

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

J. Paul Hamilton, Madison Farmer, Phoebe Fogelman, and Ian H. Gotlib

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

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

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

weighted binary indicator maps. Next, we summed the indicator maps at each voxel (v) to obtain the meta-analytic statistic (\hat{P}_v) such that:

$$\hat{P}_v = \sum_{n=1}^N w_n I_n$$

where w_n is the square root of the number of subjects in the full study group (depressed plus comparison subjects) of the n th of N studies. Finally, we thresholded this map voxelwise using Monte Carlo simulation and clusterwise using 3dClustSim in AFNI (NIMH Scientific and Statistical Computing Core, Bethesda, Maryland) (40) so that familywise error was held at $p = .05$ (voxelwise $p = .0001$; cluster threshold = 271 mm^3). See previous meta-analyses (37,39) for more details about this approach.

We found highly reliable increases in MDD in functional connectivity between the DMN and the subgenual prefrontal cortex (sgPFC), as well as the medial-dorsal thalamus (MDT), dorsal ACC, and posterior lateral parietal cortex (Figure 1). Importantly, Berman *et al.* (32) and Zhu *et al.* (35) reported that stronger connectivity between sgPFC and the DMN predicted higher levels of ruminative responding in MDD. Further confirming these findings, we conducted effective connectivity analysis using sgPFC as a seed region and found evidence of mutually propagating activation between sgPFC and vmPFC in MDD that, predicted higher levels of rumination about depressive symptomatology (36).

Resting Regional Cerebral Blood Flow

Given both the purported role of the DMN in the self-relational aspects of rumination and the high prevalence of rumination in depression, we might expect to see abnormally increased activation in nodes of the DMN in MDD in studies using techniques like positron emission tomography and single photon emission computed tomography, both of which assess resting-state regional cerebral blood flow (rCBF). For purposes of this review, we updated a recent meta-analysis of resting

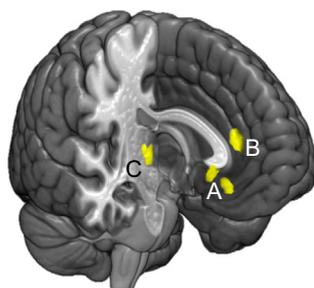
rCBF abnormalities in MDD [four studies added to Hamilton *et al.* (39); see Table S1 in Supplement 1 for details on the 18 studies included] and compared the resulting meta-analytic map with a map of the DMN as defined by Greicius *et al.* (41). Notably, we did not find statistically reliable, or even trend-level, differences between depressed and control samples in rCBF in any region of the DMN (see Figure 2 for a rendering of both MDD versus control rCBF maps and the DMN in the same standard space). We did find in both our original (39) and updated meta-analyses, however, statistically reliable increases in sgPFC rCBF in MDD—a finding that converges with findings from region-of-interest approaches investigating rCBF abnormalities in MDD (42–44). While the region of the sgPFC in which we found increased baseline activation (39) is lateral to regions that we found showed increased DMN connectivity in MDD, it is important to consider that subregions of the sgPFC have reliably shown similar response profiles and are thought to comprise a functionally homogenous region (45–50).

DMN Dominance And Depressive Rumination

In a recent investigation, we computed an index of the degree to which DMN activity exceeded activity in the task positive network—a network that shows an anticorrelated relation with the DMN and is involved in effortful tasks requiring attention (12)—over the course of a resting-state fMRI scan in depressed and nondepressed individuals (6). In both of these groups, we then computed correlations between DMN dominance and three types of rumination: reflection, brooding, and rumination about depressive symptoms. Reflective rumination has been construed as a process that entails agency and adaptive focus and has been found to predict lower levels of depressive symptoms (51); in contrast, other forms of rumination are considered to be maladaptive and have been found to be associated with attentional bias to negative stimuli in MDD (52). Although the depressed and nondepressed groups did not differ with respect to DMN dominance, we did find only in the group with MDD that higher DMN dominance was associated with higher levels of maladaptive rumination about depressive symptoms and with lower levels of more adaptive reflective rumination (6).

Interim Summary

Above, we note several neural functional and behavioral regularities in MDD. First, a hallmark feature of depression is negative, self-focused rumination. Second, across 18 whole-brain rCBF investigations of MDD, there are no reliable findings suggesting that components of the DMN are overactive in depression—a finding that stands in apparent contrast to our data showing that DMN dominance predicts levels of rumination in MDD. Further, increased sgPFC rCBF in MDD has been reliably observed but, as we detail below, is not well understood in terms of its contributions to the pathophysiology of depression. Next, from the functional connectivity literature, we show that depressed individuals are characterized by reliably increased connectivity of the sgPFC and the MDT with the DMN, where levels of connectivity between the sgPFC and DMN in MDD often predict levels of rumination in depression. Below, we present a model in which we explain the enigmatic rCBF findings in MDD in terms of the DMN-



Region	Voxels	X	Y	Z	Figure
Subgenual prefrontal cortex (bimodal cluster)	1281	0	26	-10	A
Left dorsal anterior cingulate	976	-6	37	12	B
Right medial dorsal thalamus	891	9	-18	5	C
Right posterior lateral parietal cortex	734	42	-67	29	

Figure 1. Regions showing reliably increased connectivity with the default-mode network in major depressive disorder.

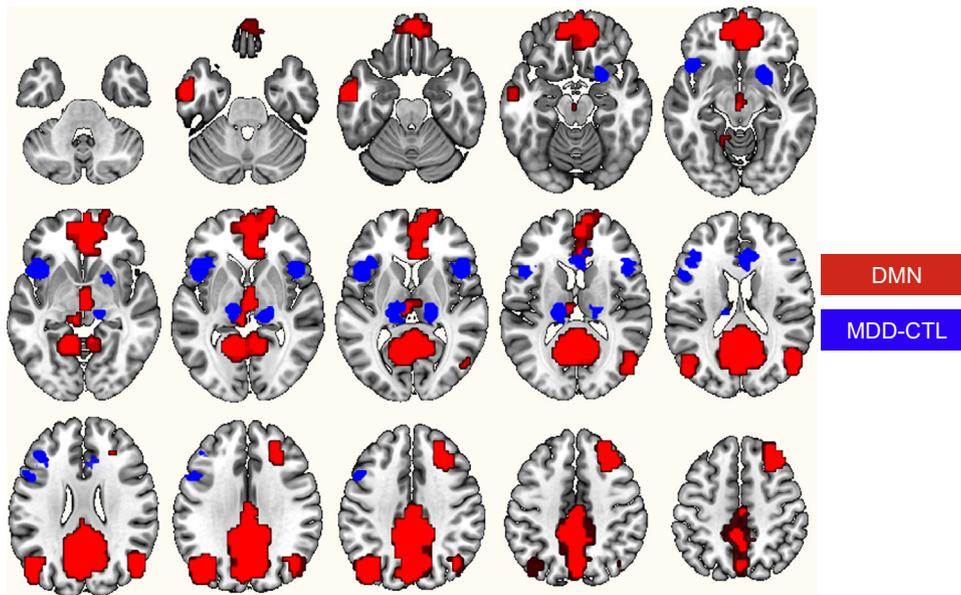


Figure 2. Maps of the default-mode network (DMN) (red) and meta-analytically reliable regional cerebral blood flow differences between samples with major depressive disorder (MDD) and healthy control (CTL) samples (blue).

related functional connectivity findings in depression. In doing this, we integrate a broad and paradoxical body of data and provide a more explicit account of the role of functional abnormalities of sgPFC in MDD.

A NEURAL MODEL OF RUMINATION IN MDD

The Function of sgPFC

Most work examining the functioning of sgPFC has been conducted in the context of clinical depression and sad mood. Specifically, researchers frequently report elevated sgPFC activity associated with a state of depression (42–44) or with response to negative affective challenge in MDD (46) or, in nondepressed persons, with sad mood induced either through elaboration of sad autobiographical scripts (43) or through inflammation challenge (53). Although these are important findings, they beg questions concerning the role of sgPFC functioning in depression and sadness. In addressing these questions, it is informative to consider the results of studies examining sgPFC activity in the context of normal affective processing. Early formulations of affective processing in the ACC and adjacent periculate regions proposed opposing and complementary functions for the dorsal and ventral aspects of this region (49). Specifically, researchers posited that dorsal ACC and sgPFC functioning are complementary with respect to a continuum of autonomic tone, with dorsal ACC involved in active, energy-expending functions (54) and sgPFC subserving behavioral withdrawal, resource conservation, and the promotion of safety behaviors (55,56). Subsequent work showing that increased sgPFC response is associated with feelings of guilt resulting from behaviors that run counter to social values (57) indicates that the behavioral withdrawal supported by sgPFC also involves affective appraisal. Further confirming this formulation, investigators have documented increased sgPFC activity in response to

peer rejection during fMRI scanning, activity that predicts the subsequent development of depressive symptomatology (58).

Integrating the Data

To synthesize and reconcile the bodies of work presented above, we posit that findings of increased functional connectivity between the DMN and sgPFC in MDD constitute a neural-level rendering of depressive rumination. Specifically, we propose that increased functional connectivity between the DMN and sgPFC in MDD reflects a functional integration of properties of the sgPFC and DMN. Thus, we propose that in MDD the DMN-supported processes of imbuing internal stimuli with valence and an egocentric frame of reference are united with sgPFC-related processes that support affectively laden behavioral withdrawal to produce a ruminative state that is self-focused, valenced, and withdrawn. See Figure 3 for a visual rendering of this model.

Reliably increased connectivity between sgPFC and the DMN in MDD helps to explain the enigmatic literature described above concerning DMN function in depression. Specifically, our formulation explains why investigators using measures of rCBF have not found overactivation of DMN nodes in MDD (39), even though depressed persons to a much greater extent than nondepressed individuals report engaging in self-reflective, ruminative thought considered to be supported by the DMN (6). Specifically, in proposing that functional integration of sgPFC and the DMN subserves depressive rumination, our model does not imply that additional demands are made of the DMN in MDD, only that the normal functions of this network are united to an abnormal degree with sgPFC functions—an integration of functions that underlies a maladaptive pattern of thought.

An additional advantage of our sgPFC-DMN model of rumination in MDD is that it provides an explicit functional account of increased DMN-MDT functional connectivity in depression (Figure 1). Given that communication among cortical sites can be either direct or indirect and routed through the

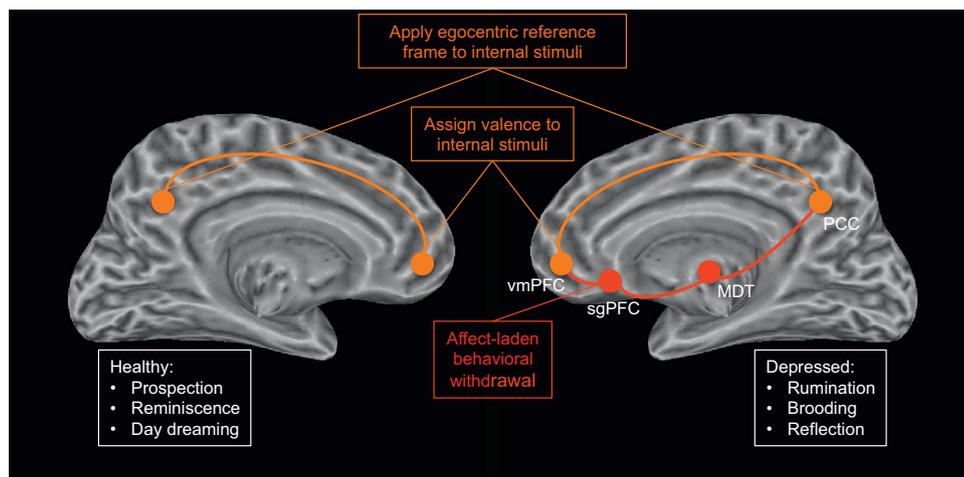


Figure 3. Graphical rendering of our default-mode network–subgenual prefrontal cortex (sgPFC) functional integration model of depressive rumination. Orange nodes and connections represent normal functionality; red nodes and connections represent depressotypic functioning. Note: We present our model using left and right cerebral hemisphere underlays not to indicate interhemispheric anomalies associated with major depressive disorder but to juxtapose default-mode network functioning in depressed and nondepressed individuals. MDT, medial dorsal thalamus; PCC, posterior cingulate cortex; vmPFC, ventromedial prefrontal cortex.

thalamus and that tractography studies of sgPFC have failed to reveal direct connectivity between sgPFC and nodes of the DMN either in humans (59) or in nonhuman primates (60), it is likely that the increased correlation in activity between sgPFC and the DMN observed in MDD is mediated through the MDT, the part of the thalamus that receives information from ACC and the amygdala before routing that information back to the cortex (61). Because connectivity between sgPFC and the DMN is abnormally elevated in MDD and is likely mediated by the MDT, we posit that the additional burden on the MDT in MDD of mediating communication between the sgPFC and DMN accounts for increased functional connectivity between the MDT and DMN in depression (Figure 3).

An Analogy To The Current Model

To further explain our model, we make an analogy with bonding of atoms into molecules. Elemental sodium can be joined with chlorine to form the ionic compound sodium chloride or table salt. Elemental sodium can also be combined with water, however, to form the caustic compound sodium hydroxide. In contributing to a desirable, as opposed to an undesirable, outcome, nothing needs to change about sodium, only the elements or compounds with which it is combined. Further, natural variations in a given sample of sodium—such as its purity—can influence the compound it helps to produce, whether healthy or caustic. We propose that the relation between sodium and water is analogous to that between the DMN and sgPFC in depression. Thus, we posit that the primary dysfunction in the DMN in MDD involves its relation with sgPFC: the DMN need not be overactive, only functionally united with sgPFC to contribute to depressive rumination. Our formulation still allows that natural variation in DMN activity and in the egocentric attributions it subserves—which, we argue, are necessary but not sufficient conditions for depressive rumination—can influence levels of rumination in MDD, thereby providing an account of our recent finding that while DMN dominance is not abnormal in depression, it still predicts levels of depressive rumination (6). This phenomenon of a network that contributes to depression but does not

show overt dysfunction in terms of anomalies in rCBF or fMRI activation motivates the title of this article. We propose, further, that provided they show anomalous functional connectivity with specific structures in MDD (62), normal variation in activity in other intrinsic networks can constitute similar dark matter in the clinical neuroscience of depression that can be observed only through their capacity to predict patterns of depressive thought and affect. Thus, in continuing to develop more comprehensive neural models of MDD, we believe that it will be necessary to examine patterns of correlations between neural activity and measures of depressive thought and affect, even if these neural measures do not differentiate depressed from nondepressed individuals.

LIMITATIONS

It is important to acknowledge that while the current synthesis presents a plausible and integrative neural account of depressive rumination, it would benefit from elaboration in two ways. First, our model does not specify a mechanism underlying increased functional connectivity between sgPFC and the DMN in MDD. In this context, given findings that gamma-aminobutyric acid (GABA) deficits are prevalent in MDD (63) and that GABA concentrations in pericingulate cortex may control fluctuations of activity in the DMN (64), future work might explore more explicitly the relation between the DMN and the pericingulate GABAergic system in MDD. Second, the model we present relies strongly on functional connectivity findings from neuroimaging investigations of depression. In this context, it is important to consider that the nature of the neural computations associated with fMRI functional connectivity is still not well understood. Thus, while increased functional connectivity has been observed across a variety of cognitive and perceptual domains requiring distinct contributions of functionally specialized regions—from autobiographical planning tasks in normal participants (65) to cross-modal perceptual integration in grapheme-color synesthesia (66)—investigators have remained noncommittal about the computational significance of fMRI functional connectivity, typically ascribing to it, as we do here, integrative or uniting properties (67).

SUMMARY AND FUTURE DIRECTIONS

In this review, we discussed findings suggesting that increased functional connectivity between sgPFC and the DMN in MDD is a neural substrate of depressive rumination. We demonstrated how this neural conceptualization of rumination in MDD can account both for the involvement of the DMN in ruminative responding in depression and for the lack of DMN rCBF abnormalities documented in MDD. We also described how our neural model of ruminative responding in MDD provides an explicit and intuitive formulation of the involvement of sgPFC and the MDT in the pathophysiology of depression.

The model presented in this article generates at least two novel and testable predictions. First, recently developed techniques for inhibiting DMN activity via repetitive transcranial magnetic stimulation of the frontoparietal central executive network (68) should have the simultaneous effects of changing DMN connectivity with sgPFC and MDT in depression and selectively ameliorating depressive rumination. The second prediction from our model is that specialized therapies focused on reducing depressive rumination, such as rumination-focused cognitive-behavioral therapy (69), should selectively reduce the hyperconnectivity between the DMN and both sgPFC and the MDT in depression. Moreover, we predict further that successful rumination-focused cognitive-behavioral therapy should selectively reduce rCBF in sgPFC in MDD.

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ARTICLE INFORMATION

From the Laureate Institute for Brain Research and College of Health Sciences (JPH, MF), University of Tulsa, Tulsa, Oklahoma; Department of Engineering (PF), University of Tennessee, Knoxville, Tennessee, and Department of Psychology (IHG), Stanford University, Stanford, California.

Address correspondence to J. Paul Hamilton, Ph.D., Laureate Institute for Brain Research, Faculty of the Community School of Medicine, 6655 S Yale Ave, Tulsa, OK 74136-3326; E-mail: paul.hamilton@laureateinstitute.org.

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