (PCC), two regions implicated most reliably in this network. Investigators have documented activation in vmPFC during valuation of goal-directed choices (13), while individuals are forming preference judgments (14), and as people are determining the financial value of a transaction (15). These findings, in addition to data documenting impairment in the ability to form preferences following damage to vmPFC (16), indicate that this structure plays a vital role in the valuation of appetitive goals. Further, investigators have found that vmPFC activates more strongly when individuals receive a stimulus

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they believe is of higher value than when they receive a stimulus of lower value [e.g., expensive vs. cheap wine (17)] and when stimuli are presented in more versus less appealing ways [e.g., cheese odor vs. foot odor (18)]. Considered collectively, these findings indicate that the vmPFC is involved broadly in assigning abstract properties of reward value to stimuli.

A growing functional neuroimaging literature is also elucidating the properties of PCC. Sestieri *et al.* (19) documented early activation of PCC, but not of vmPFC, in a task that required episodic memory retrieval and elaboration, suggesting that PCC plays a special role in autobiographical search and retrieval processes, as opposed to elaborating on stimuli. In addition, two meta-analyses found that PCC is reliably involved in spatial navigation from a self-centered reference frame (20) and in knowledge of the sensory attributes of concrete objects but not in verbal knowledge (21). Finally, in a graph theoretic study incorporating both structural and functional connectivity analyses, Hagmann *et al.* (22) found that PCC was among a small number of regions with hub-like properties that integrated information across the cerebral cortex. Together, these studies suggest that the broad role of PCC is in integrating self-relational information within a spatial-temporal context.

Although we are acquiring a more comprehensive understanding of the unique functions of vmPFC and PCC, their combined function in the context of the DMN is not as well understood. Given that vmPFC activation tracks consistently with assigning reward labels to stimuli and that PCC functions to add layers of egocentric spatiotemporal context to stimuli, we propose that the function of the DMN complements that of another intrinsic functional network, the salience network. This latter network comprises the dorsal anterior cingulate cortex (ACC), fronto-insular cortex, and amygdala (23) and plays a pivotal role in determining the biological significance of external stimuli. Thus, and as other investigators have found (24), we posit that in contrast to assessing the significance of external stimuli, the DMN assigns valence to internally represented stimuli, and to an extent consistent with the intensity of the assigned valence, elaborates on these stimuli from an egocentric perspective. Findings that attenuation of the deactivation characteristic of the DMN during task performance is associated with internal mentation at both state and trait levels (25) are consistent with this formulation. For readers interested in additional perspectives on functioning of the DMN, we recommend prior studies (20,26–29).

THE DMN IN MDD

Resting-State Functional Magnetic Resonance Imaging

There are now a number of studies that have examined resting-state functional magnetic resonance imaging (fMRI) connectivity of the DMN in MDD. To identify the most robust findings in this literature, we conducted for this review a systematic meta-analysis of these studies. Briefly, we searched the Web of Science for articles with titles or topics matching the search phrase [depress* AND (fMRI OR "functional MRI" OR "functional magnetic") AND default]. Among the articles that met these search criteria, we kept for subsequent meta-analysis those that compared DMN connectivity in currently and never depressed individuals across the whole brain using either seed-based functional connectivity or independent components analysis. In addition, we retained only those articles in which coordinates for regions showing between-groups differences in DMN connectivity were provided in Montreal Neurological Institute or Talairach space. Six studies (30–35) met criteria for inclusion in our meta-analysis (see Table 1 for characteristics of included studies); to add to this, we conducted an additional analysis of DMN functional connectivity in MDD [using the method presented in Hamilton *et al.* (36)] in a sample of 17 unmedicated unipolar depressed and 17 matched healthy control participants from our laboratory.

To the coordinates of between-groups differences in DMN connectivity reported in the seven studies meeting our inclusion criteria, we applied a multilevel kernel density analysis approach (37–39) to meta-analysis in which we first converted reported coordinates from each of *N* studies into sample size

Table 1. Demographic, Clinical, and Analytic Data for Studies Meeting Inclusion Criteria for the Meta-analysis

	Number of Participants per Group		Characteristics of MDD Samples				
Study	Major Depressive Disorder	Healthy Control Subjects	Medicated (%)	Female (%)	Mean Age	Current Comorbidities in MDD Samples	Technique Used to Estimate DMN Connectivity
Alexopoulos *et al.* (30)	16	10	0	NR	69.0	None	Seed region
Berman *et al.* (32)	15	15	40	66	25.7	Anxiety (2)	Seed region
Gaffrey *et al.* (33)	21	18	0	57	9.5	Internalizing disorder (3), internalizing and externalizing disorders (12)	Seed region
Greicius *et al.* (34)	28	29	71	57	38.5	Psychosis (11)	ICA
Sambataro *et al.* (31)	20	20	70	75	33.6	None	ICA
Zhu *et al.* (35)	32	33	0	56	20.5	None	ICA
Hamilton *et al*. novel sample; J. Paul Hamilton, PhD, unpublished data, April 14, 2014	17	17	0	65	32.1	None	Seed region

DMN, default-mode network; ICA, independent components analysis; MDD, major depressive disorder; NR, not reported.