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Magnetic Resonance Imaging Predictors of Treatment Response in Late-Life Depression

Howard J. Aizenstein[1,2], Alexander Khalaf[2], Sarah E. Walker[2], and Carmen Andreescu[1,2]

Abstract

In older adults, depression not only results in more years lived with disability than any other disease but it also carries additional risks of suicide, medical comorbidities, and family caregiving burden. Because it can take many months to identify an effective treatment regimen, it is of utmost importance to shorten the window of time and identify early on what medications and dosages will work effectively for individuals having depression. Late-life depression (LLD) has been associated with greater burden of age-related changes (eg, atrophy, white matter ischemic changes, and functional connectivity). 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 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 was associated with poorer treatment outcomes. Studies using fMRI have reported that lower task-based activity in the prefrontal cortex and limbic regions was associated with poorer outcome. These imaging markers may be integrated into clinical decision making to attain better treatment outcomes in the future.

Keywords

MR imaging, late-life depression, neuroimaging

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 of suicide, medical comorbidity, disability, and family caregiving 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 is one of the most challenging clinical features of LLD.[7,8] Thus, in the elderly individuals, 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 magnetic resonance imaging (MRI) predictors of treatment response in geriatric depression.

The current standard of care for clinical evaluation of geriatric depression uses MRI to rule out medical or neurologic causes or complications (eg, tumor or cerebral vascular accident) but does not recommend using MRI to personalize depression treatment. Although a growing literature has demonstrated that structural and functional MRI (fMRI) markers are associated with LLD treatment response, evidence-based medicine recommendations are not yet clear.[17] Part of the limitation is the paucity of randomized controlled trials testing how well imaging biomarkers can help in selecting treatment.[18] The current set of studies, however, demonstrates that MRI is a predictive biomarker of response to standard first-line antidepressant treatment.[10-12,15,16,19-39]

Magnetic resonance imaging can be used in at least 2 different ways to inform treatment in LLD. First, the imaging markers may advise on the treatment response profile:

[1] Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA
[2] Geriatric Psychiatry Neuroimaging Lab, University of Pittsburgh, Pittsburgh, PA, USA

Corresponding Author:
Carmen Andreescu, Department of Psychiatry, 3811 O'Hara St, Pittsburgh, PA 15213, USA.
Email: andrcx@upmc.edu

individuals with particular imaging markers (eg, increased white matter hyperintensities [WMH] burden) may need higher initial doses of antidepressant. Second, MR markers may advise early on the trajectory of treatment response. Typically, it takes 3 to 4 weeks to see clinical signs of treatment response, significantly delaying the ability to choose the optimal medication at the optimal dose.[40] Since the standard antidepressants increase synaptic serotonin within hours of first exposure,[41] 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 MRI in Clinical Management of LLD

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 treatments.[44] With respect to the APA's depression-specific guidelines, imaging is only indicated for electroconvulsive therapy's preoperative assessment of relative contraindications that mostly include the above-mentioned conditions.[45] As depression can be misdiagnosed as dementia, especially in the case of pseudo-dementia, the current recommended clinical use of neuroimaging in suspected patients with dementia is also relevant. The APA, American Neurological Association (ANA), and Alzheimer Association (AA) currently support the use of either computed tomography 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 Disease (AD) neuroimaging criteria to stratify patients into stages and AD risk categories. Specifically, MRI-quantified medial temporal lobe atrophy, fludeoxyglucose–positron emission tomographic (PET), and PET amyloid imaging were deemed appropriate to assess for the presence of AD pathophysiological processes that help stratify patients within preclinical AD, mild cognitive impairment due to AD, and dementia due to AD.[48-51] Finally, a joint article recently published by the AA and the Society of Nuclear Medicine and Molecular Imaging provides appropriate use criteria for PET amyloid imaging in a narrow subset of patients in clinical nonresearch settings. This patient subset includes criteria such as early-onset progressive dementia, atypical clinical course, or an etiologically mixed presentation.[52]

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 functional connectivity (FC) changes.[53,54] Much of this work stems from the vascular depression hypothesis[55,56] that 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 depression.[56]

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 (less than 60 years), the incidence of cerebrovascular brain changes commonly seen on MRI (ie, WMH) is rare.[57] In midlife, the MRI research has focused on identifying depression-specific functional brain changes. In a series of studies and review articles, Price and Drevets, Mayberg, and Phillips et al[58-60] have proposed functional brain circuit models for depression, which involve altered affective reactivity and regulation, that is, 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 group[61] 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.

Pretreatment 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 echocardiogram or magnetization prepared rapid gradient echocardiogram 3-dimensional acquisition) was used for assessing gray matter; T2-weighted fluid-attenuated inversion recovery imaging was used to assess ischemic white matter burden by estimating the

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[10]	41 Patients with depression 22 remitters (71.0 ± 5.6) 19 Nonremitters (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	Nonremitters demonstrated significantly smaller pretreatment dorsal and rostral anterior cingulate GM volumes
	Hsieh et al[30]	60 Patients with depression 22 Remitters (66.1 ± 5.0) 38 Nonremitters (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[31]	42 Patients with depression 19 Responders (68.0 ± 4.7) 23 Nonresponders (72.4 ± 7.5)	Randomized to 12-week course of either venlafaxine or nortriptyline Response: reduction in at least 50% of score on MADRS or a final score of 10 or less on MADRS	Nonresponders demonstrated no significant difference in volumes of GM, WM, WMH, orbitofrontal cortex, or hippocampus
	Bella et al[24]	89 Patients with depression 26 Remitters (68.1 ± 7.1) 63 Nonremitters (71.4 ± 7.4)	12-Week course of escitalopram Remission: complete functional recovery or HDRS (17-item) score <7 after 12 weeks of treatment	Nonremitters demonstrated significantly greater deep WMH than remitters
	Gunning-Dixon et al[11]	42 Patients with depression 22 Remitters (69.6 ± 4.7) 20 Nonremitters (71.2 ± 7.0) 25 Control participants (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	Nonremitters demonstrated significantly greater signal WM and subcortical nuclei hyperintensities burden compared to remitters and controls.
	Hickie et al[12]	19 Patients with depression(64.4, range 28-86)	Patient-specific pharmacologic treatment regimen throughout inpatient admission (mean = 15.7 weeks) Remission not defined	Improvement in depressive symptoms was significantly negatively correlated with pretreatment DWMH, PVH, and total hyperintensity severities
	Salloway et al[36]	59 Patients with depression (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[15]	190 Patients with depression 72 Remitters (69.2 ± 7.7) 118 Nonremitters (67.6 ± 6.7)	12-week course of sertraline Remission: MADRS score <7 after 8 weeks of treatment	Nonremitters 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[37]	75 Patients with depression(75.7) 24 Control participants (74.9 ± 6.3)	12-Week course of nonuniform 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[16]	38 Patients with depression 10 Remitters (64.7 ± 6.5) 28 Nonremitters (66.5 ± 7.9)	Randomized to 12-week treatment course of either sertraline or nortriptyline Remission: HDRS (24-item) score < 7 for 2 consecutive observations	Nonremitters were significantly more likely to have DWMH, PVH, and total hyperintensity volumes classified as high
Fractional anisotropy	Alexopoulos et al[21]	13 Patients with depression(range 60-77) 8 Remitters 5 Nonremitters	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[22]	48 Patients with depression 25 Remitters (70.1 ± 5.5) 23 Nonremitters (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	Nonremitters demonstrated significantly decreased FA throughout WM
	Taylor et al[38]	74 Patients with depression 37 Remitters (65.8 ± 5.7) 37 Nonremitters (70.5 ± 8.0)	12-Week course of sertraline Remission: MADRS score <10 at any assessment	Nonremitters demonstrated significantly greater FA in anterior cingulate cortices frontal gyri

Abbreviations: *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); 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

volume of WMH; white matter integrity was assessed in these studies using diffusion tensor imaging and calculating fractional anisotropy (FA) that is a marker of myelin integrity.

The earliest report that we identified was by Hickie et al,[12] which studied 19 older adults with depression and found that total WMH burden and 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 scores.[15] After 8 weeks of treatment, there was no significant difference in WMH burden between the remitters and the nonremitters, 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 MADRS, 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 (eg, cognitive performance) may be involved in attaining remission.

A smaller literature has examined with mixed results of other brain markers (gray matter volume and FA) as predictors of treatment response. Of the 3 studies, 2 found that anterior cingulate cortex and hippocampus gray matter volume were associated with poorer response,[10,30] but the third study[31] did not a 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: 2 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 outcomes.[38] 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 Midlife Depression

Since the literature on fMRI predictors of treatment response in LLD is somewhat sparse, we first review the literature on midlife depression (Table 2), which sets the context for reviewing the smaller number of studies in LLD. We review 8 studies in which fMRI activation is correlated with treatment response.[26-29,32-35] As with the structural MRI studies described earlier, there is significant variability among these studies in the definitions of response or remission; these are in the table 2. The studies are divided into those that examine FC while the participant is awake but resting (ie, not performing a particular task) and studies that use a cognitive or affective task to probe particular circuits.

The 2 resting-state FC studies we reviewed found that resting-state fMRI markers were significantly associated with response to antidepressant treatment in a group of midlife individuals with MDD.[27,35] The study by Lui et al[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 nonresponders had significantly increased FC between the left amygdala and the cingulate cortex and between the right insula and the cingulate and precuneus. The study by Franco et al[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 6 task-based fMRI treatment studies of midlife depression, 5 using different affective tasks and 1 using a cognitive task.[26,28,29,32-34] All of these studies reported that lower pretreatment 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[34] show that lower orbitofrontal cortex (OFC) and motor FC during an emotional face–matching task were associated with poorer treatment outcome; the reverse pattern was observed for OFC and cerebellum FC.

Functional MRI Treatment Studies in LLD

As noted earlier, there are fewer fMRI treatment studies of LLD. We found a total of 5 studies that are reviewed in Table 3.[19,20,23,25,39] This includes 2 studies of resting-state fMRI[20,23] and 3 task-based fMRI studies (1 using a cognitive task and 2 using affective tasks).[19,25,39] These studies generally replicate the fMRI patterns of depression and treatment response previously reported for midlife 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 regardless of the task being affective or cognitive. The 2 resting-state fMRI studies found that decreased activity within the DMN was associated with poorer treatment outcomes.[20,23] The study of Andreescu et al[23] also reported that increased FC between the posterior cingulate and the striatum was associated with poorer treatment response.

Conclusion

In summary, the preponderance of the MRI literature on treatment response in LLD has focused on structural MR following

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[35]	60 Patients with depression 32 Nonresponders (32 ± 10) 28 Responders (33 ± 11) 48 Control participants (35 ± 12)	Patient-specific, 12-week pharmacotherapy treatment regimen Response: reduction >50% in HDRS (17-item) score after 6 weeks of treatment	Resting state	Pretreatment Nonresponders demonstrated significantly greater FC between the left amygdala and cingulate cortex and between the right insula and cingulate and precuneus
	Franco et al[27]	45 Patients with depression	Randomized to 12-week course of either escitalopram or CBT Response not defined	Resting state	Pretreatment 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 parahipoocampus 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[26]	17 Patients with depression (44.1 ± 8.36)	8-Week course of fluoxetine Remission not defined	Visual presentations of varying intensities of sadness	Pretreatment Decreased rate of remission was significantly associated with lower activation in anterior cingulate cortex
	Fu et al[29]	19 Patients with depression (43.2 ± 8.8) 19 Control participants (42.8 ± 6.7)	8-Week course of fluoxetine Response not defined	Visual representations of varying intensities of happiness	Pretreatment Lower response capacity in hippocampus and extra-striate visual regions was significantly associated with decreased symptomatic improvement
	Fu et al[28]	19 Patients with depression (43.2 ± 8.8) 19 Control participants (42.8 ± 6.7)	8-Week course of fluoxetine Remission not defined	Visual presentations of varying intensities of sadness	Pretreatment A trend towards statistical significance was noted in the ability of whole brain neural activity to predict remission
	Langenecker et al[32]	20 Patients with depression (41.0 ± 12.2) 22 Control participants (34.2 ± 11.0)	10-Week course of escitalopram Remission not defined	Parametric go/no-go task A contextual inhibitory control task	Pretreatment 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.[33]	8 Patients with depression (33.1 ± 9.0) 8 Control participants (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 that patients were required to judge in relation to themselves and society	Posttreatment Patients with depression in aggregate experienced a significant decrease in symptom severity (according to MADRS and BDI scores) Patients with depression posttreatment compared to pretreatment demonstrated significantly greater activation of left dLPFC during societal evaluations
	Lisiecka et al[34]	23 Patients with depression 12 Responders (34.4 ± 8.8) 11 Nonresponders (43.8 ± 8.2)	Randomized to 4-week course of either venlafaxine or mirtazapine Response: 50% drop in HDRS score between initial and follow-up assessments	Emotional face–matching task	Pretreatment Nonresponders demonstrated significantly greater OFC-cerebellum connectivity, and lower OFC-left motor area connectivity compared to responders

Abbreviations: BDI, Beck 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 Response/ Remission Definition	Task	Findings
Resting state	Alexopoulos et al[20]	16 Patients with depression 8 Remitters (67.9 ± 4.7) 8 Nonremitters (70.1 ± 6.3) 10 Control participants (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	Pretreatment Decreased rate of remission significantly predicted by low resting FC within Cognitive Control Network
	Andreescu et al[23]	21 Patients with depression 10 Responders (67.9 ± 4.9) 11 Nonresponders (68.5 ± 7.9) 46 Control participants (72.9 ± 7.9)	12-Week course of venlafaxine, duloxetine, escitalopram Response: HDRS score ≤10 at the end of treatment	Resting state	Pretreatment 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 Posttreatment Non-responders compared to responders demonstrated a significantly greater FC within the left striatum
Functional Task	Aizenstein et al[19]	13 Patients with depression (69.1 ± 5.5) 13 Control participants (68.8 ± 5.79)	12-Week course of paroxetine Remission not defined	Preparing to overcome prepotency task (specific for the cognitive control network)	Pretreatment Patients with depression demonstrated significantly decreased activity in dLPFC and lower FC between dLPFC and dACC Posttreatment Patients with depressionin aggregate experienced a significant decrease in symptom severity (mean HDRS: 19.7 → 7.5) Patients with depression posttreatment demonstrated significantly increased activity in dLPFC compared to depressed patients pre-treatment
	Brassen et al[25]	13 Patients with depression (66.4 ± 6.1) 13 Control participants (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	Pretreatment Patients with depressiondemonstrated significantly decreased neural response in vmPFC during the emotional evaluation of negative words compared to positive words Posttreatment 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[39]	12 Patients with depression (69.1 ± 6.0) 15 Remitted patients (70.8 ± 5.5) 20 Control participants (73.1 ± 5.3)	Patients with acute depression 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	Posttreatment Acutely depressed patients compared to control participants 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

Abbreviations: 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.

the framework of the vascular depression hypotheses.[55] These studies support the view that loss of brain volume and white matter integrity was associated with poorer treatment outcomes. The findings are most consistent for WMH burden. However, since many of the same age-related etiopathologic pathways (eg, 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 midlife populations. These studies, which have used both resting-state and task-based fMRI, have reported that lower task-based activity in the prefrontal cortex and limbic regions was associated with poorer outcome. The resting-state fMRI results are topographically selective, showing that both increased and decreased FC were 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.[23]

In conclusion, there is a growing literature focused on both structural and fMRI 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 (eg,[62]). Future studies, including randomized clinical trials, are needed to evaluate the clinical potential of MRI markers of treatment response.

Authors' Note

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References

1. Casten RJ, Rovner BW, Shmuely Dulitzki Y, Pasternak RE, Pelchat R, Ranen N. Predictors of recovery from major depression among geriatric psychiatry inpatients: the importance of caregivers' beliefs. *Int Psychogeriatr*. 1999;11(2):149-157.
2. Garcia Pena C, Wagner FA, Sanchez-Garcia S, et al. Late-life depressive symptoms: prediction models of change. *J Affect Disord*. 2013;150(3):886-894.
3. Hinrichsen GA, Hernandez NA. Factors associated with recovery from and relapse into major depressive disorder in the elderly. *Am J Psychiatry*. 1993;150(12):1820-1825.
4. Katon W, Unutzer J, Russo J. Major depression: the importance of clinical characteristics and treatment response to prognosis. *Dep Anxiety*. 2010;27(1):19-26.
5. Mulsant BH, Houck PR, Gildengers AG, et al. What is the optimal duration of a short-term antidepressant trial when treating geriatric depression? *J Clin Psychopharmacol*. 2006;26(2):113-120.
6. Nelson JC, Delucchi KL, Schneider LS. Moderators of outcome in late-life depression: a patient-level meta-analysis. *Am J Psychiatry*. 2013;170(6):651-659.
7. Reynolds CF, Dew MA, Pollock BG, et al. Maintenance treatment of major depression in old age. *N Engl J Med*. 2006;354(11):1130-1138.
8. Andreescu C, Reynolds CF 3rd. Late-life depression: evidence-based treatment and promising new directions for research and clinical practice. *Psychiatr Clin North Am*. 2011;34(2):335-355, vii-iii.
9. Andreescu C, Lenze EJ, Mulsant BH, et al. High worry severity is associated with poorer acute and maintenance efficacy of antidepressants in late-life depression. *Depress Anxiety*. 2009;26(3):266-272.
10. Gunning FM, Cheng J, Murphy CF, et al. Anterior cingulate cortical volumes and treatment remission of geriatric depression. *Int J Geriatr Psychiatry*. 2009;24(8):829-836.
11. Gunning-Dixon FM, Walton M, Cheng J, et al. MRI signal hyperintensities and treatment remission of geriatric depression. *J Affect Disord*. 2010;126(3):395-401.
12. Hickie I, Scott E, Mitchell P, Wilhelm K, Austin MP, Bennett B. Subcortical hyperintensities on magnetic resonance imaging: clinical correlates and prognostic significance in patients with severe depression. *Biol Psychiatry*. 1995;37(3):151-160.
13. Shah PJ, Ebmeier KP, Glabus MF, Goodwin GM. Cortical grey matter reductions associated with treatment-resistant chronic unipolar depression. Controlled magnetic resonance imaging study. *Br J Psychiatry*. 1998;172(6):527-532.
14. Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biol Psychiatry*. 2001;50(9):651-658.
15. Sheline YI, Pieper CF, Barch DM, et al. Support for the vascular depression hypothesis in late-life depression. *Arch Gen Psychiatry*. 2010;67(3):277-286.
16. Sneed JR, Culang-Reinlieb ME, Brickman AM, et al. MRI signal hyperintensities and failure to remit following antidepressant treatment. *J Affect Disord*. 2011;135(1-3):315-320.
17. Ownby RL. Evidence-based medicine and geriatric psychiatry. *Curr Psychiatry Rep*. 2004;6(1):14-19.
18. McGrath CL, Kelley ME, Holtzheimer PE, et al. Toward a neuroimaging treatment selection biomarker for major depressive disorder. *JAMA Psychiatry*. 2013;70(8):821-829.
19. Aizenstein HJ, Butters MA, Wu M, et al. Altered functioning of the executive control circuit in late-life depression: episodic and persistent phenomena. *Am J Geriatr Psychiatry*. 2009;17(1):30-42.
20. Alexopoulos GS, Hoptman MJ, Kanellopoulos D, Murphy CF, Lim KO, Gunning FM. Functional connectivity in the cognitive control network and the default mode network in late-life depression. *J Affect Disord*. 2012;139(1):56-65.
21. Alexopoulos GS, Kiosses DN, Choi SJ, Murphy CF, Lim KO. Frontal white matter microstructure and treatment response of late-life depression: a preliminary study. *Am J Psychiatry*. 2002;159(11):1929-1932.

22. Alexopoulos GS, Murphy CF, Gunning-Dixon FM, et al. Microstructural white matter abnormalities and remission of geriatric depression. *Am J Psychiatry*. 2008;165(2):238-244.
23. Andreescu C, Tudorascu DL, Butters MA, et al. Resting state functional connectivity and treatment response in late-life depression [published online October 18, 2013]. *Psychiatry Res*. 2013.
24. Bella R, Pennisi G, Cantone M, et al. Clinical presentation and outcome of geriatric depression in subcortical ischemic vascular disease. *Gerontology*. 2010;56(3):298-302.
25. Brassen S, Kalisch R, Weber-Fahr W, Braus DF, Büchel C. Ventromedial prefrontal cortex processing during emotional evaluation in late-life depression: a longitudinal functional magnetic resonance imaging study. *Biol Psychiatry*. 2008;64(4):349-355.
26. Chen CH, Ridler K, Suckling J, et al. Brain imaging correlates of depressive symptom severity and predictors of symptom improvement after antidepressant treatment. *Biol Psychiatry*. 2007;62(5): 407-414.
27. Franco AR, Holtzheimer PE, Kelley ME, Dunlop BW, Craighead WE, Mayberg HS.Pretreatment resting state fMRI predicts differential response to CBT or medication. *Biol Psychiatry*. 2011; 69(9):165 S.
28. Fu CH, Mourao-Miranda J, Costafreda SG, et al. Pattern classification of sad facial processing: toward the development of neurobiological markers in depression. *Biol Psychiatry*. 2008;63(7): 656-662.
29. Fu CHY, Williams SCR, Brammer MJ, et al. Neural responses to happy facial experessions in major depression following antidepressant treatment. *Am J Psychiatry*. 2007;164(4):599-607.
30. Hsieh MH, McQuoid DR, Levy RM, Payne ME, MacFall JR, Steffens DC. Hippocampal volume and antidepressant response in geriatric depression. *Int J Geriatr Psychiatry*. 2002;17(6): 519-525.
31. Janssen J, Hulshoff Pol HE, Schnack HG, et al. Cerebral volume measurements and subcortical white matter lesions and short-term treatment response in late life depression. *Int J Geriatr Psychiatry*. 2007;22(5):468-474.
32. Langenecker SA, Kennedy SE, Guidotti LM, et al. Frontal and limbic activation during inhibitory control predicts treatment response in major depressive disorder. *Biol Psychiatry*. 2007; 62(11):1272-1280.
33. Lemogne C, Mayberg H, Bergouignan L, et al. Self-referential processing and the prefrontal cortex over the course of depression: a pilot study. *J Affect Disord*. 2010;124(1-2):196-201.
34. Lisiecka D, Meisenzahl E, Scheuerecker J, et al. Neural correlates of treatment outcome in major depression. *Int J Neuropsychopharmacol*. 2011;14(4):521-534.
35. Lui S, Wu Q, Qiu L, et al. Resting-state functional connectivity in treatment-resistant depression. *Am J Psychiatry*. 2011;168(6): 642-648.
36. Salloway S, Correia S, Boyle P, et al. MRI subcortical hyperintensities in old and very old depressed outpatients: the important role of age in late-life depression. *J Neurol Sci*. 2002;203-204:227-233.
37. Simpson S, Baldwin RC, Jackson A, Burns S. Is subcortical disease associated with a poor response to antidepressants? neurological, neuropsychological and neuroradiological findings in late-life depression. *Psychological Med*. 1998;28(5):1015-1026.
38. Taylor WD, Kuchibhatla M, Payne ME, et al. Frontal white matter anisotropy and antidepressant remission in late-life depression. *PLoS One*. 2008;3(9):e3267.
39. Wang L, Krishnan KR, Steffens DC, Potter GG, Dolcos F, McCarthy G. Depressive state- and disease-related alterations in neural responses to affective and executive challenges in geriatric depression. *Am J Psychiatry*. 2008;165(7):863-871.
40. Gildengers AG, Houck PR, Mulsant BH, et al. Trajectories of treatment response in late-life depression: psychosocial and clinical correlates. *J Clin Psychopharmacol*. 2005;25(4 suppl 1): S8-S13.
41. Harmer CJ, Goodwin GM, Cowen PJ. Why do antidepressants take so long to work? a cognitive neuropsychological model of antidepressant drug action. *Br J Psychiatry*. 2009; 195(2):102-108.
42. Bigos KL, Pollock BG, Aizenstein HJ, Fisher PM, Bies RR, Hariri AR. Acute 5-HT reuptake blockade potentiates human amygdala reactivity. *Neuropsychopharmacology*. 2008;33(13):3221-3225.
43. Rawlings NB, Norbury R, Cowen PJ, Harmer CJ. A single dose of mirtazapine modulates neural responses to emotional faces in healthy people. *Psychopharmacology (Berl)*. 2010;212(4):625-634.
44. Botteron KC, Carter C, Castellanos FX, et al. *Consensus Report of the APA Work Group on Neuroimaging Markers of Psychiatric Disorders*. Arlington, VA: American Psychiatric Association; 2012.
45. Gelenberg AJ, Freeman MP, Markowitz JC, et al. *Practice Guideline for the treatment of patients with Major Depressive Disorder*. Arlington, VA: American Psychiatric Association; 2010.
46. Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: diagnosis of dementia (an evidence-based review): report of the quality standards subcommittee of the american academy of neurology. *Neurology*. 2001;56(9):1143-1153.
47. Rabins PV, Blacker D, Rovner BW, et al. Practice guideline for the treatment of patients with alzheimer's disease and other dementias. *Am J Psychiatry*. 2007;164(12):5-56.
48. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the national institute on aging-alzheimer's association workgroups on diagnostic guidelines for alzheimer's disease. *Alzheimers Dement*. 2011;7(3):270-279.
49. Jack CR, Jr, Albert MS, Knopman DS, et al. Introduction to the recommendations from the national institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):257-262.
50. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the national institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):263-269.
51. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the national institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):280-292.
52. Johnson KA, Minoshima S, Bohnen NI, et al.Appropriate use criteria for amyloid PET: a report of the amyloid imaging task force,

the society of nuclear medicine and molecular imaging, and the Alzheimer's association. *Alzheimers Dement*. 2013;9(1):e-1-16.
53. Sexton CE, Allan CL, Masurier ML, et al. Magnetic resonance imaging in late-life depression. *Arch Gen Psychiatry*. 2013; 69(7):680-689.
54. Vu NQ, Aizenstein HJ. Depression in the elderly: brain correlates, neuropsychological findings, and role of vascular lesion load. *Curr Opin Neurol*. 2013;26(6):656-661.
55. Alexopoulos GS, Meyers BS, Young RC, Kakuma T, Silbersweig D, Charlson M. Clinically defined vascular depression. *Am J Psychiatry*. 1997;154(4):562-565.
56. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Mol psychiatry*. 2013;18(9):963-974.
57. Hopkins RO, Beck CJ, Burnett DL, Weaver LK, Victoroff J, Bigler ED. Prevalence of white matter hyperintensities in a young healthy population. *J Neuroimaging*. 2006;16(3): 243-251.
58. Price JL, Drevets WC. Neural circuits underlying the pathophysiology of mood disorders. *Trends Cogn Sci*. 2012;16(1):61-71.
59. Mayberg HS. Defining the neural circuitry of depression: Toward a new nosology with therapeutic implications. *Biol Psychiatry*. 2007;61(6):729-730.
60. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception II: implications for major psychiatric disorders. *Biol Psychiatry*. 2003;54(5):515-528.
61. Aizenstein HJ, Andreescu C, Edelman KL, et al. fMRI correlates of white matter hyperintensities in late-life depression. *Am J Psychiatry*. 2011;168(10):1075-1082.
62. Steffens DC, Taylor WD, Krishnan KRR. Progression of subcortical ischemic disease from vascular depression to vascular dementia. *Am J Psychiatry*. 2003;160(10):1751-1756.