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Frontocingulate Dysfunction in Depression: Toward Biomarkers of Treatment Response

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Increased rostral anterior cingulate cortex (rACC) activity has emerged as a promising predictor of treatment response in depression, but neither the reliability of this relationship nor the mechanisms supporting it have been thoroughly investigated. This review takes a three-pronged approach to these issues. First, I present a meta-analysis demonstrating that the relationship between resting rACC activity and treatment response is robust. Second, I propose that the rACC plays a key role in treatment outcome because of its 'hub' position in the default network. Specifically, I hypothesize that elevated resting rACC activity confers better treatment outcomes by fostering adaptive self-referential processing and by helping to recalibrate relationships between the default network and a 'task-positive network' that comprises dorsolateral prefrontal and dorsal cingulate regions implicated in cognitive control. Third, I support this hypothesis by reviewing neuropsychological, electrophysiological, and neuroimaging data on frontocingulate dysfunction in depression. The review ends with a discussion of the limitations of current work and future directions.

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INTRODUCTION

Major depressive disorder (MDD) is common, recurrent, and disabling. According to the World Health Organization, MDD is the third leading cause of global disease burden and a leading cause of disability worldwide (World Health Organization, 2008). In the United States, 16.6% of individuals will meet criteria for MDD at least once in their life (Kessler *et al*, 2005). In addition to profound personal suffering, MDD is associated with significant impairments in social and occupational functioning (Lopez *et al*, 2006) and places a staggering economic burden on society. For example, in the United States alone, workplace-related costs linked to depression have been estimated to exceed 50 billion dollars each year (Greenberg *et al*, 2003).

Despite the availability of a variety of treatments, up to 40–50% of patients fail to respond to antidepressant medication (eg, Trivedi *et al*, 2006) or psychological treatment (eg, cognitive behavioral therapy; DeRubeis *et al*, 2005). The likelihood of remission (ie, complete recovery) is even lower. For example, only one in three patients achieved remission in the nationally representative Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Trivedi *et al*, 2006). For those achieving remission, up to 40% will relapse within 2 years (Boland and Keller, 2009). Unfortunately, attempts to identify clinical, sociodemographic, or biological variables predicting treatment response have met with very limited success (eg, Bagby *et al*, 2002; Nierenberg, 2003). Clearly, a better understanding of treatment mechanisms and identification of reliable predictors of treatment response would constitute major progress in the battle against depression.

In 1997, Mayberg and colleagues reported that increased resting glucose metabolism in the rostral anterior cingulate cortex (rACC; Brodmann area 24a/b) before the onset of pharmacological treatment predicted better treatment response in MDD (Mayberg *et al*, 1997), extending earlier reports of a link between increased resting rACC perfusion/metabolism and antidepressant response to sleep deprivation (Ebert *et al*, 1991; Wu *et al*, 1992). Despite these promising findings, no systematic analysis has been performed to quantify the strength and reliability of the relationship between pre-treatment rACC activity and

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antidepressant response. Furthermore, in spite of numerous replications, the reason for the existence of this particular relationship remains poorly understood, and few attempts have been made to integrate this finding with the larger experimental and neuroimaging literature on depression.

The current review is organized around three goals designed to address these limitations. The first goal is to perform a meta-analysis to evaluate the strength of the link between resting rACC activity and treatment response (for rACC anatomical details, as well as differentiation between the rACC and other ACC subdivisions implicated in MDD, see Box 1). The second goal is to advance hypotheses concerning psychological and neurobiological mechanisms that might explain this link. In this context, I summarize emerging evidence indicating that the rACC represents one of the main 'hubs' within the default network (DN), an intrinsically organized functional network that has been associated with a variety of self-referential processes, including introspective processing, remembering the past, and planning the future (Buckner *et al*, 2008; Raichle *et al*, 2001). I argue that elevated resting rACC activity might foster better treatment outcome through (1) adaptive forms of reflective, self-focused processing and (2) adaptive interactions between the default network and a second network, the task-positive network, which includes dorsolateral prefrontal cortex (DLPFC) and dorsal ACC (dACC; eg, caudal area 24′ and 32′) regions that become activated during tasks requiring cognitive and attentional control. In light of this network-based conceptualization of depression, the third goal is to review neuropsychological, functional, and structural neuroimaging work that has probed frontocingulate pathways in depression. Based on these data, I suggest that frontocingulate dysfunction contributes to key cognitive and affective abnormalities in depression, including maladaptive ruminative tendencies, difficulty in disengaging from and inhibiting negative information, and emotion dysregulation. The review ends with a discussion of the limitations of current work and identification of future directions.

META-ANALYSIS OF ROSTRAL ACC ACTIVITY AS A PREDICTOR OF ANTIDEPRESSANT TREATMENT RESPONSE

Study Sources

Computerized searches using the databases PubMED, Cochrane Library, and PsycINFO were performed to identify neuroimaging studies that investigated predictors of treatment response. Several antidepressant treatments were considered, including pharmacology, electroconvulsive therapy (ECT), rapid transcranial magnetic stimulation (rTMS), sleep deprivation, and psychotherapy (eg, cognitive behavior therapy). Similarly, multiple imaging modalities were considered, including electroencephalogram/magnetoencephalogram (EEG/MEG), functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT). Keyword combinations used in the search included 'fMRI OR PET OR SPECT OR EEG OR MEG AND depression AND antidepressant' and 'neuroimaging AND depression.' Abstracts of all articles were reviewed with respect to inclusion criteria (see below). Reference lists of relevant articles were checked to identify additional studies that might be relevant.

Study Selection

In all, 70 empirical studies were identified as candidates for the meta-analysis. Studies were included if they: (1) included individuals with unipolar depression (but not other mood disorders); (2) measured brain activity *before* the onset of antidepressant treatment; (3) included a standardized treatment; (4) directly compared eventual responders and nonresponders in their *pre-treatment* activity *or* evaluated correlations between *pre-treatment* activity and pre-to-post changes in depression severity; (5) used voxel-based or regions-of-interest analyses that allowed identification of ACC regions; (6) reported sufficient data to compute an effect size (means, standard deviations, *p*-values, F-values, or *r* values); and (7) were published in English, German, or Italian. Medication status at the pre-treatment neuroimaging assessment was not constrained.

Based on these criteria, 3 studies were excluded because they included individuals with bipolar disorder (Benedetti *et al*, 2007; Ketter *et al*, 1999; Speer *et al*, 2009); 4 studies were excluded because the first neuroimaging assessment occurred after treatment onset (Brockmann *et al*, 2009; Conway *et al*, 2006; Joe *et al*, 2006; Keedwell *et al*, 2009); 1 study was excluded because no standardized treatment was provided (Halloran *et al*, 1999); 26 studies were excluded because no direct *pre-treatment* comparison between eventual responders and nonresponders *or* correlation between *pre-treatment* activity and pre-to-post changes in depression severity was performed (Aihara *et al*, 2007; Awata *et al*, 1998, 2002; Bench *et al*, 1995; Brody *et al*, 2001; Brunovsky *et al*, 2006; Buchsbaum *et al*, 1997; Davies *et al*, 2003; Goodwin *et al*, 1993; Henry *et al*, 2001; Holthoff *et al*, 2004; Hornig *et al*, 1997; Ishizaki *et al*, 2008; Kennedy *et al*, 2001, 2007; Kito *et al*, 2008a; Kohn *et al*, 2007; Mayberg *et al*, 2000, 2002; Nobler *et al*, 2001; Robertson *et al*, 2007; Scott *et al*, 1994; Segawa *et al*, 2006; Smith *et al*, 1999, 2009; Vlassenko *et al*, 2004); 1 study was excluded because no region-of-interest or voxel-based analyses were performed to allow for a clear delineation of brain regions associated with treatment response (Navarro *et al*, 2004); 6 studies were excluded because no information was reported to permit computation of effect sizes pertaining to ACC regions (Costafreda *et al*, 2009b; Little *et al*, 2005; Marquand *et al*, 2008; Milak *et al*, 2009; Siegle *et al*, 2006; Teneback *et al*, 1999); 5 studies were excluded because they presented a partial or full reanalysis of a prior study (Clark *et al*, 2006; Keedwell *et al*,

Box 1 Anterior cingulate cortex anatomy and relevance to depression

Depression has been associated with dysfunction in various ACC regions. In addition to the link between increased rACC and better treatment response, hyperactivity in subgenual ACC regions (Mayberg, 2003) but hypoactivity in dorsal ACC (dACC) regions (Davidson *et al*, 2002) have been generally described in MDD. Anatomically, the rACC (often referred to in the literature as 'pregenual' or 'perigenual') is located anterior to the genu, and includes Brodmann area (BA) 32 and inferior parts of BA24 (eg, Vogt *et al*, 1995; see Figure 1). The subgenual ACC is located underneath the genu of the corpus callosum and corresponds mainly to BA25 and caudal portions of BA32 and BA24. Finally, the dACC includes caudal area 24′ and 32′, and cingulate motor area.

The complex pattern of findings in MDD likely reflects the fact that in terms of function, cytology, and receptor architecture, the ACC is highly heterogeneous (eg, Devinsky *et al*, 1995; Palomero-Gallagher *et al*, 2008; Vogt *et al*, 2005). In general, an 'affect subdivision' encompassing rACC and subgenual areas and a dorsal 'cognitive subdivision' of the ACC (dACC) have been distinguished (Devinsky *et al*, 1995). By virtue of strong connections with limbic and paralimbic structures (amygdala, nucleus accumbens, orbitofrontal cortex, periaqueductal grey, and autonomic brainstem motor nuclei), the affective subdivision has been found to play key roles in regulating visceral and autonomic responses to stressful events, assigning emotional valence to internal and external stimuli, and emotional expression. The cognitive subdivision, on the other hand, shows strong connections with DLPFC regions, supplementary motor areas, parietal cortex, and spinal cord and has been implicated in response selection and processing of cognitively demanding information (Figure 1).

Recent studies have further highlighted that the rACC and subgenual ACC (BA25) differ in terms of anatomical connectivity, cytology, and neurotransmitter receptor organization (Johansen-Berg *et al*, 2008; Palomero-Gallagher *et al*, 2008). Although a full discussion of these data is beyond the scope of this review, it is important to emphasize that the rACC has stronger connection with the medial prefrontal and dACC regions, whereas the subgenual ACC shows stronger connections with the OFC, nucleus accumbens, amygdala, hippocampus, and hypothalamus (Johansen-Berg *et al*, 2008; Chiba *et al*, 2001). In virtue of these anatomical connections, it has been suggested that normalization of subgenual ACC (BA 25) hyperactivity—which might be linked in MDD to dysregulation in sleep, appetite, libido, and endocrine function and regulation of negative affect—is a prerequisite for symptom remission (Mayberg, 2003). In this review, it is argued that elevated resting rACC activity increases the likelihood of treatment response by fostering adaptive self-referential processing and by helping to recalibrate relationships between the default network and a 'task-positive network' that comprises DLPFC and dACC regions that implement cognitive control.

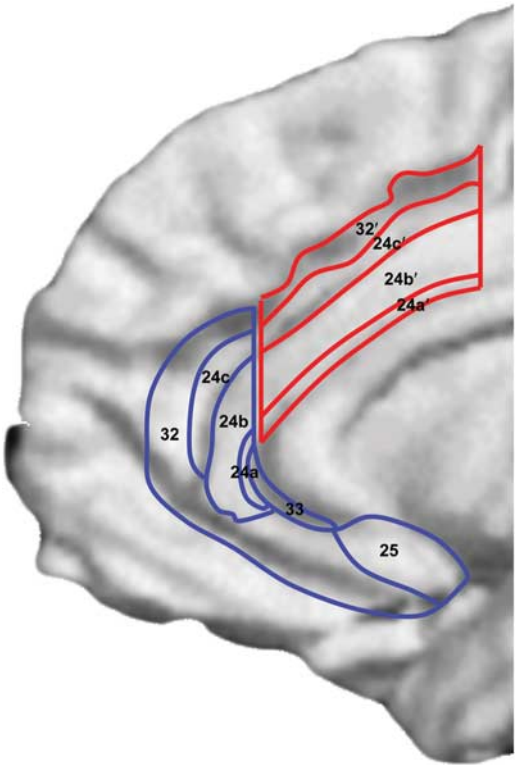

Figure 1. Schematic representation of ACC cytoarchitectural areas displayed on an inflated, medial cortical surface. Affective and cognitive ACC subdivisions are highlighted in blue and red, respectively (Reprinted from Bush *et al*, 2000; with permission from Elsevier).

2010; Mulert *et al*, 2007b; Seminowicz *et al*, 2004; Smith *et al*, 2002); and finally, 1 study was excluded because of a small sample size that precluded statistical analyses ($n = 3$; Clark *et al*, 2001).

The remaining 23 studies were entered in the meta-analysis (Table 1). For each study, only one statistical test contributed to the analyses. In order to standardize the effect sizes across studies, Cohen's *d* was calculated. For most of the studies, the mean pre-treatment rACC signal for eventual nonresponders was subtracted from the mean pre-treatment rACC signal for eventual responders, and the difference was divided by the pooled standard deviation. In cases where means and standard deviations were unavailable, d-values were calculated from exact *r*-, *p*-, *t*-, or F-values using standard formulae (Wolf, 1986). In eight cases, a *d*-value was computed from the correlation between

TABLE 1. Summary of Neuroimaging Studies Investigating rACC Activity as a Predictor of Treatment Response in MDD Subjects

Treatment	Study	Imaging	Task	Numbers of subjects	Increased pre-treatment rACC in responders	Effect size (Cohen's d)
Pharmacology						
Various AD	*Mayberg *et al*, 1997	PET	Resting	8 Resp. *vs* 10 Non-Resp.	X[a]	1.43
Paroxetine	*Brody *et al*,1999	PET	Resting	9 Resp. *vs* 7 Non-Resp.	Reversed finding	−1.20
Nortriptyline	*Pizzagalli *et al*, 2001	EEG	Resting	9 Resp. *vs* 9 Non-Resp.	X	1.43
Paroxetine	*Saxena *et al*, 2003	PET	Resting	44 MDD subjects	X[b]	0.80
Venlafaxine	*Davidson *et al*, 2003	fMRI	Picture processing	12 MDD subjects	X[b]	1.04
Bupropion or Venlafaxine	Little *et al*, 2005	PET	Attentional task	13 Resp. *vs* 27 Non-Resp	Null finding[c]	Not available
Citalopram or Reboxetine	*Mulert *et al*, 2007a	EEG	Resting	10 Resp. *vs* 10 Non-Resp.	X	1.33
Fluoxetine	*Chen *et al*, 2007	fMRI	Face perception	16 MDD subjects	X[b]	2.34
Escitalopram	*Langenecker *et al*, 2007	fMRI	Go/NoGo	15 MDD subjects	X[b]	1.23
Venlafaxine (or CBT)	*Konarski *et al*, 2009	PET	Resting	16 Resp. *vs* 8 Non-Resp.	Reversed finding	−1.49
Paroxetine	Milak *et al*, 2009	PET	Resting	11 Resp. *vs* 22 Non-Resp	Null finding[c]	Not available
Fluoxetine or Venlafaxine	*Korb *et al*, 2009	EEG	Resting	22 Resp. *vs* 15 Non-Resp.	X	0.70
Ketamine	*Salvadore *et al*, 2009	MEG	Face perception	11 MDD subjects	X[b]	2.27
Sleep deprivation						
Total SD	*Ebert *et al*, 1991	SPECT	Resting	5 Resp. *vs* 3 Non-Resp.	X	2.46
Total SD	*Wu *et al*, 1992	PET	Attentional task	4 Resp. *vs* 11 Non-Resp.	X[d]	1.35
Total SD	*Ebert *et al*, 1994	SPECT	Resting	11 Resp. *vs* 9 Non-Resp.	X	1.92
Partial SD	*Volk *et al*, 1997	SPECT	Resting	9 Resp. *vs* 6 Non-Resp.	X[e]	0.61
Total SD	*Wu *et al*, 1999	PET	Resting	12 Resp. *vs* 24 Non-Resp.	X	0.87
Total SD	*Holthoff *et al*, 1999	SPECT	Resting	8 Resp. *vs* 6 Non-Resp.	X	3.80
Partial SD	*Clark *et al*, 2006	fMRI	Resting	5 Resp. *vs* 12 Non-Resp.	X	1.14
ECT						
	*McCormick *et al*, 2007	PET	Resting	5 Resp. *vs* 5 Non-Resp.	Reversed finding	−1.77
rTMS						
	Teneback *et al*, 1999	SPECT	Resting	6 Resp. *vs* 6 Non-Resp.	Null finding[c]	Not available
	*Mottaghy *et al*, 2002	SPECT	Resting	17 MDD subjects	Reversed finding[b]	−1.37
	*Nadeau *et al*, 2002	SPECT	Attentional task	8 MDD subjects	X[b]	1.46
	*Langguth *et al*, 2007	SPECT	Resting	24 MDD subjects	X[b]	1.01
	*Kito *et al*, 2008b	SPECT	Resting	6 Resp. *vs* 8 Non-Resp.	X	1.96
CBT						
	Siegle *et al*, 2006	fMRI	Self-referential task	14 MDD subjects	Null finding[c]	Not available

Abbreviation: Resp., responders; Non-Resp., non-responders.

[a]Hypothesized pattern was observed.
[b]Refers to a correlation between pre-treatment rACC activity and changes in depression severity.
[c]Not included in the meta-analysis (no information was provided allowing the computation of effect sizes pertaining to ACC regions).
[d]Effect size for an aggregate 'limbic system' (ACC, amygdala, and hippocampus).
[e]Effect size for an aggregate region (OFC and 'basal ACC').
*Included in the meta-analysis.

pre-treatment rACC signal and pre-to-post changes in depression severity (Chen *et al*, 2007; Davidson *et al*, 2003; Langenecker *et al*, 2007; Langguth *et al*, 2007; Mottaghy *et al*, 2002; Nadeau *et al*, 2002; Salvadore *et al*, 2009; Saxena *et al*, 2003). Next, a combined (weighted) effect size across all studies was computed using a random-effects model implemented in the statistical package Comprehensive Meta-analysis V2 (Borenstein and Rothstein, 1999); this yielded a *Z*-value that was tested against the null hypothesis of $d = 0.00$. Based on prior recommendations (Cohen, 1988), d values < 0.2, between 0.4 and 0.6, and > 0.8 were regarded as representing small, moderate, and large effects, respectively.

A homogeneity test (Cochran's Q test) evaluated whether the studies shared a common population effect size. Finally, to explore the possibility of publication bias (ie, bias toward non-publication of studies with no effects), Orwin's Fail-Safe Number of studies test was performed (Orwin, 1983; Rosenthal, 1991). The Fail-Safe Number reflects the number of unpublished studies required to reduce the observed effect size to a negligible level, and is computed as:

$$\text{Fail-Safe Number} = \text{k} * [(\text{ES}_k/\text{Es}_c) - 1]$$

where k is the number of studies ($n = 23$), ES_k is the mean weighted effect size, and Es_c is the criterion effect size (Lipsey and Wilson, 2001; Orwin, 1983). In two separate analyses, Es_c was set to 0.10 and 0.20.

Results

The 23 studies included in the meta-analysis yielded a total sample of 426 MDD subjects (Table 1). A random-effects analysis comparing pre-treatment mean rACC activity between eventual responders ($n = 136$) and nonresponders ($n = 143$) (15 studies) or considering the correlation between *pre-treatment* rACC signal and pre-to-post changes in depression severity (8 studies; $n = 147$) indicated that the mean weighted effect size was 0.918 (95% confidence interval 0.442–1.393; $Z = 3.782$, $p < 0.00017$), reflecting a large effect. [In light of recent controversy concerning possible overestimates of brain–behavior relationships in correlational analyses of neuroimaging data (Vul *et al*, 2009; but see Lieberman *et al*, 2009; Nichols and Poline, 2009; Poldrack and Mumford, 2009), effect sizes emerging from the 8 studies reporting correlations between pre-treatment rACC signal and pre-to-post changes in depression severity were compared with those emerging from the remaining 15 non-correlational studies. The mean effect sizes were similar (1.098 ± 1.115 *vs* 0.969 ± 1.496) and statistically indistinguishable ($t(21) = 0.211$, $p = 0.84$). Based on this finding, and the fact that some of the studies implemented statistically independent analyses (eg, the rACC was anatomically defined; Langguth *et al*, 2007; Nadeau *et al*, 2002) or did not use whole-brain corrrelational analyses to identify supra-threshold clusters (eg, Davidson *et al*, 2003; Salvadore *et al*, 2009), the mean weighted effect size emerging from the current meta-analysis was interpreted as representing a reliable estimate of the link between rACC activity and treatment response.] Of the 23 studies, 19 found an association between increased pre-treatment rACC activity and eventual treatment response, whereas 4 found an association between *low* pre-treatment rACC activity and better response. Orwin's Fail-Safe Number test indicated that 160 unpublished studies with null effects would be required to reduce the observed effect size to a negligible level ($d = 0.10$; 69 null results would be required to reduce the effect size to $d = 0.20$). Cochran's Q test was also significant ($Q = 92.93$, $df = 22$, $p < 0.001$), indicating heterogeneity of study effect sizes. Thus, separate meta-analyses were computed for each treatment modality (pharmacology, ECT, rTMS, sleep deprivation), imaging modality (EEG/MEG, fMRI, PET, SPECT), and medication status at pre-treatment assessment (medicated, unmedicated). As summarized in Table 2, all effects were significant and in the moderate–large range with the exception of a highly significant negative effect size for ECT, which was because of a single negative finding (McCormick *et al*, 2007). Thus, the finding of higher pre-treatment rACC activity predicting better treatment response generalizes to different treatments (with the exception of ECT), assessment methods, and medication status. In the following, a brief summary of these findings is provided.

Sleep Deprivation (SD). Ebert *et al* (1991) were the first to report that eventual responders to SD had increased pre-treatment rACC perfusion, which normalized after successful treatment (see also Ebert *et al*, 1994). Increased pre-treatment rACC activity in eventual responders to SD has been replicated with SPECT (Holthoff *et al*, 1999; Volk *et al*, 1997) and PET (Wu *et al*, 1992, 1999). Similarly, normalization of rACC activity after SD has been confirmed in four additional studies (Smith *et al*, 1999; Volk *et al*, 1997; Wu *et al*, 1992, 1999). In Volk *et al* (1997), pre-treatment cingulate perfusion was correlated with post-SD decreases in depression severity ($r = 0.77$). More recently, using arterial spin labeling, Clark *et al* (2006) found that MDD

TABLE 2. Meta-Analyses of Links Between Increased Pre-Treatment rACC Activity and Treatment Response for (a) All Studies, and for Studies Split Based on (b) Treatment Modality, (c) Imaging Modality, and (d) Pre-Treatment Medication Status

Analysis	Mean weighted effect size	95% CI	Number of studies	Z value	P value
(a) Overall[a]	0.918	0.442 to 1.393	23	3.782	0.000016
(b) By treatment[b]					
ECT	−1.773	−3.173 to −0.374	1	−2.484	0.013
Pharmacology	0.674	0.391 to 0.958	11	4.659	<0.00001
rTMS	0.718	0.078 to 1.358	4	2.199	0.028
Sleep deprivation	1.319	0.901 to 1.737	7	6.182	<0.00001
(c) By imaging modality[b]					
EEG/MEG	1.085	0.609 to 1.560	4	4.470	<0.00001
fMRI	1.350	0.658 to 2.041	4	3.827	0.00013
PET	0.339	0.019 to 0.658	7	2.079	0.038
SPECT	1.219	0.762 to 1.677	8	5.224	<0.00001
(d) By medication status[b]					
Medicated	1.218	0.816 to 1.619	8	5.946	<0.00001
Unmedicated	0.619	0.360 to 0.878	15	4.679	<0.00001

Abbreviation: CI, confidence interval.
[a]Random-effects model.
[b]Fixed-effects model.

subjects responding to partial SD had increased pre-treatment perfusion in the ventral ACC and left rACC relative to nonresponders. In responders only, perfusion normalized (ie, decreased) after SD.

Pharmacology. In an influential paper, Mayberg *et al* (1997) observed that eight MDD patients who responded to various pharmacological treatments after 6 weeks showed higher pre-treatment resting rACC metabolism than both non-responders ($n = 10$) and controls ($n = 13$) (Figure 1a). Relative to controls, nonresponders showed lower pre-treatment rACC metabolism, indicating that blunted rACC activity predicted poor response. In a subsequent study from this group, MDD subjects demonstrated higher metabolic rates in the right rACC than controls (Cohen's $d = 0.78$; Kennedy *et al*, 2001). As all MDD subjects showed at least a 50% reduction in Hamilton Rating Scale for Depression (HRSD) score after 6 weeks of paroxetine treatment, these data also highlight a link between rACC hyperactivity and response.

Measuring resting EEG data before an open-label trial with nortriptyline, we replicated these findings using a source localization technique (Pizzagalli *et al*, 2001; Figure 1b). Specifically, resting rACC activity in the theta frequency band (6.5–8 Hz) predicted degree of treatment response to nortriptyline 4–6 months later. It is noteworthy that this link emerged exclusively for the theta band, as there is evidence implicating the ACC in theta oscillations (Asada *et al*, 1999; Feenstra and Holsheimer, 1979; Pizzagalli *et al*, 2003). A recent re-analysis of these data revealed that a specific cutoff of pre-treatment rACC activity correctly classified 88.9% of eventual responders and 89.9% of eventual nonresponders, highlighting a promising sensitivity/specificity profile (DA Pizzagalli, unpublished observation). As in Holthoff *et al* (1999) and Mayberg *et al* (1997), the rACC was the only region differentiating eventual responders and nonresponders.

These findings were replicated in two additional studies that used the same EEG source localization technique. Taking a region-of-interest approach, Mulert *et al* (2007a) reported that in comparison to nonresponders, MDD subjects responding to either citalopram or reboxetine treatment had increased pre-treatment resting theta activity within the rACC. The effect size differentiating responders and nonresponders ($d = 1.33$) was similar to that in our

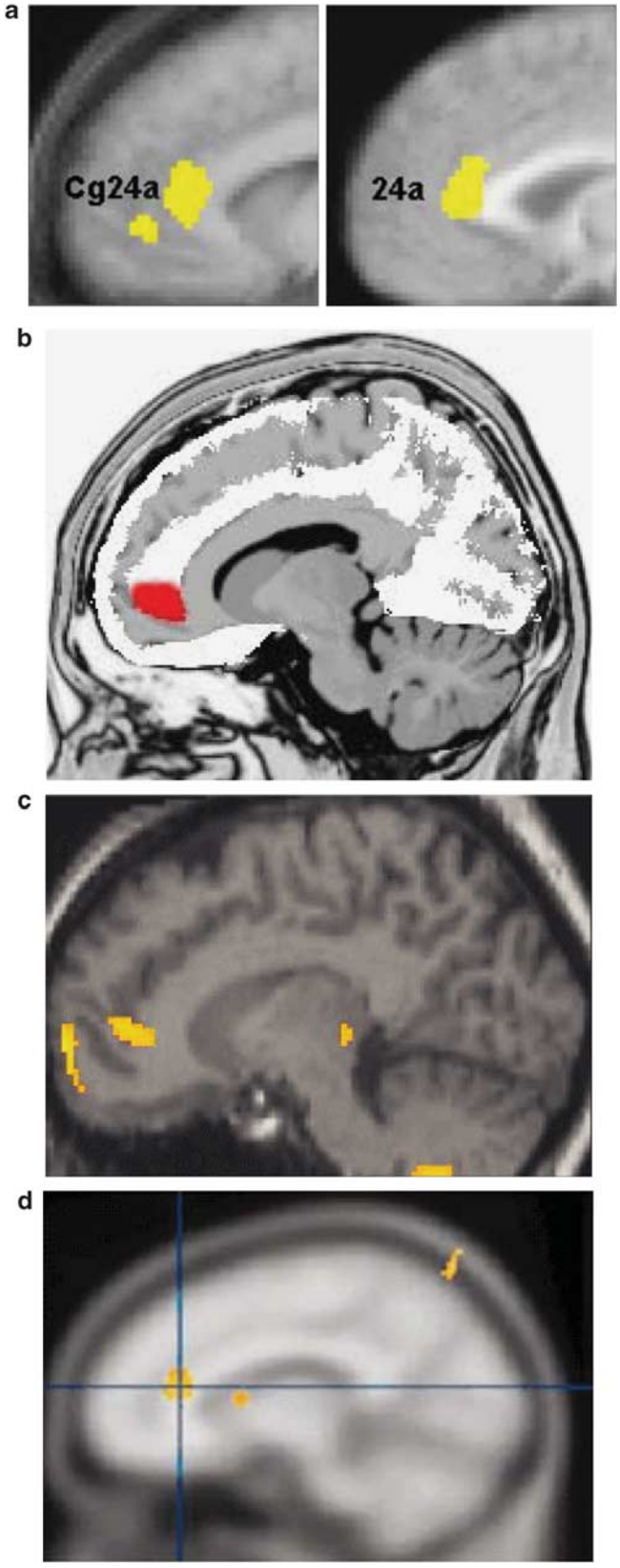

Figure 1. Selected findings implicating the rACC in treatment response in MDD. (a) Mayberg *et al* (1997): Increased pre-treatment rACC metabolism in responders relative to nonresponders (yellow). This finding was replicated in a larger sample of 25 responders *vs* 20 nonresponders (Brannan *et al*, 2000) (see right panel). (b) Pizzagalli *et al* (2001): Increased pre-treatment resting rACC theta activity in responders relative to nonresponders (red). (c) Holthoff *et al* (2004): Decreased rACC rCBF with symptom remission (yellow). (d) Davidson *et al* (2003): Increased BOLD signal in the rACC in response to emotional pictures correlated with lower post-treatment depressive symptoms (yellow). (Modified with permission from Mayberg, 2003 (with permission by Oxford University Press), Pizzagalli *et al*, 2001 (with permission by American Psychiatric Associations), Holthoff *et al*, 2004 (with permission by John Wiley and Sons), and Davidson *et al*, 2003 (with permission by American Psychiatric Associations)).

earlier report ($d = 1.43$). Moreover, in a placebo-controlled, double-blind study, Korb *et al* (2009) reported that drug responders had significantly higher resting theta current density in the rACC relative to nonresponders prior to treatment. Notably, findings were specific to drug responders and not placebo responders, and emerged when considering both a selective serotonin reuptake inhibitor (SSRI; fluoxetine) and a serotonin–norepinephrine reuptake inhibitor (SNRI; venlafaxine). Altogether, these findings suggest that the link between resting rACC theta activity and treatment response generalizes across antidepressant classes but does not extend to placebo response.

In an open-label PET study, Saxena *et al* (2003) reported a positive link between pre-treatment rACC/medial PFC metabolism and response to 8–12 weeks of paroxetine in a sample of MDD individuals, some of whom had comorbid obsessive compulsive disorder. Another PET study reported decreased rACC blood flow from baseline to remission after open-label treatment with citalopram or mirtazapine (Holthoff *et al*, 2004; Figure 1c). Because the second scan occurred after remission, this decrease is consistent with rACC normalization (no analyses focusing on pre-treatment predictors were performed).

Finally, a link between increased pre-treatment rACC activity and response to antidepressants has emerged from three studies in which participants were engaged in either passive observation of emotionally valenced stimuli or a response inhibition task. Davidson *et al* (2003) found that greater rACC activation to negative *vs* neutral pictures correlated with fewer symptoms after 8 weeks of open-label venlafaxine treatment (Figure 1d). Similarly, Chen *et al* (2007) reported that a greater rACC response to increasing levels of sadness in facial stimuli predicted increasingly rapid responses to fluoxetine. Moreover, increased rACC activation to repeated presentation of fearful faces predicted a rapid (230-min post-administration) antidepressant response to ketamine, an *N*-methyl-D-aspartate receptor antagonist (Salvadore *et al*, 2009). Finally, increased rACC activation in response to commission errors in a GO/NOGO task predicted greater treatment response after a 10-week escitalopam trial ($r = 0.52$, S Langenecker, personal communication, 23 March 2010; Langenecker *et al*, 2007), although the region emerging from this study was anatomically superior and anterior to the pregenual rACC.

rTMS. Five studies have investigated the relationship between pre-treatment rACC activity and response to rTMS. In a small SPECT study ($n = 7$), Nadeau *et al* (2002) found that pre-treatment rACC blood flow was correlated with reduction in depression severity following 10 days of rTMS over the left DLPFC ($r = -0.59$, S Nadeau, personal communication, 28 March 2010). Similarly, increased pre-treatment rACC activity was found to predict reduction of depressive symptoms in MDD patients on stable medication receiving a 2-week add-on rTMS treatment ($r = -0.49$, B Langguth, personal communication, 23 March 2010; Langguth *et al*, 2007) or a 3-week low-frequency stimulation over the right DLPFC (Kito *et al*, 2008b). In contrast, Mottaghy *et al* (2002) found that *lower* pretreatment rCBF in the rACC was linked to greater rTMS response, whereas Teneback *et al* (1999) found no relationship between rACC and response to rTMS.

Additional findings. There is additional evidence supporting the proposed link between the rACC and antidepressant response. First, smaller rACC volume has been found to predict poor treatment response and more frequent hospitalization in depressed patients (Chen *et al*, 2007; Costafreda *et al*, 2009a; Frodl *et al*, 2008a; Gunning *et al*, 2009). Second, reduced magnetization transfer ratio—assumed to reflect reduced integrity of myelinated white matter—in the rACC has been associated with treatment-resistant depression (Zhang *et al*, 2009). Third, illness chronicity and refractoriness in late-life depression have been linked to decreased pre-treatment rACC activity, which persisted even after responding to ECT (Awata *et al*, 2002). In line with the hypothesis that sustained paralimbic hypoactivation during resting states predicts lack of antidepressant response, an earlier study from this group showed that subjects with refractory MDD had significantly lower PFC and ACC perfusion than nonrefractory subjects, who in turn displayed lower perfusion than healthy controls (Awata *et al*, 1998). Moreover, Kennedy *et al* (2007) reported that nonresponse to an 8-week treatment with venlafaxine or CBT was associated with decreased metabolism in the rACC. Together, these findings suggest that a hypoactive rACC during resting states is a reliable biomarker of treatment nonresponsiveness in MDD.

Although the link between rACC hyperactivity and treatment response has been observed in 19 studies, it is important to mention two sets of inconsistencies. First, no pre-treatment rACC differences between responders and nonresponders emerged in four studies, which administered paroxetine (alone or in combination with other antidepressants) (Milak *et al*, 2009), buproprion or venlafaxine (Little *et al*, 2005), rTMS (Teneback *et al*, 1999), and CBT (Siegle *et al*, 2006). Second, a link between *lower* pretreatment rACC rCBF and greater antidepressant response to rTMS in treatment-resistant MDD patients (Mottaghy *et al*, 2002) and individuals with psychotic depression (McCormick *et al*, 2007) has been described. Similarly, Brody *et al* (1999) reported that lower pre-treatment ventral ACC (including rACC) metabolism correlated with greater reductions on the HRSD after paroxetine treatment. Moreover, Siegle *et al* (2006) found that decreased pre-treatment subgenual PFC (BA 25) and increased amygdalar activation during processing of negative words were linked to better CBT response (see also Konarski *et al*, 2009). Because the subgenual PFC has been implicated in regulating limbic activity, Siegle *et al* (2006) proposed that CBT might be most beneficial for patients characterized by increased emotional reactivity and deficient emotional regulation. These findings contrast with data linking increased pre-treatment subgenual PFC resting blood flow to citalopram response (Brockmann *et al*, 2009).

Although these data appear inconsistent with the evidence emerging from the meta-analysis, it is important to emphasize that the subgenual and ventral ACC regions identified in these studies do not spatially overlap with the rACC, raising the possibility that different ACC subdivisions might be implicated in response depending on the treatment modality.

Summary. At least 19 studies have found that increased pre-treatment rACC activity predicts better antidepressant response. Among these studies, 13 probed rACC function during resting states, whereas the remaining 6 used relatively simple tasks (eg, passive observation of emotional pictures; but see Langenecker *et al*, 2007). The relationship between increased rACC activity and positive antidepressant response appears to be robust, as it emerged across treatments that included various drugs (eg, SSRIs, atypical antidepressants, ketamine), sleep deprivation, and rTMS, and has been replicated across imaging modalities (fMRI, PET, SPECT, EEG).

THE ROSTRAL ACC AS A KEY HUB WITHIN THE DN

The DN

The observed link between rACC resting activity and treatment response is interesting in light of evidence that the rACC is a hub in the DN. The DN comprises the vmPFC/rACC, posterior cingulate, retrosplenial cortex, lateral parietal cortex, lateral temporal cortex, dorsal medial PFC, and hippocampal formation (eg, Buckner *et al*, 2008; Raichle *et al*, 2001; Figure 2). Activity and functional connectivity within the DN increases during resting states or when participants engage in internally focused tasks (Gusnard *et al*, 2001; Simpson *et al*, 2001). Conversely, DN regions consistently deactivate during processing of external stimuli (Shulman *et al*, 1997). As discussed in more detail below, these data have generally been interpreted as suggesting that resting DN activity reflects a variety of adaptive self-referential functions (Broyd *et al*, 2009; Buckner *et al*, 2008; Raichle *et al*, 2001), which might explain the link between increased resting rACC activity and better treatment outcome.

Providing insight into the possible functional significance of the DN, reduced deactivation of DN regions, including the rACC, was reported in an early study in which participants attended to their affective responses to emotional pictures relative to physical aspects of the picture itself (Gusnard *et al*, 2001). Similar results have been obtained in more recent studies employing a variety of self-referential tasks (eg, evaluating negative personality traits with respect to oneself; Schmitz and Johnson, 2006; van Buuren *et al*, 2010; Yoshimura *et al*, 2009; see Northoff *et al*, 2006 for a review). Notably, the level of rACC deactivation was negatively correlated with the extent to which pictures were judged as personally relevant: the more self-relevant

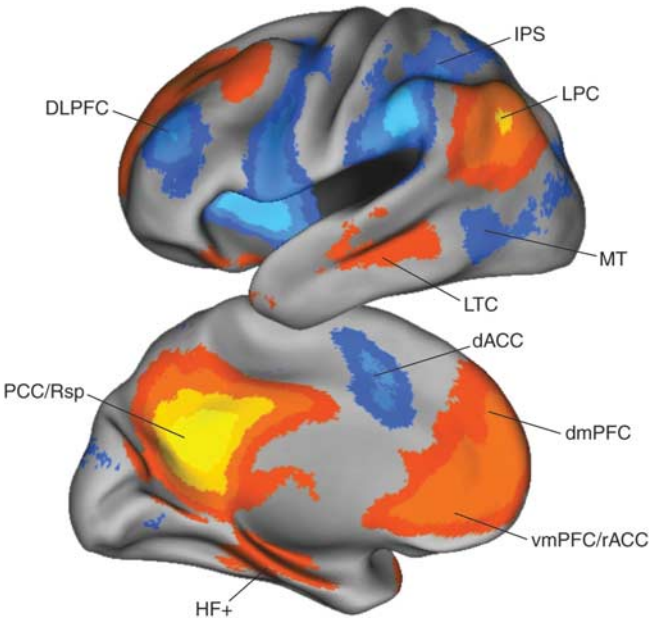

Figure 2. The default network (orange colors) includes regions that deactivate during processing of external stimuli, including the vmPFC/rACC, posterior cingulate (PCC), retrosplenial cortex (Rsp), lateral parietal cortex (LPC), lateral temporal cortex (LTC), dorsal medial PFC (dmPFC), and hippocampal formation (HF+), which includes the entorhinal cortex and surrounding cortex (eg, parahippocampal cortex). The task-positive network (blue color) includes, among others, the DLPFC, dACC, intraparietal sulcus (IPS), and middle temporal (MT) area and becomes activated during tasks requiring cognitive and attentional control. Blue colors: regions that negatively correlate with the default network; red: regions that positively correlate with the default network. (Modified with permission from Buckner *et al*, 2008; with permission by John Wiley and Sons).

the pictures (as measured by participant ratings), the weaker the rACC deactivation (Phan *et al*, 2004). These findings are complemented by a report of increased functional connectivity between the rACC/ventromedial PFC (vmPFC) and a variety of limbic/paralimibic regions, including the amygdala and insula, when healthy participants related negative and positive traits to themselves *vs* when they simply judged the valence of the stimuli (Schmitz and Johnson, 2006). These data suggest that increased resting rACC activity in treatment responders may be linked to adaptive forms of self-referential processing.

A critical point for the current review is that the DN appears to consist of two subsystems that converge on a midline core with two main hubs, the rACC and posterior cingulate cortex (Andrews-Hanna *et al*, 2010). The first subsystem, referred to as the medial temporal lobe system, includes the vmPFC, the retrosplenial cortex, and the hippocampus (among other regions). It is typically recruited when participants imagine themselves in the future. The second subsystem, referred to as the dorsomedial prefrontal cortex (dmPFC) subsystem, includes the dmPFC and lateral temporal cortex (among other regions), and it is most strongly activated when participants think about their

present mental states. These and other findings have led to the hypothesis that the DN is associated with a variety of self-referential functions, including introspection, remembering, and planning (Broyd *et al*, 2009; Buckner *et al*, 2008; Raichle *et al*, 2001). In this conceptualization, the DN allows 'event scenarios to be construed, replayed, and explored to enrich the remnants of past events in order to derive expectations about the future' (p. 31; Buckner *et al*, 2008).

How are these data relevant to the association between increased resting rACC activity and better treatment response? Given the link between introspection and increased activation of the DN, including the rACC, one might expect that increased resting rACC activity would be linked with rumination, a repetitive and passive focus on depressive symptoms, and their causes and consequences (Nolen-Hoeksema, 1991). This is important because increased rumination has been found to predict depression onset, higher levels of depressive symptoms, and poor outcome (eg, Kuehner and Weber, 1999; see Nolen-Hoeksema *et al*, 2008 for review). However, emerging evidence suggests that rumination also has adaptive components. For example, analysis of a widely used rumination scale—the Ruminative Responses Scale (RRS)—identified two different components: reflective pondering and brooding (Treynor *et al*, 2003). Reflective pondering included items such as, 'analyze recent events to try to understand why you are depressed,' and was conceptualized as capturing 'a purposeful turning inward to engage in cognitive problem solving to alleviate one's depressive symptoms' (p. 256). In contrast, brooding included items like, 'Think 'What am I doing to deserve this?'' and was conceived as 'a passive comparison of one's current situation with some unachieved standard' (p. 256). In line with this multidimensional conceptualization of rumination, elevated scores on the reflective and brooding subscales predicted *lower* and *higher* levels of depressive symptoms 1 year later, respectively (Treynor *et al*, 2003).

Along similar lines, additional research indicates that the self-focused nature of rumination is not necessarily associated with negative effects. Rather, it is the mode of processing adopted during self-focused attention that appears to distinguish the maladaptive rumination often observed in depression (eg, Crane *et al*, 2007; Sanders and Lam, 2010; Watkins and Teasdale, 2004). Specifically, a mindful, nonevaluative focus on thoughts, feelings, and physical sensations occurring in the moment can have beneficial cognitive effects (Crane *et al*, 2007; Watkins and Teasdale, 2004) and prevent relapse (eg, Ma and Teasdale, 2004) in depression. Conversely, an 'analytic self-focus,' in which participants think about the causes, meaning, and consequences of depressed mood (analogous to brooding) has been found to exacerbate depression (Nolen-Hoeksema *et al*, 2008; Watkins and Teasdale, 2004).

Based on these findings, I propose that increased resting rACC activity may be linked to adaptive aspects of rumination characterized by cognitive problem solving (Treynor *et al*, 2003), the development of alternative interpretations of negative thoughts and feelings (Watkins and Teasdale, 2004), adaptive preparation and anticipatory planning (Watkins, 2008), and/or a mindful, nonevaluative self-focus. As discussed in the next section, these kinds of adaptive interactions between affective and cognitive processes might also involve interplay between the DN and the task-positive network, which includes the DLPFC and dACC, as well as modulation of limbic regions, particularly the amygdala (Figure 3a). Critically, depression has been associated with dysregulated interactions among these networks (Figure 3b), as well as functional and structural abnormalities in the rACC, dACC, and DLPFC. I suggest that dysregulated interplay among these networks is linked to maladaptive forms of rumination and other important psychological facets of depression, including prolonged negative affect, increased elaboration of negative information, impaired ability to disengage from negative cues, and reduced cognitive control when challenged with negative information (see Gotlib and Joormann, 2010 for an excellent review of the clinical and experimental literature on biased emotional processing in depression).

Anticorrelated Functional Networks

Because activity in the DN typically decreases during performance of laboratory tasks, the DN is often referred to as a *task-negative network* (Broyd *et al*, 2009; Fox *et al*, 2005). The DN contrasts with a *task-positive network* (TPN), which includes the DLPFC, dACC, the intraparietal sulcus, and middle temporal area, among other regions (Figure 2). As its name implies, the TPN becomes activated during tasks requiring cognitive and attentional resources (Corbetta and Shulman, 2002; Sounuga-Barke and Castellanos, 2007). Critically, these two networks are temporally anticorrelated during both resting and activated states (Drevets and Raichle, 1998; Fox *et al*, 2005; Kelly *et al*, 2008; Mannell *et al*, 2010; Margulies *et al*, 2007; but see Van Dijk *et al*, 2010 for important methodological caveats regarding the interpretation of anticorrelations in functional neuroimaging data). For example, studies of resting state functional connectivity report negative correlations between the rACC and dACC, along with positive correlations between the DLPFC and dACC, the two regions implicated in cognitive control (Fox *et al*, 2005; Margulies *et al*, 2007).

Supplementing these resting data, increases in cognitive load and task difficulty have been associated with increased activation of the TPN and greater deactivation of the DN (eg, McKiernan *et al*, 2003; Pallesen *et al*, 2009; Tomasi *et al*, 2006), including the rACC (Pallesen *et al*, 2009; Persson *et al*, 2007; Polli *et al*, 2005). In controls, reduced suppression of the DN during demanding tasks has been linked to attentional lapses (Weissman *et al*, 2006) and errors in performance (Li *et al*, 2007a). Collectively, these findings suggest that in cognitively demanding situations, introspective processing is replaced by a state of alertness and attention to environmental cues (Broyd *et al*, 2009; Buckner *et al*, 2008). Thus, adaptive regulation of cognition

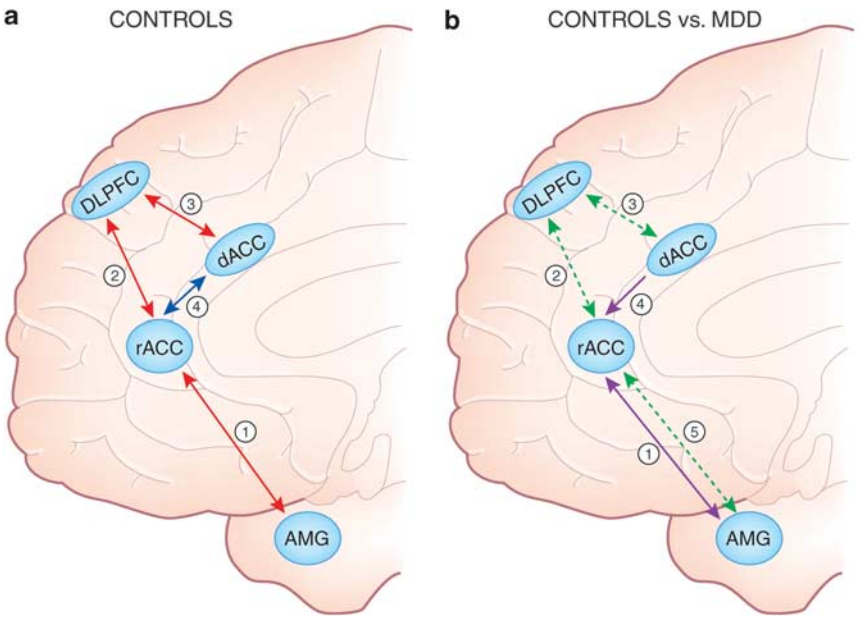

Figure 3. (a) Schematic representation of frontocingulate and frontolimbic interactions associated with adaptive forms of reflective, self-focused processing, as well as adaptive regulation of cognition and emotions. In controls, increased resting rACC activity as well as functional coupling (positive correlations) between the rACC and amygdala (see arrow 1) are observed during resting states (Margulies *et al*, 2007) and self-referential processing (Schmitz and Johnson, 2006). When confronted with cognitive or affective challenges, healthy controls show increased coupling (positive correlations) between the (1) rACC and DLPFC (arrow 2; Holmes and Pizzagalli, 2008b; Etkin *et al*, 2006) and (2) DLPFC and dACC (arrow 3; Aizenstein *et al*, 2009; Fox *et al*, 2005; Margulies *et al*, 2007; Schmitz and Johnson, 2006). The interplay among these regions is hypothesized to reduce task-induced rACC activation (arrow 4; Drevets and Raichle, 1998; Fox *et al*, 2005; Margulies *et al*, 2007) and downregulate amygdala activation, fostering adaptive regulation of cognition and emotions. (b) Relative to controls, MDD subjects show stronger functional coupling (positive correlations) between the rACC and the amygdala during negative self-referential processing (arrow 1; Yoshimura *et al*, 2010) as well as reduced structural connectivity between these two regions (arrow 5; Cullen *et al*, 2010). In addition, relative to controls, MDD subjects show reduced functional connectivity between the (1) rACC and DLPFC (arrow 2; Holmes and Pizzagalli, 2008b; Siegle *et al*, 2007) and (2) DLPFC and dACC (arrow 3; Aizenstein *et al*, 2009; Schlösser *et al*, 2008), but abnormally elevated functional connectivity between the dACC and rACC (arrow 4; Schlösser *et al*, 2008) during cognitive and/or affective challenges. The dysregulated interplay among these regions is hypothesized to lead to failures to deactivate the rACC and amygdala during affective and cognitive challenges, fostering the emergence of maladaptive forms of rumination, and ultimately treatment nonresponse. Numbers do not reflect chronological unfolding of interactions among brain regions.

appears to include suppression of resting rACC activity during demanding tasks. [Note: It should be noted that four studies have reported a link between *increased* task-related rACC activity and favorable antidepressant response. With one exception (Langenecker *et al*, 2007), these studies involved passive observation of emotionally valenced stimuli (Chen *et al*, 2007; Davidson *et al*, 2003; Salvadore *et al*, 2009), and thus minimal cognitive challenge. The observation of rACC activity in these studies is consistent with data in healthy controls showing that simple tasks requiring minimal cognitive demands are associated with relatively preserved DN activity (Grecius *et al*, 2003; Wilson *et al*, 2008)].

In MDD, functional and structural abnormalities within frontocingulate pathways (see the section 'Frontocingulate dysfunction in major depression: the empirical evidence and clinical correlates') might disrupt coupling between the DN and TPN, which could contribute to maladaptive forms of self-focused processing and rumination. Specifically, I speculate that the inability to reduce activity in the DN, and/or dominance of the DN over the TPN, coupled with impairments in modulating amygdalar activity, is linked to excessive negative self-introspection and maladaptive (eg, brooding) rumination (Sheline *et al*, 2009; Yoshimura *et al*, 2009). This disrupted coupling might also affect the recruitment of cognitive control in situations requiring inhibition of negative information or adaptive adjustments following errors, which is relevant to the widely reported finding of impaired post-error performance in MDD (see the section 'Frontocingulate dysfunction in major depression: the empirical evidence and clinical correlates').

Converging evidence for this hypothesis comes from the fact that various disease states associated with blunted resting rACC activity, including schizophrenia (Fletcher *et al*, 1998), dementia (Lustig *et al*, 2003), and autism (Kennedy *et al*, 2006), are characterized by reduced task-induced rACC deactivation, although the possibility that this reflects a floor effect needs to be evaluated. Initial evidence suggests that this link extends to depression (Grimm *et al*, 2009). Complementary evidence includes the fact that conditions characterized by diminished cognitive control, including sleep deprivation (eg, Chee and Choo, 2004) and aging (Persson *et al*, 2007), are associated with reduced DN deactivation. Thus, I propose that decreased *resting* rACC activity—hypothesized to reflect reduced ability to engage in adaptive self-focused processing—and

reduced *task-induced* rACC deactivation—hypothesized to reflect an inability to deactivate the DN, recruit the TPN, and/or provide top-down regulation of limbic regions during cognitively challenging or affectively evocative situations—represent important components of frontocingulate dysfunction linked to maladaptive emotional and self-focused processing, cognitive control impairments, and poor treatment outcome (Figure 3). The evidence pointing to abnormalities within frontocingulate pathways in depression is reviewed next.

FRONTOCINGULATE DYSFUNCTION IN MAJOR DEPRESSION: THE EMPIRICAL EVIDENCE AND CLINICAL CORRELATES

Neuropsychological Studies

A large literature points to wide-ranging neuropsychological deficits in MDD (for reviews, see Austin *et al*, 2001; Castaneda *et al*, 2008; Hammar and Ardal, 2009). Impaired executive functions—which rely on frontal lobe structures and are pivotal for directing attention, inhibiting behavior, generating strategies, planning, monitoring ongoing performance, and coding representations in working memory (Baddeley, 1998; Leh *et al*, 2010; Smith and Jonides, 1999)—have emerged as one of the core cognitive deficits in depression (eg, Austin *et al*, 2001). Executive dysfunction: (1) is evident in the acute depressed phase (eg, Channon and Green, 1999; Pizzagalli *et al*, 2006; Porter *et al*, 2003); (2) is exacerbated in more severely depressed subjects (eg, Paelecke-Habermann *et al*, 2005); (3) persists after remission (eg, Hammar *et al*, 2009; Paelecke-Habermann *et al*, 2005; Paradiso *et al*, 1997; Smith *et al*, 2006; Trichard *et al*, 1995; Weiland-Fiedler *et al*, 2004; but see Biringer *et al*, 2007); (4) predicts poor response to pharmacological treatment (eg, Alexopoulos *et al*, 2005; Dunkin *et al*, 2000; Gorlyn *et al*, 2008; Sneed *et al*, 2007); and (5) worsens with increasing numbers of prior depressive episodes (Kessing, 1998; Sweeney *et al*, 2000). Altogether, these data indicate that executive dysfunction is an important feature of depression, and that recovery from depression precedes normalization of executive dysfunction.

Several points emerging from this literature are particularly important for the current review, and will be emphasized. First, executive deficits have emerged more consistently in tasks requiring effortful (rather than automatic) processing as opposed to speeded motor output (eg, Gorlyn *et al*, 2008; Hammar *et al*, 2009; Levens *et al*, 2009; Weiland-Fiedler *et al*, 2004; but see Den Hartog *et al*, 2003). These selective deficits point to impairments in cognitive control, which encompasses attentional allocation, inhibition of task-irrelevant information, monitoring of performance, and adaptive behavioral adjustments after committing errors or receiving performance-related feedback (MacDonald *et al*, 2000; Ridderinkhof *et al*, 2004) Second, numerous studies have found that, relative to controls, currently as well as formerly depressed subjects perform less accurately immediately after committing a mistake, raising the possibility that oversensitivity to errors might play a key role in cognitive control deficits in depression (Beats *et al*, 1996; Compton *et al*, 2008a; Elliott *et al*, 1996; Elliott *et al*, 1997b; Holmes and Pizzagalli, 2007, 2008b; Jones *et al*, 2010; Murphy *et al*, 2003; Pizzagalli *et al*, 2006; Steffens *et al*, 2001; but see Purcell *et al*, 1997 and Shah *et al*, 1999). These findings have been extended by observations that negative feedback disrupts performance and decision making in the subsequent trial in both currently depressed (Murphy *et al*, 2003) and unmedicated remitted (Taylor Tavares *et al*, 2007) samples.

Collectively, these findings suggest that 'catastrophic responses to failures' (Beats *et al*, 1996), that is, deterioration of executive function and performance after error commission or negative performance feedback, might represent a trait-like marker of depression. This is consistent with the fact that psychiatrically healthy individuals carrying genetic variants linked to increased risk of depression also demonstrate abnormal behavioral, electrophysiological, and hemodynamic responses to errors (eg, Beste *et al*, 2010; Fallgatter *et al*, 2004; Holmes *et al*, 2010).

Psychological concomitants of executive dysfunction in depression. Although the neuropsychological literature reviewed above has provided important clues about the nature, extent, and persistence of executive dysfunction in MDD, little is known about associated psychological processes. One possibility is that the tendency to engage in maladaptive rumination might interfere with or deplete cognitive resources needed to perform a primary task, resulting in poor behavioral performance (Beck, 2008; Holmes and Pizzagalli, 2008b; Jones *et al*, 2010). Although a direct test of this hypothesis is challenging, promising evidence has emerged from both behavioral and functional neuroimaging literature.

With respect to behavioral evidence, several studies deserve mention. Davis and Nolen-Hoeksema (2000) showed that people with high ruminative tendencies committed more perseverative errors in the Wisconsin Card Sorting Task. In a more recent study, individuals with MDD were found to have difficulties ignoring negative (but not positive or neutral) distractors embedded in narratives, as indexed by increased reading time (Lau *et al*, 2007). These impairments emerged despite normative performance in a Stop Signal task, suggesting that deficits in cognitive control/inhibition may be dissociated from motor/behavioral response inhibition (Dillon and Pizzagalli, 2007). Furthermore, MDD subjects with the greatest difficulty in inhibiting task-irrelevant negative cues reported the greatest degree of negative automatic thinking and trait ruminative tendencies. These findings indicate that deficits in cognitive inhibition may be a key mechanism underlying the development and maintenance of depressive cognition (eg,

Joormann and Gotlib, 2010; see Gotlib and Joormann, 2010 for review).

Additional evidence of a link between impaired performance in executive tasks and resource allocation to task-independent, self-focused processing emerged from a study measuring pupil motility in depressed and control subjects during a task requiring continuous controlled processing—the Paced Auditory Serial Addition Task (PASAT) (Jones *et al*, 2010). The authors hypothesized that pupil motility occurring at the frequency of the stimulus presentation would reflect task-relevant processing. Conversely, pupil motility at lower frequencies was assumed to index task-irrelevant processing, including longer lasting intrinsic processing (eg, rumination). Relative to controls, MDD subjects committed more consecutive errors and displayed less task-related frequencies and more off-task frequencies during the PASAT. Moreover, off-task power (a putative index of intrinsic, non-task-related processing) was positively correlated with rumination and partially mediated the link between poor post-error adjustments and depression status. These findings were interpreted as suggesting that engagement in self-focused processing (eg, maladaptive rumination) might deplete or interfere with controlled processing.

Although these findings are interesting, the direction of causality between executive dysfunction and rumination is unclear: does a primary dysfunction in executive function (particularly, cognitive control) allow the emergence of maladaptive ruminative thought, or does rumination cause executive dysfunction because it constitutes a cognitive load that leads to diminished cognitive flexibility? [In this context, it is important to emphasize that, unlike maladaptive forms of rumination (eg, brooding, analytic self-focus attention), adaptive forms of rumination (eg, a mindful, nonevaluative focus) have been hypothesized to be cognitively less effortful (Teasdale, 1999). Accordingly, adaptive forms of rumination linked to increased resting rACC activity might be less cognitively taxing.] In an initial step toward exploring putative links between executive dysfunction and rumination, Watkins and Brown (2002) engaged depressed patients and matched controls in an executive task (random number generation) after inducing rumination or distraction. In contrast to controls, depressed participants who engaged in maladaptive rumination displayed stereotyped counting behavior (an index of reduced inhibitory executive control), but there were no group differences after the distraction induction. These results suggest that depression may confer vulnerability to the disruptive effects of rumination on cognitive control. Because MDD subjects presumably had varying degrees of executive dysfunction, these findings, although promising, do not provide definitive answers about the causal links between executive dysfunction and rumination.

Structural Neuroimaging Studies

Volumetric studies. Findings in the previous sections indicate that depression is characterized by impaired executive function, especially deficient cognitive control. A large body of work has pointed to the frontal cortex as the major brain region implicated in executive function (eg, Luria, 1971; Shallice, 1982; see Leh *et al*, 2010 for a recent review). Cognitive control can be further decomposed into *evaluative* and *executive* components (Botvinick *et al*, 2001; van Veen and Carter, 2006). The evaluative component (assumed to be subserved by the dACC) has been hypothesized to monitor whether events or outcomes are worse than expected. The executive component (assumed to rely on the DLPFC) has been hypothesized to use such evaluations to implement adaptive behavioral adjustments. In light of the behavioral data reviewed above, it is plausible to expect structural abnormalities within frontocingulate pathways in MDD. In the following sections, a summary of studies investigating morphometric and volumetric features of the ACC and DLPFC in depression is provided (see Koolschijn *et al*, 2009; Lorenzetti *et al*, 2009 for reviews summarizing other brain regions).

rACC volume in depression. Relative to controls, individuals with MDD—including medication-naive individuals with a first major depressive episode (MDE) (Tang *et al*, 2007)—are often characterized by reduced rACC volume or gray matter concentration (Abe *et al*, 2010; Boes *et al*, 2008; Frodl *et al*, 2008b; Leung *et al*, 2009; Mak *et al*, 2009; Tang *et al*, 2007; Treadway *et al*, 2009). In a 3-year prospective study, MDD subjects showed a significantly larger decline in rACC and DLPFC volume than controls, and reductions were largest in individuals failing to remit during the 3 years (Frodl *et al*, 2008b).

Particularly relevant to the current review are findings highlighting clinical and functional correlates of these volumetric abnormalities. In MDD treatment studies, a smaller rACC volume predicts poor treatment response and more frequent hospitalization (Chen *et al*, 2007; Costafreda *et al*, 2009a; Frodl *et al*, 2008a; Gunning *et al*, 2009). Moreover, among depressed individuals, reduced rACC volume or gray matter concentration has been linked to greater depression severity (Boes *et al*, 2008; Leung *et al*, 2009), attentional biases toward negative words (Leung *et al*, 2009), and diminished ability to downregulate negative (but not positive) emotions in a laboratory task (Mak *et al*, 2009). These findings are complemented and extended by the observation of reduced magnetization transfer ratio—assumed to reflect demyelination—in the rACC and dACC of individuals with treatment-resistant depression (Zhang *et al*, 2009). Together, these data indicate that reduced rACC volume: can be seen at the first MDE; is exacerbated by illness severity; characterizes nonremission; predicts poor outcome; and is associated with selective attention toward negative cues in the environment and difficulty in downregulating negative emotion.

dACC volume in depression. Relatively few studies have investigated dACC volume in depression, and inconsistencies exist. Reduced dACC volume has been reported in some

(eg, Ballmaier *et al*, 2004; Caetano *et al*, 2006; Vasic *et al*, 2008) but not all (Frodl *et al*, 2008a; Yuan *et al*, 2008) studies. dACC volume reduction has been observed in unmedicated subjects with a past history of MDD (Caetano *et al*, 2006), raising the possibility that reduced dACC volume might not normalize after remission. These findings contrast, however, with null findings emerging from medicated samples, in which normative dACC volume was reported in both currently depressed (Frodl *et al*, 2008a) and remitted depressed (Bremner *et al*, 2002) individuals. Finally, reduced dACC gray matter volume was associated with worse executive function (Vasic *et al*, 2008) and lack of initiative and interest, flat affect, and emotional indifference (Lavretsky *et al*, 2007).

DLPFC volume in depression. Reduced volume or gray matter concentration in the DLPFC (generally involving the superior and middle frontal gyrus in both hemispheres; BA 9/46) has emerged in several studies (Abe *et al*, 2010; Ballmaier *et al*, 2004; Bell-McGinty *et al*, 2002; Coffey *et al*, 1993; Frodl *et al*, 2008b, 2010; Kumar *et al*, 1998; Leung *et al*, 2009; Li *et al*, 2010; Mak *et al*, 2009; Vasic *et al*, 2008; Yuan *et al*, 2008). Reduced left DLPFC volume predicted longer illness duration (Frodl *et al*, 2010), correlated with increased depression severity (Kumar *et al*, 1998; Li *et al*, 2010), and was linked to nonremission after a 6-week antidepressant treatment (Li *et al*, 2010). Moreover, decreased gray matter concentration in the right DLPFC correlated with increased depression severity and worse executive functioning (Vasic *et al*, 2008), as well as attentional biases toward negative cues (Leung *et al*, 2009).

Diffusion Tensor Imaging (DTI) Studies

Data reviewed in the last section highlight morphometric abnormalities within frontocingulate pathways in MDD. Although important, these data do not speak to the issue of possibly abnormal structural connectivity in these pathways in MDD (eg, Mayberg *et al*, 2002). In the following sections, I review emerging data, mostly obtained with DTI, that point to structural abnormalities within frontocingulate and frontolimbic pathways.

DTI is a relatively new technique that can be used to investigate white matter tracts through the study of the diffusion of water in tissues, which can be indexed by fractional anisotropy (Taylor *et al*, 2004). Anisotropy indexes the extent to which diffusion of water molecules is directionally dependent, and is high in healthy white matter (because water mostly moves parallel—rather than perpendicular—to fibers). Accordingly, reduced fractional anisotropy can be interpreted as a marker of white matter abnormalities or fiber density reduction. In depression, reduced fractional anisotropy within PFC and ACC white matter has been described in adolescent (Cullen *et al*, 2010), young adult (Li *et al*, 2007b), and elderly (eg, Bae *et al*, 2006; Nobuhara *et al*, 2006; Shimony *et al*, 2009) samples. This abnormality, which has also emerged in first-episode, treatment-naive young adults with MDD (Ma *et al*, 2007), is important because it affects fibers of the DLPFC circuit implicated in executive function and effortful regulation of behavior (Tekin and Cummings, 2002). Medicated depressed adolescents were also characterized by reduced fractional anisotropy in tracts connecting the supragenual ACC to the right amygdala (Cullen *et al*, 2010), suggesting the possibility of diminished regulatory input to the amygdala. In a recent study, fractional anisotropy in the left frontal and dACC white matter was inversely correlated with total days depressed (Abe *et al*, 2010), raising the possibility that cumulative disease burden is associated with increasing disconnection between frontoncingulate pathways. Moreover, reduced fractional anisotropy within frontal white matter thought to project to limbic regions was found to be related to increased depression severity (Nobuhara *et al*, 2006).

Of primary relevance to the current review, reduced anisotropy in white matter lateral to the cingulate gyrus (ie, tracts containing fibers of the ACC and DLPFC pathways) predicted poor treatment response in a small sample with geriatric depression (Alexopoulos *et al*, 2002). In an extension of this work, nonremission after a 12-week escitalopram treatment was associated with reduced fractional anisotropy in multiple frontal areas, including the rACC, dACC, and DLPFC (Alexopoulos *et al*, 2008; but see Taylor *et al*, 2008 for contrasting findings). Finally, relatively preserved integrity of these white matter tracts positively correlated with better Stroop performance (better response inhibition) (Alexopoulos *et al*, 2002; Murphy *et al*, 2007) and cognitive processing speed (Shimony *et al*, 2009).

Functional Neuroimaging Studies

Frontocingulate activation during executive tasks. In line with the view that depression is characterized by abnormalities within the TPN, dysfunctional frontocingulate activation during a variety of executive tasks is one of the most consistent findings in the neuroimaging literature of depression, although interesting dissociations have emerged depending on behavioral performance. In general, reports of blunted activation in dACC and DLPFC regions have emerged from studies reporting *reduced* task-related behavioral performance in MDD subjects (eg, Audenaert *et al*, 2002; Elliott *et al*, 1997a; Elliott *et al*, 1997b; George *et al*, 1997; Holmes and Pizzagalli, 2008a; Okada *et al*, 2003; but see Halari *et al*, 2009; Harvey *et al*, 2005; Hugdahl *et al*, 2004). Recent data indicate that reduced activation in DLPFC and dACC: (1) can be observed in unmedicated adolescents with MDD, indicating that such dysfunctions appear early in the disorder (Halari *et al*, 2009); and (2) does not normalize in medicated individuals in recovery with multiple MDEs (Aizenstein *et al*, 2009). Furthermore, consistent with the possibility that blunted dACC activation might be associated with increased depression vulnerability, decreased dACC blood flow has been observed in healthy controls with personal or familial history of depression after tryptophan depletion (Talbot and Cooper, 2006).

Findings of blunted frontocingulate activation contrast with numerous reports of *over-recruitment* of these brain regions during executive tasks in depression. Interestingly, potentiated rACC (Rose *et al*, 2006; Wagner *et al*, 2006; Walter *et al*, 2007), dACC (Harvey *et al*, 2005; Rose *et al*, 2006; Wagner *et al*, 2006), and left DLPFC (Fitzgerald *et al*, 2008; Harvey *et al*, 2005; Holmes *et al*, 2005; Matsuo *et al*, 2007; Wagner *et al*, 2006; Walter *et al*, 2007) activation has emerged from studies in which MDD subjects performed at the same level as healthy comparison subjects. For example, relative to controls, medicated MDD subjects showed significantly higher left DLPFC activation during the highest cognitive load condition of a delayed match-to-sample working memory task in the context of no behavioral differences (Walter *et al*, 2007; see also Harvey *et al*, 2005). Critically, increased DLPFC and ACC activation in executive control tasks in the context of normative behavioral performance has emerged in both medicated (eg, Harvey *et al*, 2005; Rose *et al*, 2006; Walter *et al*, 2007) and unmedicated (eg, Matsuo *et al*, 2007) individuals with MDD, indicating that over-recruitment of frontocingulate pathways is not due to medication status. Moreover, recent findings suggest that rACC hyperactivation during executive tasks persists after remission (Schoning *et al*, 2009).

Mounting evidence indicates that higher rACC activation in depressed individuals relative to healthy controls during executive tasks might stem from a failure to deactivate the rACC as cognitive load increases (Rose *et al*, 2006; Vasic *et al*, 2009; Wagner *et al*, 2006). For example, during incongruent Stroop trials, MDD subjects showed hyperactivity in the rACC but normative dACC activation and performance (Wagner *et al*, 2006). Within-group analyses showed a stronger deactivation of the rACC during the incongruent relative to congruent condition for controls, consistent with prior findings that task-related rACC deactivation is required for optimal cognitive control (Bush *et al*, 2000; Drevets and Raichle, 1998). Notably, in the depressed group this pattern was reversed, as they showed elevated rACC activation during incongruent relative to congruent trials. Finally, among MDD subjects, task-related rACC hyperactivity correlated with increased Stroop interference effects. Collectively, these findings are consistent with the notion that a failure to deactivate the DN during cognitively demanding tasks is an important concomitant of executive dysfunction in depression.

However, a failure to suppress one of the main DN hubs (rACC) may only be one aspect of abnormal emotion–cognition interplay in MDD. In line with this proposition, two recent studies have provided important insights into unfolding of functional connectivity between ACC regions implicated in automatically responding to salient cues and DLPFC regions implicated in cognitive control. Using high-density ERPs and source localization techniques, Holmes and Pizzagalli (2008b) recently reported that unmedicated MDD subjects were characterized by (1) potentiated rACC responses 80 ms after committing an error in a Stroop task (Figure 4a), and (2) decreased functional connectivity between rACC activation 80 ms post-error and left DLPFC 472 ms post-error (Figure 4b). Thus, unlike controls, MDD subjects showing the strongest rACC reactivity to errors

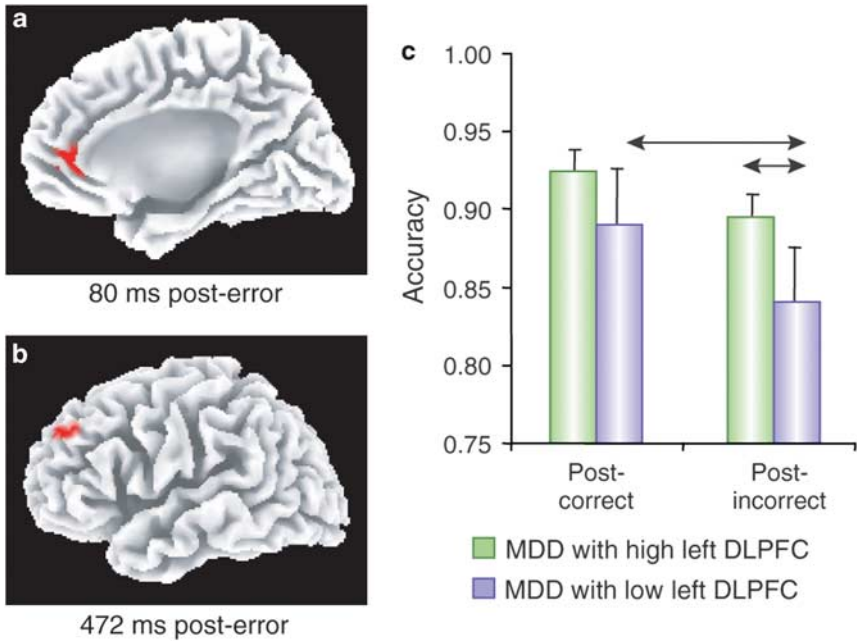

Figure 4. Relative to healthy controls, unmedicated individuals with MDD showed (a) potentiated rACC responses 80 ms after committing an error in a Stroop task, and (b) decreased functional connectivity between rACC activation 80 ms post-error and left DLPFC 472 ms post-error. Among the depressed sample, individuals with the highest left DLPFC activation 472 ms post-error showed more adaptive post-error behavioral adjustments (higher accuracy after errors) relative to MDD participants with the lowest DLPFC recruitment. (Modified with permission from Holmes and Pizzagalli, 2008b.)

failed to recruit left DLPFC regions implicated in cognitive control (Kerns *et al*, 2004). Interestingly, in the depressed sample, individuals with the highest left DLPFC activation 472 ms post-error showed more adaptive post-error behavioral adjustments (higher accuracy and slower response after errors) relative to MDD participants with the lowest DLPFC recruitment (Figure 4c). These findings are consistent with prior evidence in healthy controls that ACC activation during a high-conflict trial predicted greater DLPFC activation, which in turn was linked to more adaptive behavioral adjustments (Kerns *et al*, 2004). Interestingly, these behavioral and neural differences emerged in spite of virtually identical depression severity scores between the two MDD subgroups (mean Beck Depression Inventory scores: 22.11 ± 9.45 *vs* 22.22 ± 9.46), suggesting the existence of MDD subgroups that may not be readily identified by differences in self-reported symptoms (Holmes and Pizzagalli, 2008b).

These findings were conceptually replicated and extended by Aizenstein *et al* (2009), who engaged an elderly depressed sample in a modified version of the Stroop task. When presented with high-load trials, MDD subjects showed reduced left DLPFC activation relative to controls. Moreover, relative to controls, MDD subjects showed reduced functional connectivity between dACC in the current trial and the DLPFC in the subsequent trial (Aizenstein *et al*, 2009). Of primary relevance, whereas DLPFC activation normalized (ie, increased) after a 12-week treatment with paroxetine, reduced frontocingulate functional connectivity persisted after symptom improvements, highlighting a possible marker linked to increased vulnerability for future depression.

Summary. Altogether, these data indicate that, relative to controls, depressed individuals must recruit frontocingulate regions to a greater extent in order to achieve similar levels of behavioral performance, highlighting inefficiency within frontocingulate pathways during tasks requiring cognitive control. In more challenging cognitive tasks, blunted DLPFC and dACC activation has generally accompanied reduced behavioral performance in depressed individuals. In addition, in contrast to controls, depressed individuals fail to deactivate the rACC during cognitively demanding tasks and are characterized by reduced recruitment of DLPFC regions in situations requiring increased cognitive control (high-conflict trials and post-error trials). As discussed in the section 'The rostral ACC as a key hub within the DN,' difficulties in deactivating this hub of the DN, bringing online the TPN during cognitive tasks, and providing top-down regulation of limbic (amygdala) regions might foster the emergence of maladaptive emotional and self-focused processing, leading to treatment nonresponse. Two sets of findings are consistent with this assumption. First, in a recent MEG study, Salvadore *et al* (2010) reported that patients with the smallest rACC recruitment as a function of increasing working memory load in an N-back task showed the greatest reduction in depressive symptoms after acute ketamine administration. Second, in studies with healthy subjects, reduced task-induced rACC deactivation has been associated with increased interference during an affective Eriksen flanker task (Ochsner *et al*, 2009) and predicted errors in both an executive task (Li *et al*, 2007a) and an antisaccade task (Polli *et al* 2005). In spite of this promising evidence, no study has investigated putative links among resting ACC activity, task-induced rACC deactivation, and treatment outcome in depression, or has probed psychological mechanisms underlying these associations. Along similar lines, it is currently unknown whether the rACC region whose resting activity predicts better antidepressant response overlaps anatomically with the one showing reduced task-related deactivation in MDD and/or whether each region might possess stronger functional/structural connectivity with the TPN or amygdala.

Frontocingulate Activation During Affective Tasks

A failure to deactivate rACC regions and abnormal patterns of frontocingulate activation have also emerged in studies testing depressed individuals with a variety of affective tasks, highlighting the robustness of these findings. Specifically, hyperactivation or reduced deactivation of rACC regions in MDD subjects has been observed during (1) affective evaluation and cognitive reappraisal of negative pictures (Grimm *et al*, 2009; Sheline *et al*, 2009; Walter *et al*, 2009); (2) self-referential processing of negative words (Siegle *et al*, 2007; Yoshimura *et al*, 2010); (3) inhibition of negative (but not positive) words (Eugene *et al*, 2010); and in response to (4) sad words in an emotional Stroop task (Mitterschiffthaler *et al*, 2008); (5) sad nogo words in an affective go/nogo task (Elliott *et al*, 2002); and (5) errors in an emotional conflict task (Fales *et al*, 2008) and Stroop task (Holmes and Pizzagalli, 2008b).

Several features of the findings deserve emphasis. First, reduced task-related rACC deactivation during affective evaluation of emotional pictures correlated with increasing illness severity, in particular depressed mood, depressive cognitions, and suicidal ideation (Grimm *et al*, 2009; see also Yoshimura *et al*, 2010). Along similar lines, a failure to deactivate rACC regions in response to negative stimuli has been associated with increased interference to sad words in an emotional Stroop task (Mitterschiffthaler *et al*, 2008). In a study investigating neural correlates of grief regulation, Freed *et al* (2009) reported that rACC activation in response to words associated with the deceased correlated with intrusive thoughts of the deceased; moreover, functional connectivity between rACC and left amygdala correlated with ratings of sadness and yearning/missing. Collectively, these findings are consistent with the assumption that failure to suppress the DN is associated with biased emotional processing and maladaptive cognition in depression, which would negatively impact treatment response. Providing initial evidence for this hypothesis, potentiated rACC responses to sad faces 2 weeks after onset of

antidepressant treatment predicted poor response at least 8 weeks later (Keedwell *et al*, 2010).

Second, relative to controls, depressed individuals are not only characterized by a failure to deactivate rACC regions in affective tasks, but also by reduced ability to recruit the DLPFC (Fales *et al*, 2008; Holmes and Pizzagalli, 2008b; Mitterschiffthaler *et al*, 2008; Wang *et al*, 2008a, 2008b; Siegle *et al*, 2007) and dACC (Fales *et al*, 2008; Wang *et al*, 2008a, 2008b) when required to ignore task-irrelevant negative cues or adjust behavior after committing errors. Deficient recruitment of task-positive regions has been further accompanied by potentiated activation in the amygdala when (1) viewing and reappraising negative pictures (Sheline *et al*, 2009), (2) processing negative words self-referentially (Siegle *et al*., 2007), (3) attempting to ignore negatively (but not positively) valenced distractors (Fales *et al*, 2008), and (4) in response to negative feedback (Taylor Tavares *et al*, 2008) and maternal criticisms (Hooley *et al*, 2009). In addition, relative to controls, MDD subjects have been found to show higher functional connectivity between the rACC and amygdala during negative self-referential processing (Yoshimura *et al*, 2010). Together, these data point to a dominance of the DN and limbic regions implicated in automatic responses to emotional cues (eg, amygdala) over TPN regions in MDD, highlighting deficits in implementing top-down processes over emotional responsiveness (see also Mayberg *et al*, 2002).

An important question is whether the frontocingulate and limbic dysfunctions described above normalize after successful treatment. Initial data suggest that some, but not all, components normalize after symptom remission. For example, Fales *et al* (2009) recently reported that after 8 weeks of antidepressant treatment with SSRIs, MDD subjects showed similar responses in the DLPFC and amygdala as controls when instructed to ignore sad faces. In contrast, relative hyperactivity in the rACC and hypoactivation in the dACC persisted after treatment response. Persistent dACC hypoactivation and failure to deactivate the DN was also observed in a remitted sample tested with an emotional oddball task (Wang *et al*, 2008a).

Whereas these studies provide clues about normalization of activation level within single regions, two studies probed treatment-induced changes in resting state functional connectivity. Common among these studies was the finding that antidepressant treatment and reductions in depressive symptoms were associated with increased functional connectivity between frontocingulate regions (rACC and right DLPFC) and the amygdala (Anand *et al*, 2005; Chen *et al*, 2007). In light of neuroimaging data highlighting the role of frontocingulate-mediated downregulation of amygdalar reactivity in emotion regulation (Ochsner and Gross, 2005), increased corticolimbic coupling might reflect better emotional regulation abilities. Providing some support for this speculation, increased connectivity between the pregenual/dACC and limbic regions at rest correlated with decreased fMRI amygdalar activation to negative stimuli (Anand *et al*, 2007).

Summary. During affective challenges, acutely depressed as well as euthymic individuals with a history of depression are characterized by hyperactivation and/or reduced deactivation in rACC regions implicated in evaluating the subjective, emotional, and motivational significance of events (Bush *et al*, 2000; Simoes-Franklin *et al*, 2010; Taylor *et al*, 2006). This dysfunction is accompanied by deficits in recruiting regions critical for cognitive control and emotional regulation, such as the DLPFC and dACC (Miller and Cohen, 2001; Ochsner and Gross, 2005), and potentiated amygdalar responses in tasks requiring passively observing, actively ignoring, or cognitively reappraising negative information. Collectively, these data indicate that dysfunction within frontocingulate pathways, and in particular reduced task-induced rACC deactivation, is associated with diminished cognitive control over emotional responses and reduced ability to divert attention from negative emotional states (Fales *et al*, 2008; Sheline *et al*, 2008). Although very few studies have investigated functional correlates of frontocingulate dysfunction in depression (eg, Eugene *et al*, 2010; Mitterschiffthaler *et al*, 2008), these neuroimaging data are consistent with behavioral evidence linking depression with difficulties in disengaging from and inhibiting negative cues (Goeleven *et al*, 2006; Koster *et al*, 2005; Lau *et al*, 2007), potentiated interference from negative distractors (Gotlib *et al*, 2004), amplification of the significance of failure (Wenzlaff and Grozier, 1988), and 'catastrophic' reactions to errors.

CONCLUSIONS AND FUTURE DIRECTIONS

MDD remains a leading cause of disability worldwide and is associated with profound personal suffering and staggering costs to society (Greenberg *et al*, 2003; Holma *et al*, 2010; Lopez *et al*, 2006). Despite an array of antidepressant options and psychotherapies, there is currently no empirically validated approach to selection of treatment that is based on an individual's likelihood of response to a given therapy. As a result, treatment in clinical practice follows a trial-and-error approach. The goals of the current review were: (1) to perform a meta-analysis to evaluate the promise of resting rACC activity as a biomarker of treatment response in depression; (2) to advance hypotheses concerning psychological and neurobiological mechanisms that might explain this link; and (3) to integrate these findings and hypotheses within the larger literature implicating frontocingulate dysfunction in depression.

Results from the current meta-analysis indicate that increased pre-treatment rACC activity is a reliable marker of treatment response in depression, which is associated with a large effect size (Cohen's *d* value: 0.918) and has been replicated across 19 studies. Highlighting the robustness of this finding, a link between increased rACC activity and positive antidepressant response has emerged across treatments, including various classes of antidepressant drugs (eg, SSRIs, atypical antidepressants, ketamine), sleep deprivation, and rTMS. The clinical and research implica-

tions of these findings are substantial. From a clinical perspective, the current meta-analysis indicates that it is possible to identify *a priori* individuals with a low probability of response to monotherapy, who might benefit from a combination of treatment interventions at the outset. From a research perspective, the findings contribute to a better understanding of mechanisms associated with treatment response. In this context, through an integration of neuropsychological, electrophysiological, and neuroimaging data, I proposed that elevated resting rACC activity may foster better treatment outcome through (1) adaptive forms of reflective, self-focused processing, and (2) adaptive modulations between the DN and TPN, including ability to suppress rACC activation in situations requiring inhibition of emotional responding and recruitment of cognitive control. Future studies will be required to test the hypothesis that low resting rACC activity is associated with deficits in deactivating this DN hub and bringing online the TPN during cognitive tasks, which might foster the emergence of maladaptive emotional and self-focused processing, leading to treatment nonresponse. Along similar lines, the possibility that reduced task-induced rACC deactivation during cognitive and affective challenges represents a floor effect due to low resting rACC activity needs to be carefully investigated.

Although reduced ability to suppress rACC activation during emotional and cognitively demanding tasks has emerged as one of the most consistent findings in the functional neuroimaging literature in depression, several outstanding questions remain. First, because this finding has emerged almost exclusively from currently depressed samples, it is currently unknown whether reduced task-induced rACC deactivation is a correlate of depression or rather a vulnerability factor. Initial findings of potentiated rACC responses to errors during an executive task in psychiatrically healthy individuals carrying genetic variants linked to increased risk for depression (Holmes *et al*, 2010) are consistent with the view of a putative vulnerability factor; these findings await replication and studies in additional at-risk samples (eg, unaffected offspring of individuals with depression) will be required for conclusive tests of this hypothesis.

Second, the neurobiological underpinnings of rACC dysfunction remain poorly understood. Initial evidence suggests that reduced task-induced rACC deactivation in MDD might be linked to altered glutamatergic metabolism. Specifically, in a combined fMRI-spectroscopy study, Walter *et al* (2009) reported that in unmedicated MDD subjects, task-related rACC deactivation during an emotional judgment task correlated with levels of glutamate, the main excitatory neurotransmitter, in the rACC. These findings contrast with data in controls indicating that resting rACC levels of the main inhibitory neutransmitter, γ-aminobutyric acid (GABA), correlated positively with rACC deactivation during an emotional task (Northoff *et al*, 2007; Walter *et al*, 2009). Together, these findings raise the possibility that resting state activity in MDD might shift from a mainly GABA- to glutamate-meditated modulation. In light of an emerging role of glutamate in the pathophysiology of MDD and the mechanism of action of antidepressants (Hashimoto, 2009; Sanacora *et al*, 2008), future studies are needed to understand the significance of these findings and explore the relevance of these neurochemical abnormalities to treatment response and biased emotional processing in depression.

Third, studies investigating cognitive behavioral therapy have not observed links between rACC activity and treatment outcome (Siegle *et al*, 2006; see also Konarski *et al* 2009). The reasons for these discrepancies are not immediately clear, particularly considering that strategies targeting maladaptive cognition and rumination are important components of CBT. In light of the hypothesis that increased resting rACC activity fosters treatment outcome by supporting adaptive forms of rumination, including a mindful, nonevaluative focus, it will be important to test whether this biomarker predicts outcome to mindfulness-based cognitive therapy, which is an effective treatment for preventing depressive relapse and recurrence (eg, Godfrin and van Heeringen, 2010; Kuyken *et al*, 2008; Ma and Teasdale, 2004).

Finally, in spite of the robust link between rACC activity and antidepressant response, there are three important weaknesses in this literature that should be addressed. First, with a few exceptions (eg, Korb *et al*, 2009; Mayberg *et al*, 2000), most studies have used naturalistic designs without placebo control, likely because of several practical and ethical considerations (eg, expenses of fMRI/PET scans and possible concerns about exposing placebo-treated patients to radioactive PET tracers). Nevertheless, as placebo effects appear in 25–60% of treated individuals (Quitkin, 1999), 'active' drug responders may in fact be placebo responders. This makes it difficult to differentiate between specific and nonspecific components of treatment response. The report from Korb *et al* (2009) that increased resting rACC activity predicted antidepressant—but not placebo—response is encouraging, but additional placebo-controlled studies are warranted. In light of findings emerging from the current meta-analysis, EEG methodologies might be especially useful to circumvent some of the practical and ethical considerations mentioned above.

Second, few studies have compared responders with both nonresponders *and* healthy controls (eg, Pizzagalli *et al*, 2001), and the author is not aware of any study that has contrasted treatment responders to *both* nonresponders and healthy controls *both* before and after treatment in a placebo-controlled design. These contrasts are essential for identifying predictors *vs* mediators of outcome, as well as for pinpointing the effects of antidepressants on the neural mechanisms under investigation. Third, all studies reviewed have implemented simple univariate statistical models and have not integrated measures of rACC activity with other biological, clinical, genetic, or behavioral data. The development of more advanced, multivariate statistical algorithms might improve our ability to predict outcome on an

individual basis, which remains a critical priority for the field (Insel, 2009).

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