Functional Neuroimaging of Major Depressive Disorder: A Meta-Analysis and New Integration of Baseline Activation and Neural Response Data

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Objective: Functional neuroimaging investigations of major depressive disorder can advance both the neural theory and treatment of this debilitating illness. Inconsistency of neuroimaging findings and the use of region-of-interest approaches have hindered the development of a comprehensive, empirically informed neural model of major depression. In this context, the authors sought to identify reliable anomalies in baseline neural activity and neural response to affective stimuli in major depressive disorder.

Method: The authors applied voxel-wise, whole-brain meta-analysis to neuroimaging investigations comparing depressed to healthy comparison groups with respect to baseline neural activity or neural response to positively and/or negatively valenced stimuli.

Results: Relative to healthy subjects, those with major depression had reliably higher baseline activity, bilaterally, in the pulvinar nucleus. The analysis of neural response studies using negative stimuli showed greater response in the amygdala, insula, and dorsal anterior cingulate cortex and lower response in the dorsal striatum and dorsolateral prefrontal cortex in individuals with major depressive disorder than in healthy subjects.

Conclusions: The meta-analytic results support an elegant and neuroanatomically viable model of the salience of negative information in major depressive disorder. In this proposed model, high baseline pulvinar activity in depression first potentiates responding of the brain's salience network to negative information; next, and owing potentially to low striatal dopamine levels in depression, this viscerally charged information fails to propagate up the cortical-striatal-pallidal-thalamic circuit to the dorsolateral prefrontal cortex for contextual processing and reappraisal.

(Am J Psychiatry Hamilton et al.; AiA:1–11)

Advancing neural theory of major depressive disorder is of great importance given both that this disorder is predicted to be the most burdensome disease in the world in the 21st century (1) and that it is often unresponsive to conventional pharmacologic intervention (2). Over the past two decades, investigations using functional neuroimaging have provided important insights about its neural substrates. Several of these investigations have supported a neural model of depressed mood in which, within a mutually inhibitory limbic and dorsal cortical architecture, limbic activation overcomes dorsal cortical activation, which reciprocally fails to inhibit limbic activation in major depressive disorder (3); researchers examining neural aspects of emotional reactivity in major depression have proposed similar frameworks (4). Investigators examining network-level connectivity in major depressive disorder have reported evidence of limbic inhibition of dorsal cortical activation, partially supporting corticolimbic inhibition models of major depression (5).

While current neural models of major depressive disorder have been important in both understanding and treating this disorder (6), they are equivocal with respect to the primary neural mechanisms of the illness and do not integrate contemporary knowledge of major neuroanatomical pathways and functional subdivisions of the brain. In formulating a more mechanistic and neuroanatomically viable model of major depression, it is important that we first identify and address issues concerning the data that inform neural theories of the disorder. In this context, it is noteworthy that even the neural findings that are considered most foundational in the neuroscience of depression, such as higher than normal baseline activity in the subgenual anterior cingulate cortex (6) and low activation in the dorsolateral prefrontal cortex (7), have not gone unchallenged (8–10). Further, region-of-interest analytic approaches, which are widely used in clinical neuroimaging (in reference 11, for instance) both to bolster statistical power and to test specific neural models of depression,

may nonetheless bias neural models of major depressive disorder by ignoring anomalies in regions that are not of current interest in the study of depression. Thus, we propose that in order to advance neural theory of depression, we must identify, across the whole brain, reliable patterns of anomalous neural response and baseline brain activation in this disorder.

In this context, voxel-wise, whole-brain meta-analysis has the potential to identify robust functional neural findings from the corpus of functional neuroimaging research in major depression; indeed, such an approach has been applied successfully to identifying reliable and interpretable neural responses in anxiety (12) and in emotional responding more generally (13). Further, voxel-wise meta-analysis allows investigators to combine and examine patterns of activation obtained across studies using different types of experimental conditions. For example, findings from studies of neural reactivity to positive stimuli in major depressive disorder can be contrasted with results of investigations of reactivity to negative stimuli, yielding findings that are typically not possible to obtain in a single study. Finally, and particularly important for developing a comprehensive neural theory of major depressive disorder, meta-analysis of whole-brain functional neuroimaging data has the potential to identify anomalous patterns of activation that may not have been accorded adequate attention in previous neural conceptualizations of depression.

While meta-analyses reported by other researchers have produced intriguing results (14), only recently has the number of functional neural investigations of major depression—particularly those using functional MRI (fMRI) to measure neural response—reached a level sufficient to warrant meta-analysis. In the present study we used a whole-brain, voxel-wise meta-analytic technique to identify reliable anomalies in major depressive disorder from both resting-state regional cerebral blood flow (rCBF) and affective-challenge fMRI studies. For affective-challenge fMRI investigations, we examined the results of studies of neural responses to negative relative to positive stimuli in depression. In conducting these analyses, our objective was to develop an empirically informed and rigorous neural model of major depressive disorder.

Method

Overview

We used multilevel kernel density analysis (12, 13) in conducting the present meta-analysis. In this analysis, we first identified functional neuroimaging studies that reported neural functional aberrations among participants diagnosed with major depressive disorder in 1) rCBF as measured with positron emission tomography (PET) or single photon emission computed tomography (SPECT) or 2) neural reactivity (task-based fMRI) to negative and/or positive stimuli. Next we converted results from each comparison of interest in each study into summary binary indicator maps (12). Finally, we merged and conducted voxel-wise comparisons of these maps separately for rCBF and fMRI studies.

Study Selection

We used the ISI Web of Science database to identify functional neuroimaging studies of depression conducted up to Jan. 15, 2011. To identify fMRI studies of major depression, we entered the terms "depress* OR mood" and "functional MRI OR fMRI" in the topic-based search field. To identify PET and SPECT studies of depression, we entered "depress* OR mood" and "positron emission tomography OR PET OR single photon emission OR SPECT OR cerebral-blood flow" in the topic-based search field. Among the studies identified—1,448 fMRI studies and 5,147 rCBF studies—we kept for subsequent meta-analysis only those that were conducted with adults between the ages of 18 and 60 who were diagnosed with a current episode of primary unipolar depression as assessed with the Structured Clinical Interview for DSM (SCID) (15) or with the International Statistical Classification of Diseases and Related Health Problems (ICD) (16). In addition, we required that studies took a whole-brain analysis approach in which the investigators reported coordinates of all suprathreshold clusters in comparing neural activity in subjects with major depressive disorder to that in a comparison group of demographically matched, SCID- or ICD-assessed nondepressed individuals. We also searched the reference lists of studies that met these criteria to ensure that our original web-based search was comprehensive. For PET and SPECT studies to be included, we required that they used a tracer amenable to estimating brain activity: [^{18}F]FDG or [^{15}O]H_2O for PET and [^{99m}Tc]ECD for SPECT. For fMRI studies to be included, we added the criterion that there was at least one condition in the study in which activation during processing of affectively valenced information was either contrasted to a neutral stimulus condition or parametrically varied. Finally, we required that typical regression analyses, i.e., those using regression to estimate the extent or "height" of the blood-oxygen-level-dependent response, were conducted on fMRI data. Fourteen rCBF studies (6, 17–29) and 24 fMRI studies (7, 8, 30–51) met our inclusion criteria; 5,133 rCBF and 1,424 fMRI studies identified in our original search were excluded for not meeting one or more of these criteria. While the fMRI studies included in this meta-analysis collectively used a broad range of negatively and positively valenced affective challenges and stimuli, we have combined these studies given that valence is a fundamental component of emotions and affective stimuli in affective circumplex models of emotion (see, for instance, reference 52). Thus, examining differential neural response in major depression to stimulus valence, regardless of its specific form, can inform us from a theoretical perspective about emotional functioning in major depressive disorder.

Computing the Meta-Analytic Statistic

As in other studies employing multilevel kernel density analysis (for instance, 12), the data for the present meta-analysis were coordinates that were reported in three-dimensional standard brain space of peak activation differences between groups. For each study that met the inclusion criteria, we constructed at 1-mm isotropic voxel resolution an indicator map in Talairach space (53) as represented in the AFNI statistical package (54). We converted coordinates reported in the standard space of the Montreal Neurological Institute to Talairach space by using the MATLAB script mni2tal.m (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). Each binary indicator map, I, was composed of spheres (value=1) of 10-mm radius—a size chosen to account for limitations in spatial resolution in functional neuroimaging data while maintaining adequate sensitivity to detect neural anomalies in smaller structures—centered at reported locations of peak between-groups difference; in instances of overlap between spheres, we valued the region of intersection at 1.

We merged indicator maps into six meta-analytic statistical maps: four from fMRI studies and two from PET/SPECT studies.

The fMRI meta-analytic maps showed regions where activation in depressed subjects was greater than in comparison subjects in response to negative stimuli (20 contrasts, 92 coordinates) and positive stimuli (10 contrasts, 40 coordinates) and where activation was greater in comparison subjects than in depressed subjects in response to negative stimuli (19 contrasts, 90 coordinates) and positive stimuli (14 contrasts, 76 coordinates). The PET/SPECT meta-analytic maps indicated where activation was greater in depressed subjects than in comparison subjects (10 contrasts, 37 coordinates) and where it was greater in comparison subjects than in depressed subjects (11 contrasts, 37 coordinates). Indicator maps from N studies per category were merged into meta-analytic statistical maps, where the meta-analytic statistic ($\hat{P}_v$) at each voxel, v, was calculated as

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

where w_n is the square root of the number of subjects in the full study group (depressed plus comparison subjects) of the nth of N studies. Weighting each map in this fashion meant that studies with larger groups and presumably more reliable results were accorded more weight in the meta-analytic statistic. This approach has several advantages relative to other meta-analytic methods used to examine patterns of brain activation in depression, such as those that use activation likelihood estimation techniques (for instance, reference 14). First, because we treated comparison maps within studies as random effects, no single map could contribute disproportionately to our meta-analytic results. Second, weighting by group size increases accuracy without introducing the complexity of z-score-based weighting for different types of analyses. Finally, relative to methods that incorporate z-score weighting, such as activation likelihood estimation, the approach taken in the present meta-analysis is better suited to examining the replicability of neural responding across studies.

Comparing Meta-Analytic Maps

We subtracted meta-analytic maps showing regions where activation was greater in comparison subjects than in depressed subjects from those showing regions in which activation was greater in depressed subjects for both rCBF studies (21 contrasts, 74 coordinates) and negative- and positive-valence fMRI studies (39 contrasts, 182 coordinates; and 24 contrasts, 106 coordinates, respectively). Further, for the fMRI studies, to test whether significant differences from these comparisons were valence specific, we also subtracted positive from negative meta-analytic maps for comparisons showing where activation was greater in depressed subjects and those showing where activation was greater in comparison subjects (63 contrasts, 288 coordinates). Null-hypothesis distributions for each comparison were calculated from 10,000 Monte Carlo simulations performed in MATLAB (www.mathworks.com) by using relevant variables from the included studies (group size, number of regions reported) but with the assumption of a random distribution of peaks in a standardized brain (AFNI's TT_N27+tlrc). We used the AFNI program AlphaSim to set the significance threshold for each comparison at α=0.05, family-wise-error-rate (FWE) controlled for comparison of multiple voxels across the whole brain. AlphaSim takes as input the parameters used in neuroimaging analysis (e.g., voxel-wise statistical threshold, size of mask over which statistical calculations are performed) and determines, using Monte Carlo simulation, a cluster threshold necessary to assure FWE control. We used a voxel-wise threshold of α=0.001 (resulting in a cluster threshold, k, of 177 voxels) for our fMRI meta-analysis and α=0.005 (k=384 voxels) for our meta-analysis of PET data. We used a more liberal voxel-wise threshold—and, therefore, a more stringent cluster size threshold—for the PET meta-analysis given the lower spatial resolution of PET data and the consequent lower incidence of intersection of PET-derived statistical maps. In addition, to address potential outlier effects and to ensure that significant meta-analytic findings are representative of results from a range of studies, we established that at least three studies had to contribute to a given meta-analytic finding for it to be reported here. Finally, we note that our null-hypothesis distributions were created under the assumption of independence across studies. Several studies that met our inclusion criteria were conducted in the same laboratory (fMRI: Cynthia Fu [7, 35, 36, 43], Thomas Frodl [34, 46], Ian Gotlib [32, 33, 37, 39], Mary Phillips [8, 48]; rCBF: Lewis Baxter [19, 27], Omer Bonne [24, 25]) or included more than one comparison per valence. Therefore, we checked significant meta-analytic findings to ensure that no study was represented more than once. We took the following exclusionary precautions to ensure independence across analyses from the same study: 1) if results from both parametric and neutral stimulus contrasts were reported, only results from the presumably more reliable parametric analyses were included; 2) if a study reported results from contrasting two levels of an emotion variable to a neutral stimulus, then results from only the comparison of the highest-level emotion and the neutral stimulus were included; and 3) if a study reported results from contrasting an experimental condition to more than one control condition, we included results from only one comparison, i.e., that which included the most coordinates. In cases where different studies from the same laboratory contributed to a significant finding, we contacted investigators to ensure that the study groups were independent.

Results

Characteristics of Included Studies

Table 1 and Table 2 present, for the included rCBF and fMRI studies, respectively, the number of subjects, gender composition, and proportion of medicated subjects in each group of depressed participants. Further, for fMRI studies we report the task that was used and the contrasts that were included in the meta-analysis.

rCBF Meta-Analysis

Our meta-analysis of resting-state PET and SPECT studies showed reliably greater activity in the depressed participants, relative to the comparison subjects, in both the right and left pulvinar nuclei of the thalamus (FWE-controlled $p<0.05$); see Figure 1. The data supplement accompanying the online version of this article contains otherwise significant regional cerebral blood flow anomalies in major depression supported by only two studies.

fMRI Meta-Analysis

Negative stimuli. Our analysis showed that individuals diagnosed with major depressive disorder had reliably greater responses to negative stimuli than did the comparison subjects in the amygdala, dorsal anterior cingulate cortex, and insula/superior temporal gyrus; we also found greater activation in response to negative stimuli in depressed individuals in precentral and middle temporal gyri. It is important to note that these effects were also evident in depressed participants when the responses to negative stimuli were contrasted with responses to positive stimuli, indicating that these aberrant responses in

TABLE 1. Studies Measuring Differences in Baseline Regional Cerebral Blood Flow Between Persons With Major Depressive Disorder and Healthy Comparison Subjects

	Number of Subjects in Group		Characteristics of Depressed Subjects		Imaging Technique	
Study	Major Depressive Disorder	Comparison	Medicated (%)	Female (%)	Method	Tracer
Aihara et al. (17)	24	23	0	63	PET	[^{18}F]FDG
Bench et al. (18)	33	23	58	36	PET	[^{15}O]H_2O
Brody et al. (19)	24	16	0	54	PET	[^{18}F]FDG
Drevets et al. (20)	13	33	0	54	PET	[^{15}O]H_2O
Germain et al. (21)	12	13	0	83	PET	[^{18}F]FDG
Kennedy et al. (22)	13	24	0	0	PET	[^{18}F]FDG
Kimbrell et al. (23)	38	37	0	66	PET	[^{18}F]FDG
Kohn et al. (24)	33	25	0	58	SPECT	[^{99m}Tc]ECD
Krausz et al. (25)	10	10	0	90	SPECT	[^{99m}Tc]ECD
Mayberg et al. (6)	6	5	100	50	PET	[^{15}O]H_2O
Périco et al. (26)	15	15	0	80	SPECT	[^{99m}Tc]ECD
Saxena et al. (27)	27	17	0	52	PET	[^{18}F]FDG
Skaf et al. (28)	9	12	0	44	SPECT	[^{99m}Tc]ECD
Videbech et al. (29)	42	47	95	71	PET	[^{15}O]H_2O

depression were specific to negative stimuli. We also found reliably lower activation in response to negative stimuli in depressed participants in the dorsolateral prefrontal cortex bilaterally and in the caudate body (dorsal striatum); however, only the lower response in the right dorsolateral prefrontal cortex in the depressed subjects was found to be specific to negative stimuli. All findings were significant at FWE-controlled $p<0.05$; see Figure 2 for a graphical rendering of these results.

Positive stimuli. Given that aberrant responses to positive stimuli in major depression do not figure prominently into the framework of this article, we present meta-analytic results relating to positive stimuli in the online supplement to this article.

Discussion

In the present study, we applied whole-brain, voxel-wise meta-analysis to a large corpus of functional neuroimaging studies of baseline activation and neural response in major depressive disorder. Our analysis of rCBF studies showed higher than normal baseline activity, bilaterally, in the pulvinar nucleus in depression. Further, our examination of fMRI studies showed that depressed individuals had greater responses than healthy comparison subjects in the amygdala, dorsal anterior cingulate cortex, and insula and lower responses to negative stimuli in the dorsolateral prefrontal cortex and dorsal striatum.

High Baseline Activity of Pulvinar Nucleus in Depression

In this meta-analysis we found high baseline activation in major depressive disorder in the pulvinar, a large (2,200 mm^3) nucleus of the thalamus. In light of evidence of monosynaptic projections from the pulvinar to the amygdala (55), early formulations of pulvinar function proposed that this structure is part of a fast, unconscious processing stream for priming behavioral response in the presence of threat (56). A more recent conceptualization of pulvinar function posits, instead, that this structure plays a key role in emotional attention and awareness (57). This position is supported by the finding that the primary neural drivers of pulvinar activity are cortical, and not subcortical, structures; indeed, both the insula and dorsal anterior cingulate cortex have strong bidirectional connectivity with the pulvinar nucleus (57, 58). Also consistent with the formulation of a central role for the pulvinar in emotional attention is evidence that this structure is necessary for feature binding (59), a key function of attention in integrating the contributions of distinct cell ensembles that code for different perceptual features (60). This model has been confirmed by a recent fMRI study examining pulvinar responding to stimuli that were either affective or neutral and were either detected or undetected. Consistent with the model just described, this study found pulvinar response only to detected affective stimuli (61). Given this role of the pulvinar nucleus in emotional attention and awareness and its connectivity with the amygdala, insula, and dorsal anterior cingulate cortex, we propose that high baseline pulvinar activation in major depressive disorder acts to potentiate response in neural structures that subserve orienting to, awareness of, and responding to affective information.

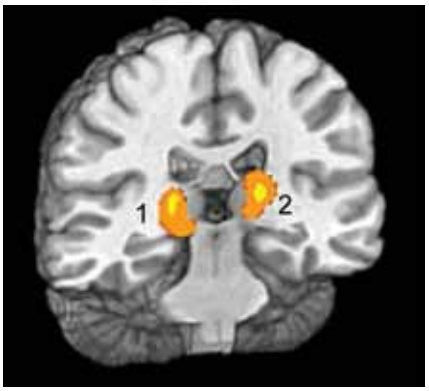
Overreactive Salience Network and Low Response of Dorsolateral Prefrontal Cortex and Dorsal Striatum to Negative Information in Depression

We found in this meta-analysis that the amygdala, dorsal anterior cingulate cortex, and insula are selectively overreactive to negative stimuli in major depressive disorder; these structures are all prominent nodes in the salience network of the brain (62). In this network, the

TABLE 2. Studies Using Functional Magnetic Resonance Imaging to Estimate Neural Response to Negative and/or Positive Stimuli in Persons With Major Depressive Disorder and Healthy Comparison Subjects

	Number of Subjects in Group		Characteristics of Depressed Subjects			Included Contrasts	
Study	Major Depressive Disorder	Comparison	Medicated (%)	Female (%)	Affective Challenge	Negative Valence	Positive Valence
Abler et al. (30)	12	12	100	100	Anticipating and viewing negative, neutral, and positive pictures	Anticipating negative versus neutral; viewing negative versus neutral	Viewing positive versus neutral
Bär et al. (31)	13	13	0	100	Experiencing variable-intensity thermal pain	Parametric thermal pain response	None
Canli et al. (32)	15	15	47	80	Performing lexical decision task for neutral, happy, sad, and threat-related words	Sad versus neutral; physical threat versus neutral; social threat versus neutral	Happy versus neutral
Cooney et al. (33)	14	14	43	57	Thinking about personal traits, abstract ideas, and physical objects	Personal traits versus abstract ideas	None
Frodl et al. (34)	12	12	67	58	Emotion (explicit) or gender (implicit) matching of negative faces to target; shape-matching control	Explicit versus control; implicit versus control	None
Fu et al., 2004 (36)	19	19	0	68	Gender identification of variable-intensity sad faces	Parametric sad face response	None
Fu et al., 2007 (35)	19	19	0	68	Gender identification of variable-intensity happy faces	None	Parametric happy face response
Fu et al., 2008 (7)	16	16	0	81	Gender identification of variable-intensity sad faces	Parametric sad face response	None
Gotlib et al. (37)	18	18	50	72	Viewing happy, sad, and neutral faces	Sad versus neutral	Happy versus neutral
Herwig et al. (38)	14	14	100	57	Viewing negative and neutral pictures	Negative versus neutral	None
Keedwell et al. (8)	12	12	92	67	Remembering happy, sad, and neutral experiences	Sad versus neutral	Happy versus neutral
Knutson et al. (39)	14	12	0	64	Anticipating and experiencing monetary gains, losses, and neutral outcomes	None	Anticipating gain versus neutral outcome; experiencing gain versus neutral outcome
Kumari et al. (40)	6	6	100	100	Viewing positive, negative, and neutral picture-caption pairs	Negative versus neutral	Positive versus neutral
Lawrence et al. (41)	9	11	100	44	Viewing high- and low-intensity happy, sad, and fearful faces; neutral-face control	High-intensity fearful versus neutral; high-intensity sad versus neutral	High-intensity happy versus neutral
Mitterschiffthaler et al., 2003 (42)	7	7	100	100	Viewing positive and neutral images	None	Positive versus neutral
Mitterschiffthaler et al., 2008 (43)	17	17	0	82	Identifying colors of sad and neutral words	Sad versus neutral	None
Osuch et al. (44)	16	17	6	69	Listening to endorsed favorite and neutral music	None	Favorite versus neutral
Pizzagalli et al. (45)	30	31	0	50	Anticipating and experiencing monetary gains, losses, and neutral outcomes	Anticipating loss versus neutral outcome; experiencing loss versus neutral outcome	Anticipating gain versus neutral outcome; experiencing gain versus neutral outcome
Scheuerecker et al. (46)	13	15	0	77	Emotion (explicit) or gender (implicit) matching of negative faces to target; shape-matching control	Explicit plus implicit versus control	None
Strigo et al. (47)	15	15	0	80	Anticipating and experiencing painful and nonpainful thermal stimuli	Anticipating pain versus nonpain; experiencing pain versus nonpain	None
Surguladze et al. (48)	16	14	100	38	Viewing variable-intensity happy and sad faces	Parametric sad face response	Parametric happy face response
Townsend et al. (49)	15	15	0	40	Matching negative faces to facial emotion or word target; shape-matching control	Face matching versus control	None
Wang et al. (50)	19	20	58	63	Oddball target detection with sad or neutral picture as background	Sad versus neutral	None
Yang (51)	10	10	0	100	Viewing erotic and neutral film clips	None	Erotic versus neutral

FIGURE 1. Statistical Map of Reliable Results From Meta-Analytic Synthesis Showing Differences in Baseline Regional Cerebral Blood Flow Between Persons With Major Depressive Disorder and Healthy Comparison Subjects[a]



Structure	Direction of Effect	Talairach Coordinates	Cluster Size (mm^3)	Number
Pulvinar nucleus	Depressed > Comparison	–15, –24, 8	3,054	1
Pulvinar nucleus	Depressed > Comparison	17, –25, 4	2,514	2

[a] Presented data were smoothed by using cubic interpolation.

amygdala is considered essential for sensory tuning to enable adaptive responding (63), whereas the dorsal anterior cingulate cortex is crucial for engaging motor and visceral efferents that constitute the sympathetic division of the autonomic nervous system (64). The insula, which shares extensive bidirectional connectivity with both the amygdala (65) and dorsal anterior cingulate cortex (66), has been postulated to subserve conscious awareness of interoceptive states (67). We also found in this meta-analysis that depressed persons have less response to negative stimuli in the dorsolateral prefrontal cortex than do healthy comparison subjects. The dorsolateral prefrontal cortex is a key component in the brain's executive network (68) and has been implicated in a variety of cognitive control processes, including allocation of attention (69) and interference resolution (70). Complementing its role in subserving cognitive processes is its role in the representation of information (71). Often in tandem with the dorsal striatum—found here to exhibit a lower than normal response to negative information in depression—the dorsolateral prefrontal cortex undergirds representation and maintenance of information (72, 73). The representational capacities of the dorsolateral prefrontal cortex and dorsal striatum have also been observed as components of more complex processes, such as the contextualization and reappraisal of information (71, 74). In the following, we present a model of how low responses of the dorsolateral prefrontal cortex and dorsal striatum to negative stimuli, as well as overreactivity of the salience network to negative information, in major depression might contribute to the pathophysiology of this disorder.

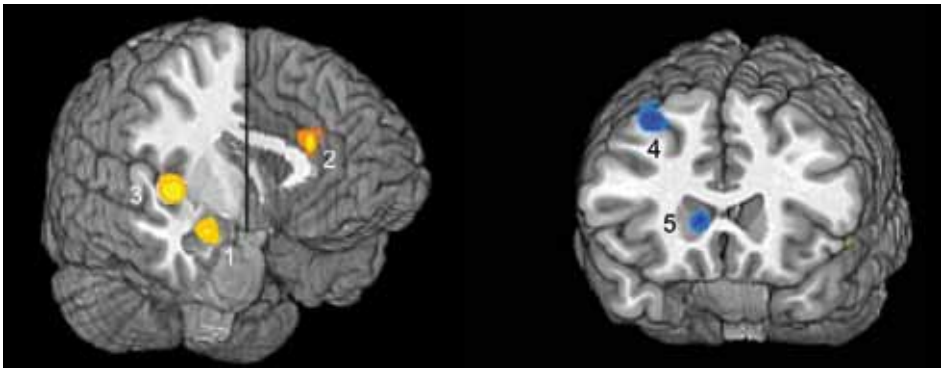
Patterns of Abnormal Neural Responding to Negative Stimuli in Depression: The Ascending Spiral Model of the Cortical-Striatal-Pallidal-Thalamic Circuit

The amygdala and dorsal anterior cingulate cortex, found in this meta-analysis to be overly responsive to negative stimuli in major depressive disorder, are primary input structures of the limbic subdivision of the cortical-striatal-pallidal-thalamic circuit. The basic architecture of this circuit has been identified from a large body of anterograde and retrograde neuronal tracing data from animals, and it provides a general architecture for the flow of information in the brain. In this architecture, information from cortical and allocortical structures travels to the striatum, then to the globus pallidus, then on to the thalamus, and finally, back to the cortex (75). Moreover, investigators have identified segregation within the circuit, in which functionally distinct inputs from limbic and cognitive subdivisions largely maintain segregation through the striatum, globus pallidus, and thalamus (76). Haber and colleagues (77) further refined this model by integrating a large body of anterograde and retrograde tracing data; these researchers posit an ascending spiral configuration of the cortical-striatal-pallidal-thalamic circuit in which information directed to limbic structures follows an upward spiraling trajectory toward dorsal cortical structures, such as the dorsolateral prefrontal cortex. It is important to note here that this upward spiraling trajectory is mediated through dopamine-dependent interactions between the striatum and substantia nigra (77). This ascending trajectory suggests that emotional significance is mapped first to sensory stimuli and that only later are higher-level attributes, such as interpretations and reappraisals, ascribed to these stimuli.

Integrative Neural Model of Heightened Salience of Negative Stimuli in Depression

For over three decades, theorists have postulated that negative cognitive biases play a critical role in the onset and maintenance of major depressive disorder (78, 79). The findings of this meta-analysis concerning baseline activity and neural response to affective stimuli cohere into a remarkably clear and neuroanatomically viable model of this greater salience of negative stimuli in depression. Given the conceptualizations we have presented of the pulvinar nucleus, salience network, and dorsal cortical function and connectivity, as well as the dopamine-mediated ascending spiral trajectory of information through the cortical-striatal-pallidal-thalamic circuit, the present meta-analytic findings support a two-step model of enhanced processing of negative information in depression. We propose, first, that through monosynaptic projections to the amygdala, dorsal anterior cingulate cortex, and insula, abnormally high baseline activation in the pulvinar nucleus in depression potentiates responding of these components of the brain's salience network to negative stimuli; this processing may be sustained both by mutually

FIGURE 2. Statistical Map of Reliable Results From Meta-Analytic Synthesis Showing Brain Structures With Different Responses[a] to Negative Stimuli Between Persons With Major Depressive Disorder and Healthy Comparison Subjects[b]



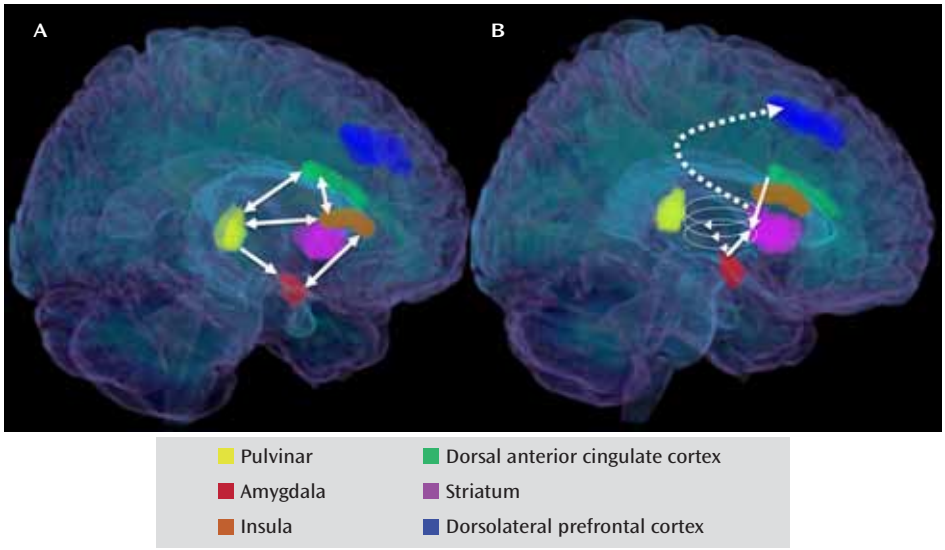
Structure	Direction of Effect	Valence Specific Effect?	Talairach Coordinates	Cluster Size (mm^3)	Number
Amygdala	Depressed > Comparison	Yes	24, –4, –13	318	1
Dorsal anterior cingulate cortex	Depressed > Comparison	Yes	–2, 30, 20	196	2
Insula and superior temporal gyrus	Depressed > Comparison	Yes	–38, –6, –8	834	3
Precentral gyrus	Depressed > Comparison	Yes	–30, –15, 44	621	–
Middle temporal gyrus	Depressed > Comparison	Yes	–39, –64, 17	440	–
Dorsolateral prefrontal cortex	Comparison > Depressed	Yes	30, 13, 47	1,380	4
Dorsolateral prefrontal cortex	Comparison > Depressed	No	–22, 27, 42	949	–
Caudate body	Comparison > Depressed	No	10, 20, 6	382	5

[a] As assessed with functional magnetic resonance imaging.
[b] Presented data were smoothed by using cubic interpolation.

excitatory connections between the insula and amygdala and between the insula and dorsal anterior cingulate cortex and by connections from the insula and dorsal anterior cingulate cortex back to the pulvinar nucleus (Figure 3A). Next, we propose that sensory data fail to propagate to the dorsal caudate and dorsolateral prefrontal cortex (Figure 3B), leading depressed individuals to fail to ascribe emotionally attenuating appraisals and contextual information to viscerally overcharged data from limbic structures. Given that nigrostriatal dopamine projections are instrumental in conducting information up the cortical-striatal-pallidal-thalamic circuit to the dorsolateral prefrontal cortex, both in vivo (80, 81) and postmortem (82) findings of low striatal dopamine activity in major depressive disorder suggest a potential mechanism by which data transfer through the dorsal caudate to the dorsolateral prefrontal cortex is attenuated in major depressive disorder. Recent meta-analytic results from Delaveau and colleagues (83) are important to consider in the present context, as they showed that key aspects of this model—overreaction of the amygdala and insula and underreaction of the dorsolateral prefrontal cortex in depression—resolve with antidepressant treatment, indicating that the present model accounts for state- as opposed to trait-related neural anomalies in major depressive disorder.

This proposed model is distinct in important ways from current cortical-limbic inhibition models of major depressive disorder. First, this model posits a unidirectional, as opposed to a cyclical, pattern of neural influence between limbic and dorsal cortical structures in depression. Consistent with this formulation are the findings in our recent study of depressed participants, providing strong evidence of greater than normal limbic-to-dorsal cortical inhibition but no evidence of lower dorsal cortical-to-limbic inhibition (84) in depression. Second, our model posits a primary neural mechanism, exaggerated tonic pulvinar activation, as critical to initiating a bias toward the processing of negative information in major depressive dis-

FIGURE 3. Neural Model of Biased Responding to Negative Information in Major Depressive Disorder[a]



[a] Part A: high pulvinar activation at baseline potentiates responding in the amygdala, dorsal anterior cingulate cortex, and insula; mutual excitation among these components of the salience network and connectivity from them back to the pulvinar may sustain their activation. Part B: possibly because of low striatal dopamine levels in major depressive disorder, signals from the dorsal anterior cingulate cortex and amygdala fail to propagate up the ascending cortical-striatal-pallidal-thalamic circuit, resulting in diminished responses to negative stimuli in the dorsal striatum and dorsolateral prefrontal cortex.

order. Finally, this model accounts for patterns of limbic overresponsiveness and dorsal striatal and dorsal cortical underresponsiveness in depression within a well-validated and integrative neural processing architecture: the upward spiral model of the cortical-striatal-pallidal-thalamic circuit (77). This aspect of the model also accounts well for the *lack* of dorsal cortical responding—as opposed to dorsal cortical *inhibition*—that is often observed in major depression (85).

While this proposed model of negative information processing in major depressive disorder offers an integrative account of findings from a large body of neuroimaging research, it nevertheless leaves an important question unaddressed. The finding from our meta-analysis of excess baseline pulvinar activation in depression is primary in our proposed model. However, the reason for this difference is not clear. In this context, it is important to note that genetics may contribute to the anomalies in pulvinar activation reported in major depressive disorder. Indeed, a postmortem brain volumetry study (86) showed higher pulvinar volume in individuals who were homozygous for the short allele in the promoter region of the serotonin transporter gene (5-HTTLPR), a polymorphism that has been associated with greater risk for major depression (87, 88).

Limitations

We should note five limitations of the present study. First, because only a few neuroimaging studies that met the criteria for our meta-analysis involved participants with remitted depression, it was not possible in this meta-analysis to determine whether the anomalies we identified in major depressive disorder are related to the state of depression or are trait-related characteristics of individuals at risk for this disorder. However, the recent meta-analytic finding that amygdala and insula overactivation and dorsolateral prefrontal cortex underreaction normalize after pharmacotherapy for depression (83) indicates that the present meta-analytic results represent state- as opposed to trait-related aspects of neural functioning in depression. Second, while the present meta-analysis was adequately powered to detect reliable functional neural anomalies in major depression, it was not adequately powered to determine the effects of extraexperimental variables, such as psychotropic medication use by the depressed participants. While the meta-analysis of Delaveau and colleagues (83) indicates that key neural anomalies found in the present analysis actually normalize with use of psychotropic medication, our findings cannot speak to the issue of medication effects. Third, we did not include in this meta-analysis data from groups experiencing forms of psychopathology other than major depression. Thus, while we were able to provide a comprehensive neural characterization of major depressive disorder, the issue of the specificity of these findings to major depression remains to be addressed. Fourth, our meta-analysis of resting-state activation studies used data from three different functional neuroimaging modalities; noise introduced by including heterogeneous modalities may have decreased the sensitivity of our analysis. Similarly, noise introduced by the variety of affective challenge techniques used in the fMRI studies that were included in our meta-analysis may have affected the power of this analysis. Finally, because in this meta-analysis we set criteria for finding the strongest and most reliable findings in the literature concern-

ing functional neuroimaging of depression, it is possible that we failed to detect weaker findings that are nevertheless important in understanding neural functioning in major depressive disorder. Indeed, results from previous meta-analytic investigations of major depression (14) indicated a broader array of neural anomalies in depression—both similar to those reported in the present analysis (e.g., greater amygdalar response to negative stimuli in depressed subjects than in healthy subjects) and different from the current findings (e.g., greater bilateral inferior frontal gyrus response to negative stimuli in depression). Certainly, these results should be accorded serious consideration in neural conceptualizations of major depressive disorder.

Summary and Future Directions

From the present meta-analytic synthesis, we formulated what we believe is an elegant and viable model of increased salience of negative information in major depressive disorder. We posit that through monosynaptic projections to the amygdala, dorsal anterior cingulate cortex, and insula, heightened baseline activity in the pulvinar nucleus in depression potentiates responding of these input nodes to the affective subdivision of the cortical-striatal-pallidal-thalamic circuit. We propose further that, potentially due to deficient striatal dopamine activity in major depression, there is a failure at nigrostriatal relays to propagate information to the dorsal striatum and dorsolateral prefrontal cortex; thus, attributions and appraisals that are typically initiated by the dorsolateral prefrontal cortex to reduce the impact of negative stimuli are not applied to viscerally charged sensory data in major depressive disorder.

Theorists have contended that biased processing of negative information plays a critical role in the etiology and maintenance of major depression (89). Moreover, the model supported by the current meta-analytic findings specifies crucial and independent neural anomalies underlying the enhanced processing of negative information in depression—specifically, high baseline pulvinar activation and low striatal dopamine levels. Thus, this model suggests that novel neural-level interventions, including neuroregulatory therapies for down-modulating pulvinar activity and pharmacotherapies for bolstering striatal dopamine availability, may be effective in the treatment of major depressive disorder.

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