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MRI Predictors of Treatment Response in Late-Life Depression

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Abstract

In older adults, depression not only results in more years lived with disability than any other disease, but it also carries additional risk for suicide, medical comorbidities, and family care-giving burden. Because it can take many months to identify an effective treatment regimen, it is of upmost importance to shorten the window of time and identify early on what medication(s) and dosages will work effectively for individuals suffering from depression. Late-life depression (LLD) has been associated with greater burden of age-related changes, including atrophy, white matter ischemic changes, and alterations in functional connectivity (FC). Depression in midlife has been shown to alter affective reactivity and regulation, and functional magnetic resonance imaging (fMRI) studies in LLD have replicated the same abnormalities. Effective treatment can normalize these alterations. This article provides a review of the current literature using structural and functional neuroimaging to identify magnetic resonance imaging (MRI) predictors of treatment response in LLD. The majority of the literature on structural MRI has focused on the vascular depression hypothesis, and studies support the view that loss of brain volume and white matter integrity is associated with poorer treatment outcomes. Studies using fMRI have reported that lower task-based activity in the prefrontal cortex (PFC) and limbic regions is associated with poorer outcome. These imaging markers may be integrated into clinical decision-making to better treatment outcomes in the future.

Introduction

Depression results in more years lived with disability than any other disease and ranks fourth in terms of disability-adjusted life years ^{1, 2}. By 2020, depression will be second only to heart disease in its contribution to the global burden of disease (measured by disability-adjusted life years) ³. As the population ages, successive cohorts of older adults will experience depressive disorders ³. Late-life depression (LLD) carries additional risk for suicide, medical comorbidity, disability, and family care giving burden ^{4–6}.

Conventional treatment of LLD often requires long trials of several antidepressants before an effective regimen can be found for an individual. This can take many months and is associated with persistent depressive symptoms, an increased risk of suicide, patients dropping out of care, and worsening of medical comorbidities. This long response time in

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LLD is one of its most challenging clinical features^{7, 8}. Thus, in the elderly, it is particularly important to shorten this window and to identify early effective medication regimens. Several studies have examined the demographic, clinical, cognitive, imaging, and physiologic predictors of treatment response^{1–6, 9–16}. The current review provides an update focused on the use of MR imaging predictors of treatment response in geriatric depression.

The current standard of care for clinical evaluation of geriatric depression uses MR imaging to rule-out medical or neurologic causes or complications (e.g., tumor or stroke), but does not recommend using MRI to personalize depression treatment. Although a growing body of literature has demonstrated that structural and functional MRI markers are associated with LLD treatment response, evidence-based medicine recommendations are not yet clear¹⁷. Part of the limitation is the paucity of randomized controlled trials testing how well imaging biomarkers can help in selecting treatment¹⁸. The current set of studies, however, demonstrates that MRI can yield predictive biomarkers of response to standard first-line antidepressant treatment^{10–12, 15, 16, 19–39}.

MRI can be used in at least two different ways to inform treatment in LLD. First, the imaging markers may advise on the treatment response profile: individuals with particular imaging markers (e.g., increased white matter hyperintensities (WMH) burden) may need higher initial doses of antidepressant. Second, MRI markers may advise early on the trajectory of treatment response. Typically, it takes three to four weeks to see clinical signs of treatment response, significantly delaying the ability to choose the optimal medication at the optimal dose⁴⁰. Since conventional antidepressants increase synaptic serotonin within hours of first exposure⁴¹, the delay in behavioral signs is attributed to a cascade of receptor remodeling stimulated by the change in synaptic serotonin. Since fMRI is able to show very early synaptic changes associated with antidepressant exposure^{42, 43}, it may be used as an early predictor of treatment response. Therefore, it can help guide titration and decide when medication changes should be implemented. As far as we are aware, no studies have tested the efficacy of early functional change in a treatment, however, a number of studies have examined the functional patterns associated with treatment and treatment response^{19, 20, 23, 25–28, 32, 34, 35, 39}. Although these studies do not distinguish medication effects from the response, they have the potential to provide an earlier target for guiding pharmacotherapy and could be used to shorten the treatment trial interval.

Current use of MR Imaging in Clinical Management of Late-Life Depression

As of 2012, the American Psychiatric Association (APA) primarily recommends the use of neuroimaging in an exclusionary capacity. This predominantly relates to neoplasms, cerebrovascular disease, hydrocephalus, or marked atrophy, which may be manifesting psychiatric symptoms with atypical presentations or that are otherwise not responsive to conventional treatments⁴⁴. With respect to the APA's depression-specific guidelines, imaging is only indicated for electroconvulsive therapy's (ECT) pre-operative assessment of relative contraindications, which mostly include the above mentioned conditions⁴⁵. As depression can be misdiagnosed as dementia, especially in the case of pseudo-dementia, the current recommended clinical use of neuroimaging in suspected dementia patients is also relevant. The APA, American Neurological Association (ANA), and Alzheimer's

Association (AA) currently support the use of either computed tomography (CT) or MRI during the initial assessment of dementia. Again, this is meant to rule out other etiologies of cognitive impairment. With respect to the primary diagnosis of dementia, the APA and ANA do not currently recommend the routine use of diagnostic neuroimaging^{46, 47}. However, in clinical research, the AA and National Institutes of Aging have together developed Alzheimer's Disease (AD) neuroimaging criteria to stratify patients into stages and AD risk categories. Specifically, MRI-quantified medial temporal lobe atrophy, fludeoxyglucose positron emission tomography (PET), and PET amyloid imaging were deemed appropriate to assess for the presence of AD pathophysiological processes which help stratify patients within pre-clinical AD, mild cognitive impairment due to AD, and dementia due to AD⁴⁸⁻⁵¹. Finally, a joint article recently published by the AA and Society of Nuclear Medicine and Molecular Imaging provides appropriate use criteria for PET amyloid imaging in a narrow subset of patients in clinical non-research settings. This patient subset includes criteria such as early onset progressive dementia, atypical clinical course, or an etiologically mixed presentation⁵².

Structural and functional brain changes associated with Depression

It has long been recognized that the brains of older adults with depression have a greater burden of age-related changes, including atrophy, white matter ischemic changes, as well as alterations in functional connectivity (FC)^{53, 54}. Much of this work stems from the vascular depression hypothesis^{55, 56}, which posits that cerebrovascular changes contribute to the onset or progression of depressive symptoms in older adults primarily with late-onset LLD. Structural MRI studies have supported the vascular depression model by showing a higher burden of vascular disease in older adults with depression relative to those without depression⁵⁶.

The focus on ischemic white matter changes as a marker of cerebrovascular burden and vascular depression, is specific to older adults, since in younger age groups (below 60 years old), the incidence of cerebrovascular brain changes commonly seen on MRI (i.e., white matter hyperintensities (WMH)) are rare⁵⁷. In mid-life, the MRI research has focused on identifying depression-specific functional brain changes. In a series of studies and review papers, Price, Mayberg, and Phillips⁵⁸⁻⁶⁰ have proposed functional brain circuit models for depression, which involve altered affective reactivity and regulation: increased activity in rostral cingulate and limbic circuits and decreased activity in dorsal cognitive regions. These models proposed that effective treatment is associated with a normalization of these alterations. The fMRI studies in LLD have generally replicated that these same circuit abnormalities are present in older adults with depression. More recently, work from our group⁶¹ has provided additional support to the vascular depression model by linking the structural brain changes of vascular depression with functional abnormalities. Therefore, our results showed that a higher burden of WMH is associated with greater limbic activation on an affective reactivity task.

Pre-treatment Structural MRI Predictors of LLD Treatment Response

As reviewed in Table 1, a number of studies have examined how structural MRI markers can predict response to antidepressant treatment in older adults with major depressive disorder (MDD). These studies examine whole-brain global markers, as well as regional gray matter volumes, ischemic white matter burden, and white matter integrity. Across these studies, T1-weighted volumetric imaging (spoiled gradient echo (SPGR) or magnetization prepared rapid gradient echo (MPRAGE) 3D acquisition) was used for assessing gray matter; T2-weighted fluid attenuated inversion recovery (FLAIR) imaging was used to assess ischemic white matter burden by estimating the volume of WMH; white matter integrity was assessed in these studies using Diffusion Tensor Imaging (DTI) and calculating fractional anisotropy, which is a marker of myelin integrity.

The earliest report that we identified was by Hickie et al. (1995)¹² which studied 19 older adults with depression and found that total WMH burden, as well as WMH restricted to the deep white matter or periventricular regions, were all negatively associated with improvement in depressive symptoms. Specific criteria for recovery or remission were not reported in this study. Across the literature, criteria for defining recovery or remission vary considerably and present a challenge in integrating the literature. In Table 1, we describe the particular criteria used in each study for defining the outcome measure. Twelve other studies with sample sizes ranging from 13 to 190 are reviewed in Table

1^{10, 11, 15, 16, 21, 22, 24, 30, 31, 36–38}. These studies have generally replicated the association of poorer treatment response with high WMH burden. The largest study involved 190 older adults with depression, those with high WMH burden having higher depression rating scores¹⁵. After eight weeks of treatment, there was not a significant difference in WMH burden between the remitters and non-remitters, but there was a statistical trend ($p < .09$). The individuals who remitted had a lower burden of vascular risk factors. Overall, this study supports the vascular depression hypothesis, given the overall association of WMH with Montgomery-Asberg Depression Rating Scale (MADRS) scores, and is consistent with previous reports correlating WMH burden with depression severity. The lack of significant finding with conservative remission criteria suggests that other factors (e.g., cognitive performance) may be involved in attaining remission.

A smaller literature has examined with mixed results other brain markers (gray matter volume and FA) as predictors of treatment response. Two of the three studies^{10, 30} found that decreased anterior cingulate cortex and hippocampus gray matter volume was associated with poorer response, but the third study³¹ did not find a significant association between global or regional gray matter volume and treatment response. Three studies^{21, 22, 38} that examined the treatment prediction power of FA are included in this review. The results of these studies differ: two of the studies found that lower FA (a marker of axonal damage) in white matter regions was associated with poorer treatment outcomes^{21, 22}, but the other study found that higher FA (a marker of axonal integrity) in the white matter of the anterior cingulum and frontal cortex was associated with poorer outcomes³⁸. Methodological differences between studies might explain some of the discrepancy, but the relationship between FA and treatment outcomes in LLD remains unclear.

Functional MRI Predictors of Treatment Response in Mid-life Depression

Since the literature on fMRI predictors of treatment response in LLD is somewhat sparse, we first review the literature on mid-life depression (Table 2), which sets the context for reviewing the smaller number of studies in LLD. We review eight studies in which fMRI activation is correlated with treatment response^{26–29, 32–35}. As with the structural MRI studies described above, there is significant variability among these studies in the definitions of response or remission; when reported these are included in the table. The studies are divided into those that examine FC while the participant is awake but resting (i.e., not performing a particular task), and studies that use a cognitive or affective task to probe particular circuits.

The two resting-state FC studies we review both found that resting-state fMRI markers were significantly associated with response to antidepressant treatment in a group of mid-life individuals with MDD^{27, 35}. The study by Lui et al (2011)³⁵ was a cross-sectional study comparing treatment responsive to treatment resistant individuals; they examined the FC among a wide range of regions identified as being involved in mood regulation and found that compared to responders, the non-responders had significantly increased FC among the following structures: left amygdala, anterior cingulate cortex, right insula, and precuneus region. The study by Franco, Mayberg, et al. (2011)²⁷ used an independent component analysis method to identify the default mode network (DMN). They reported that baseline subgenual cingulate FC in the DMN was positively correlated with antidepressant treatment response, whereas dorsolateral prefrontal cortex activity was negatively correlated with antidepressant response.

Table 2 also reviews six task-based fMRI treatment studies of mid-life depression, five using different affective tasks and one using a cognitive task^{26, 28, 29, 32–34}. All of these studies reported that lower pre-treatment fMRI activation in a number of prefrontal and limbic regions was associated with poorer treatment outcomes. Recent studies have focused on FC during task, and using this approach Lisiecka et al. (2011)³⁴ demonstrated that lower orbitofrontal cortex (OFC) and motor FC during an emotional face matching task was associated with poorer treatment outcome; the reverse pattern was seen for OFC and cerebellum FC.

Functional MRI Treatment Studies in Late-Life Depression

As noted above, there are fewer fMRI treatment studies of late-life depression. We found a total of five studies, which we review in Table 3^{19, 20, 23, 25, 39}. This includes two studies of resting-state fMRI^{20, 23} and three task-based fMRI studies (one using a cognitive task and two using affective tasks)^{19, 25, 39}. These studies generally replicate the fMRI patterns of depression and treatment response previously reported for mid-life depression: decreased task-related activity in the prefrontal cortex in LLD prior to treatment, which is normalized following treatment^{19, 25, 39}. This pattern was true whether the task was affective or cognitive. The two resting-state fMRI studies both found that decreased activity within the DMN was associated with poorer treatment outcomes^{20, 23}. The Andreescu et al. (2013)²³

study also reported that increased FC between the posterior cingulate and the striatum was associated with poorer treatment response.

Conclusion

In summary, the preponderance of MRI literature on treatment response in LLD has focused on structural biomarkers following the framework of the vascular depression hypotheses⁵⁵. These studies support the view that loss of brain volume and white matter integrity is associated with poorer treatment outcomes. The findings are most consistent for WMH burden. However, since many of the same age-related etiopathologic pathways (e.g., ischemia, inflammation) leading to WMH burden will also cause gray matter atrophy and decreased white matter FA, we suspect that future studies will confirm that all structural MR markers will be associated with poorer treatment outcomes.

Most of the studies looking at fMRI as a predictor of depression treatment response have been conducted in mid-life populations. These studies, which have used both resting-state and task-based fMRI, have reported that lower task-based activity in the PFC and limbic regions are associated with poorer treatment outcome. The resting-state fMRI results are topographically selective, showing that both increased and decreased FC are associated with poorer outcomes depending on the particular regions. Somewhat similar patterns were also reported in the LLD resting-state fMRI study by Andreescu et al. (2013)²³.

In conclusion, there is a growing literature focused on both structural and functional MRI treatment prediction markers in LLD. There have been some clinical reports suggesting how these markers (especially markers of cerebrovascular disease) may be integrated into clinical decision-making (e.g.,⁶²). Future studies, including randomized clinical trials, are needed to evaluate the clinical potential of MRI markers of treatment response

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Table 1

Pretreatment Structural MRI Markers of Treatment Response

Marker Assessed	Author	Groups/Sample Size and Mean Age, yrs	Treatment and Remission/Response Definition	Findings
Hyperintensities	Gunning et al., 2009 ¹⁰	41 depressed patients - 22 remitters (71.0 ± 5.6) - 19 non-remitters (70.0 ± 6.3)	12 week course of escitalopram - Remission: no longer meeting criteria for depression on SCID-IV-TR and HDRS (24-item) score (< 7) for 2 consecutive weeks	- Non-remitters demonstrated significantly smaller pre-treatment dorsal and rostral anterior cingulate GM volumes
	Hsieh et al., 2002 ³⁰	60 depressed patients - 22 remitters (66.1 ± 5.0) - 38 non-remitters (70.0 ± 6.8)	Patient specific pharmacotherapy based on institutionally developed guidelines for 8 weeks - Remission: MADRS score < 10	- Patients in the lowest quartile of right and total hippocampal volumes were significantly less likely to achieve remission than those in the upper three quartiles
	Janssen et al., 2007 ³¹	42 depressed patients - 19 responders (68.0 ± 4.7) - 23 non-responders (72.4 ± 7.5)	Randomized to 12 week course of either: venlafaxine, nortriptyline - Response: reduction of at least 50% of score on MADRS or a final score of 10 or less on MADRS	Non-responders demonstrated no significant difference in volumes of GM, WM, WMH, orbitofrontal cortex, or hippocampus
	Bella et al., 2010 ²⁴	89 depressed patients - 26 remitters (68.1 ± 7.1) - 63 non-remitters (71.4 ± 7.4)	12 week course of escitalopram - Remission: complete functional recovery or HDRS (17-item) score < 7 after 12 weeks of treatment	- Non-remitters demonstrated significantly greater deep WMH than remitters
	Gunning-Dixon et al., 2010 ¹¹	42 depressed patients - 22 remitters (69.6 ± 4.7) - 20 non-remitters (71.2 ± 7.0) 25 control subjects (70.7 ± 5.8)	12 week course of escitalopram - Remission: no longer meeting criteria for depression on SCID-IV-TR and HDRS (24-item) score < 7 for 2 consecutive weeks	- Non-remitters demonstrated significantly greater signal WM and subcortical nuclei hyperintensities burden compared to remitters and controls.
	Hickie et al., 1995 ¹²	19 depressed patients (64.4, range 28–86)	Patient specific pharmacologic treatment regimen throughout in-patient admission (mean = 15.7 weeks) - Remission not defined	- Improvement in depressive symptoms was significantly negatively correlated with pre-treatment DWMH, PVH, and total hyperintensity severities

Marker Assessed	Author	Groups/Sample Size and Mean Age, yrs	Treatment and Remission/Response Definition	Findings
	Salloway et al., 2002 ³⁶	59 depressed patients (69.2 ± 5.6)	8 week course of sertraline - Remission not defined	- Patients classified as having high SH severity did not demonstrate a significant difference in treatment response
	Sheline et al., 2010 ¹⁵	190 depressed patients - 72 remitters (69.2 ± 7.7) - 118 non-remitters (67.6 ± 6.7)	12 week course of sertraline - Remission: MADRS score < 7 after 8 weeks of treatment	- Non-remitters did not have a significant difference in WMH burden - WMH burden was a significant predictor of MADRS scores throughout the full treatment period.
	Simpson et al., 1998 ³⁷	75 depressed patients (75.7) 24 control subjects (74.9 ± 6.3)	12 week course of non-uniform pharmacologic monotherapy - Response: MADRS score < 10, less than 5 DSM-III-R features of depression, and CGI score of at least 4	- Non-response was significantly predicted by - > 5 basal ganglia SH - > 1 pontine reticular formation SH
	Sneed et al., 2011 ¹⁶	38 depressed patients - 10 remitters (64.7 ± 6.5) - 28 non-remitters (66.5 ± 7.9)	Randomized to 12 week treatment course of either: sertraline, nortriptyline - Remission: HDRS (24-item) score < 7 for 2 consecutive observations	- Non-remitters were significantly more likely to have DWMH, PVH, and total hyperintensity volumes classified as high
	Alexopoulos et al., 2002 ²¹	13 depressed patients (range 60–77) - 8 remitters - 5 non-remitters	12 week course of citalopram - Remission: no longer meeting criteria for depression on DSM-IV and HDRS (24-item) score < 10 for two consecutive weeks	- Decreased remission rate was significantly associated with low FA of right and left frontal WM regions above anterior and posterior commissures
	Alexopoulos et al., 2008 ²²	48 depressed patients - 25 remitters (70.1 ± 5.5) - 23 non-remitters (70.4 ± 6.2)	12 week course of escitalopram - Remission: No longer meeting DSM-IV criteria for depression and HDRS score < 7 for two consecutive weeks	- Non-remitters demonstrated significantly decreased FA throughout WM
Fractional Anisotropy	Taylor et al., 2008 ³⁸	74 depressed patients - 37 remitters (65.8 ± 5.7) - 37 non-remitters (70.5 ± 8.0)	12 week course of sertraline - Remission: MADRS score < 10 at any assessment	- Non-remitters demonstrated significantly greater FA in - anterior cingulate cortices - frontal gyri

DSM IV = Diagnostic and Statistical Manual of Mental Disorders IV; DWMH = deep white matter hyperintensities; FA = fractional anisotropy; GM = gray matter; MADRS = Montgomery-Asberg Depression Rating Scale; MRI = magnetic resonance imaging; PVH = paraventricular hyperintensities; SCID-IV-TR = Structured Clinical Interview of DSM-IV Text Revision; SH = subcortical hyperintensities; WM = white matter; WMH = white matter hyperintensities; yrs = years

Table 2
Pretreatment and Posttreatment Functional MRI Markers of Treatment Response in Midlife Depression

	Author	Groups/Sample Size and Mean Age, yrs	Treatment and Remission/Response Definition	Task	Findings
Resting State	Lui et al., 2011 ³⁵	60 depressed patients	Patient specific 12 week pharmacotherapy treatment regimen	Resting-state	Pre-Treatment
		- 32 non-responders (32 ± 10) - 28 responders (33 ± 11) 48 control subjects (35 ± 12)	- Response: reduction > 50% in HDRS (17-item) score after 6 weeks of treatment		- Non-responders demonstrated significantly greater FC between the left amygdala and cingulate cortex and between the right insula and cingulate and precuneus
Functional Task	Franco et al., 2011 ²⁷	45 depressed patients	Randomized to 12 week course of either: escitalopram, CBT	Resting-state	Pre-Treatment
			- Response not defined		- Better treatment outcome was associated with greater connectivity within the DMN (subcallosal cingulate) whereas right dLPFC was negatively correlated - Group response to course of treatment differed: - CBT: FC within left posterior parahippocampus and right posterior parietal cortex were positively correlated with outcome - Escitalopram: FC within subcallosal cingulate was positively associated with treatment outcome whereas left dorsomedial prefrontal FC was negatively correlated
Functional Task	Chen et al., 2007 ²⁶	17 depressed patients (44.1 ± 8.36)	8 week course of fluoxetine	Visual presentations of varying intensities of sadness	Pre-Treatment
			- Remission not defined		- Decreased rate of remission was significantly associated with lower activation in anterior cingulate cortex
Functional Task	Fu et al., 2007 ²⁹	19 depressed patients (43.2 ± 8.8) 19 control subjects (42.8 ± 6.7)	8 week course of fluoxetine	Visual representations of varying intensities of happiness	Pre-Treatment
			- Response not defined		- Lower response capacity in hippocampus and extra-striate visual regions was significantly associated with decreased symptomatic improvement

	Author	Groups/Sample Size and Mean Age, yrs	Treatment and Remission/Response Definition	Task	Findings
	Fu et al., 2008 ²⁸	19 depressed patients (43.2 ± 8.8) 19 control subjects (42.8 ± 6.7)	8 week course of fluoxetine - Remission not defined	Visual presentations of varying intensities of sadness	Pre-Treatment - A trend towards statistical significance was noted in the ability of whole brain neural activity to predict remission
	Langenecker et al., 2007 ³²	20 depressed patients (41.0 ± 12.2) 22 control subjects (34.2 ± 11.0)	10 week course of escitalopram - Remission not defined	Parametric Go/No-Go Task - A contextual inhibitory control task	Pre-Treatment - Lower activation during successful inhibitory events in the following regions significantly predicted decreased symptomatic improvement: bilateral inferior frontal gyri, left amygdala, insula, and nucleus accumbens - Lower activation during unsuccessful inhibitory events in the rostral anterior cingulate significantly predicted decreased symptomatic improvement
	Lemogne, Mayberg et al., 2010 ³³	8 depressed patients (33.1 ± 9.0) 8 control subjects (28.4 ± 6.1)	Patient specific pharmacologic treatment course with mean duration of 9 weeks - Remission: MADRS score < 10, and BDI score < 8	Visual presentations of varying human attributes which patients were required to judge in relation to themselves and society	Post-Treatment - Depressed patients in aggregate experienced a significant decrease in symptom severity (according to MADRS and BDI scores) - Depressed patients post-treatment compared to pre-treatment demonstrated significantly greater activation of left dLPFC during societal evaluations
	Lisiecka et al., 2011 ³⁴	23 depressed patients - 12 responders (34.4 ± 8.8) - 11 non-responders (43.8 ± 8.2)	Randomized to 4 week course of either: venlafaxine, mirtazapine - Response: 50% drop in HDRS score between initial and follow-up assessments	Emotional face matching task	Pre-Treatment - Non-responders demonstrated significantly greater OFC-cerebellum connectivity, and lower OFC-left motor area connectivity compared to responders

BDI = Beck's Depression Inventory; CBT = cognitive behavioral therapy; dLPFC = dorsolateral prefrontal cortex; DMN = default mode network; FC = functional connectivity; HDRS = Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; OFC = orbitofrontal cortex; yrs = years

Table 3
Pretreatment/Posttreatment Functional MRI Markers of Treatment Response in Late-Life Depression

	Author	Groups/Sample Size and Mean Age, yrs	Treatment and Remission/Response Definition	Task	Findings
Resting State	Alexopoulos et al., 2012 ²⁰	16 depressed patients - 8 remitters (67.9 ± 4.7) - 8 non-remitters (70.1 ± 6.3) 10 control subjects (68.6 ± 7.0)	12 week course of escitalopram - Remission: MADRS score 7 for 2 consecutive weeks and absence of DSM-IV diagnosis of depression	Resting-state	Pre-Treatment - Decreased rate of remission significantly predicted by low resting FC within Cognitive Control Network
	Andreescu et al., 2013 ²³	21 depressed patients - 10 responders (67.9 ± 4.9) - 11 non-responders (68.5 ± 7.9) 46 control subjects (72.9 ± 7.9)	12 week course of either: venlafaxine, duloxetine, escitalopram - Response: HDRS score 10 at the end of treatment	Resting-state	Pre-Treatment - Non-responders compared to responders demonstrated significantly lower connectivity between PCC and medial prefrontal cortex and precuneus - Non-responders compared to responders demonstrated significantly greater connectivity between PCC and dorsal ACC and cuneus Post-Treatment - Non-responders compared to responders demonstrated a significantly greater FC within the left striatum
Functional Task	Aizenstein et al., 2009 ¹⁹	13 depressed patients (69.1 ± 5.5) 13 control subjects (68.8 ± 5.79)	12 week course of paroxetine - Remission not defined	Preparing to Overcome Prepotency task (specific for the cognitive control network)	Pre-Treatment - Depressed patients demonstrated significantly decreased activity in dLPFC and lower FC between dLPFC and dACC Post-Treatment - Depressed patients in aggregate experienced a significant decrease in symptom severity (mean HDRS: 19.7 → 7.5) - Depressed patients post-treatment demonstrated significantly increased activity in dLPFC compared to depressed patients pre-treatment

Author	Groups/Sample Size and Mean Age, yrs	Treatment and Remission/Response Definition	Task	Findings
Brassen et al., 2008 ²⁵	13 depressed patients (66.4 ± 6.1) 13 control subjects (65.6 ± 6.1)	Patient specific treatment regimen, including: pharmacotherapy (6 patients), behavioral therapy (2 patients), none (5 patients) - Remission not defined	Emotional evaluation of positive, negative, and neutral words	Pre-Treatment - Depressed patients demonstrated significantly decreased neural response in vmPFC during the emotional evaluation of negative words compared to positive words Post-Treatment - Symptom severity improved in 12 of 13 depressed patients - Depressed patients demonstrated normalization of vmPFC response to negative words compared to positive words
Wang et al., 2008 ³⁹	12 depressed patients (69.1 ± 6.0) 15 remitted patients (70.8 ± 5.5) 20 control subjects (73.1 ± 5.3)	Acutely depressed and remitted patients were being treated with individualized pharmacotherapy regimen at time of study - Remission: absence of symptoms for a minimum of 6 months and a MADRS score < 8	Emotional Oddball task - Patients respond to infrequent attentional targets with sad and neutral pictures as distractors	Post-Treatment - Acutely depressed patients compared to control subjects demonstrated significantly decreased activation in executive system related areas, including - posterior cingulate (both anterior and posterior portions) - inferior parietal areas - right middle frontal gyrus - Remitted patients compared to controls demonstrated significantly decreased activation in the - posterior cingulate (anterior portion only) - inferior frontal gyrus

ACC = anterior cingulate cortex; dACC = dorsal anterior cingulate cortex; dLPFC = dorsolateral prefrontal cortex; FC = functional connectivity; HDRS = Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MRI = magnetic resonance imaging; OFC = orbitofrontal cortex; PCC = posterior cingulate cortex; vmPFC = ventromedial prefrontal cortex; yrs = years