Applications of magnetic resonance imaging for treatment-resistant late-life depression

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Late-life depression (LLD) is a growing public and global health concern with diverse clinical manifestations and etiology. This literature review summarizes neuroimaging findings associated with depression in older adults and treatment-response variability. LLD has been associated with cerebral atrophy, diminished myelin integrity, and cerebral lesions in frontostriatal-limbic regions. These associations help explain the depression-executive dysfunction syndrome observed in LLD, and support cerebrovascular burden as a pathogenic mechanism. Furthermore, this review suggests that neuroimaging determinants of treatment resistance also reflect cerebrovascular burden. Of the theoretical etiologies of LLD, cerebrovascular burden may mediate treatment resistance. This review proposes that neuroimaging has the potential for clinical translation. Controlled trials may identify neuroimaging biomarkers that may inform treatment by identifying depressed adults likely to remit with pharmacotherapy, identifying individualized therapeutic dose, and facilitating earlier treatment response measures. Neuroimaging also has the potential to similarly inform treatment response variability from treatment with aripiprazole (dopamine modulator) and buprenorphine (opiate modulator).
additional risks of suicide, dementia, and worsened medical comorbidity. Insufficient implementation of recommended interventions and limited access to care results in a greater burden for both patient and caregiver.

Medical and psychiatric comorbidity of LLD

Depression and associated medical and psychiatric comorbidities reciprocally aggravate each other, exacerbating the burden of disability. Frequent disabling symptoms include lack of energy (97.5%), somatic anxiety (91.7%), insomnia (86.5%), suicidality (64.6%), motor retardation (63%), and cognitive impairment (61%). Sleep disturbances independently predict poor response in LLD. Cognitive deficits associated with LLD may be a prodrome of dementia, with cognitive impairment often persisting after remission of affective symptoms. These cognitive impairments include deficits of information processing speed and executive functioning. Suicide is more prevalent in older depressed individuals than in any other age group, and more so in those with cognitive impairment. Comorbid depression frequently complicates medical conditions prevalent in older adults, such as stroke, hip surgery, diabetes, and obesity. Depression also correlates with a fourfold higher rate of death following myocardial infarction.

LLD: underdiagnosed and undertreated

Underdiagnosis worsens the burden of LLD. The stigma of depression may reduce symptom reporting and discussions about emotional distress. By default, primary care physicians (PCPs) are the first line of care. PCPs often lack the training to identify the clinical heterogeneity of LLD. As a result, older adults are less likely to be diagnosed, treated, or referred to mental health specialists than younger patients. Furthermore, the psychosocial realities of aging exacerbate depression. The coupling of caregiver strain with subsequent bereavement at the loss of a loved one may increase depression and mortality risk. Social isolation and disability from medical illness are significant psychosocial risk factors. Although effective treatments exist, undertreatment compromises outcomes. Long therapeutic response times may lead to premature discontinuation of treatment. Finding an optimal therapeutic regimen may take months. Meanwhile, the risks of undertreatment persist: noncompliance, worsening comorbidities, and suicide.

Depression hypotheses: an iterative history

The mechanistic hypotheses of depression are diverse and representative of a multifactorial etiology. The monoamine hypothesis suggests that monoamine deficiencies are responsible for depression. Several circadian rhythm disruption hypotheses have arisen involving phase shift and REM sleep advancement, both of which are affected by monoaminergic antidepressants. The discovery of elevated cortisol in depressed persons led to the hypothesis that dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may contribute to depression. The inflammation hypothesis provided a mechanistic intersection between the HPA axis and monoamines by suggesting that proinflammatory cytokines mediate depression. Cytokines both stimulate the HPA axis and modulate monoamine activity in the brain. Depression in late life is likely a convergence of multiple etiologies. Indeed, the vascular hypothesis accounts for the cumulative cardiovascular effects of inflammatory, immune, and sleep dysregulation, along with the disconnection of monoaminergic circuits affected by cerebrovascular disease.

Vascular hypothesis of depression

Vascular insufficiency was first proposed as a mechanism of mood and executive dysfunction by Binswanger in 1894. The modern vascular depression hypothesis

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**Selected abbreviations and acronyms**

- ACC: anterior cingulate cortex
- CCN: cognitive control network
- dACC: dorsal anterior cingulate cortex
- dLPFC: dorsolateral prefrontal cortex
- FA: fractional anisotropy
- FC: functional connectivity
- LLD: late-life depression
- PFC: prefrontal cortex
- PVWMH: periventricular white matter hyperintensity
- SSRI: selective serotonin reuptake inhibitor
- TRLLD: treatment-resistant late-life depression
- WMH: white matter hyperintensity
bridges the heterogeneous symptomatology of LLD with the aging-related process of cerebrovascular disease and inflammatory/immune dysregulation. The currently accepted pathogenic hypothesis of atherosclerosis and subsequent cerebrovascular disease suggests an immune-mediated chronic inflammatory response to endothelial injury. As such, vascular disease may predispose, precipitate, or perpetuate the symptoms specific to LLD, including cognitive deficits, psychomotor retardation, lack of insight, and disability disproportional to severity of depression. The imaging hallmark of vascular depression is white matter lesions (WMLs), seen on magnetic resonance imaging (MRI) as white matter hyperintensities (WMHs). The clinical expression of vascular depression has been conceptualized as a “depression-executive dysfunction syndrome,” which includes executive function deficits with planning, sequencing, organizing, and abstracting. Cumulative damage by WMLs may disconnect frontostriatal and limbic circuits responsible for mood and executive functions.

Current standard of care for LLD

First-line pharmacotherapy

Expert consensus guidelines point to selective serotonin reuptake inhibitors (SSRIs) as first-line therapy in older adults. Other medications used as first-line pharmacotherapies include: serotonin–norepinephrine reuptake inhibitors (SNRIs), mirtazapine, and bupropion. Prior to 2003, tricyclic antidepressants (TCAs) were the most well-researched antidepressants for older adults. Nortriptyline, a second-generation TCA, has been found to be particularly effective in achieving remission in bereavement-related major depression. A 2006 Cochrane review of pharmacotherapy for unipolar LLD reported no differences in acute efficacy between these different classes of antidepressants.

Efficacy of antidepressants

Despite high placebo response rates in many well-designed controlled trials, antidepressants have proven to be more effective than placebo in treating LLD. A meta-analysis of nontricyclic antidepressants in older adults showed increasing response with longer periods of exposure (response defined as ≥50% improvement from baseline on depression rating scales). Response rates for treatment of 6 to 8 weeks, relative to placebo, ranged from 35% to 45.6% (OR 1.22). Treatment for 10 to 12 weeks elicited response rates ranging from 45.7% to 68.9% (OR 1.73). When remission is achieved after acute LLD, consensus recommends that therapy be continued for 6 to 12 months. A study with paroxetine (an SSRI) found benefit of maintenance therapy of 2 years, including patients in their first lifetime episodes.

Adverse effects of antidepressants

Successful pharmacotherapy demands an acceptable ratio of therapeutic efficacy and side effects, in order to achieve a net benefit and preserve compliance. Older adults are particularly susceptible to anticholinergic effects, orthostatic effects, drug-drug interactions, and drug-comorbidity interactions. Discontinuation rates were categorically higher for antidepressants compared with placebo, and may undercut the efficacy of antidepressant medications. A meta-analysis of antidepressant efficacy in LLD found that discontinuation rates due to adverse effects of pharmacotherapy (such as fatigue, insomnia, gastrointestinal distress, headaches, genitourinary symptoms, and sweating) ranged from 8% to 27% (OR 1.84).

Psychotherapy

Psychotherapy is effective and generally well-tolerated. Expert consensus guidelines endorse psychotherapy along with antidepressant medication as the treatment of choice for LLD. Specifically, cognitive behavioral therapy, problem-solving therapy, interpersonal psychotherapy, and supportive psychotherapy are first-line psychosocial interventions. With mild depression and dysthymia, psychotherapy may be first-line treatment without pharmacotherapy. With treatment-resistant depression, a systematic review demonstrated the utility of psychotherapy compared with pharmacologic monotherapy. While the evidence may be insufficient to recommend psychotherapy as monotherapy or as augmentation to pharmacotherapy, it has been observed that the psychotherapy may reduce attrition and improve medication adherence, resulting in better clinical outcomes.
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Treatment-resistant LLD: pharmacological strategies

Up to one third of depressed older adults experience treatment-resistant late-life depression (TRLLD). There are two divergent options for escalating therapy in TRLLD. The first involves changing to a different class of medication. The second involves augmentation pharmacotherapy, if the first-line agent has led to partial response. Atypical antipsychotics (aripiprazole and olanzapine) are the only approved augmentation agents for TRLLD. Proposed involvement of D3 dopaminergic receptors in the depression-executive dysfunction syndrome makes agonism of that receptor a logical target. Other commonly used augmentation agents include lithium, thyroid hormone, and methylphenidate.

Treatment-resistant LLD: somatic interventions

Nonpharmacologic somatic interventions may also be used for TRLLD. Electroconvulsive therapy (ECT) is the most effective treatment for LLD, successful in 60% to 80% of cases of treatment-resistant depression. ECT has an important role in depression with suicidality and psychosis. Vagal nerve stimulation and transcranial magnetic stimulation are two other therapies for pharmacotherapy-resistant depression, FDA-approved in 2005 and 2008, respectively.

Neuroimaging in depression: current recommendations

The current indicated role of neuroimaging in depression by the American Psychiatric Association is as part of the safety assessment for ECT. MRI or computed tomography should be used to rule out neuroanatomical conditions (eg, space-occupying lesions) that would contraindicate ECT. Moreover, neuroimaging may be used to identify conditions with depressive symptoms that may not respond to conventional depression therapy, such as neoplasms, hydrocephalus, or marked atrophy.

Neuroimaging: potential clinical role in LLD

Support for the clinical potential of neuroimaging

The purpose of this review is to present findings from the recent literature that substantiate the potential clinical role of neuroimaging in LLD to inform therapeutic decision-making and assess therapeutic efficacy.

A growing body of literature has associated neuroimaging findings with depression subtypes and treatment response. Within the framework of the vascular hypothesis, imaging has provided insights into the etiologies, neuroanatomical distribution, and neuropharmacology of LLD. Yet, there is a paucity of controlled trials testing the efficacy of neuroimaging biomarkers in treatment selection and therapeutic assessment. There is as-yet unrealized potential for the translation of neuroimaging from the laboratory into the clinic. Controlled trials are needed to bring about the evidence-based recommendations required for clinical implementation.

Clinical neuroimaging for LLD: proposed therapeutic mechanisms

A potential clinical use of neuroimaging may be to identify the type(s) of therapy most likely to induce remission and shorten the time needed to arrive at optimal dosing. Specifically, the development of clinically validated imaging biomarkers might be used to identify older depressed adults most and least likely to respond to pharmacotherapy. These biomarkers may help determine the best initial dose of antidepressant pharmacotherapy. In order to guide early dosing adjustments, neuroimaging can potentially identify brain changes associated with effective dosing. This could reduce the lag between onset of treatment and clinical response. Overall, the goal is to develop neuroimaging biomarkers that inform the best initial therapy, decrease time between treatment onset and response, and increase remission rates for LLD.

Neuroimaging biomarkers of therapeutic response and disease progression

Studies using various MRI modalities have identified potential neuroimaging biomarkers associated with LLD, remission, and treatment response. These findings are reviewed below.

Structural MRI: description

Of neuroimaging modalities available, MRI is best suited for the subtle pervasive neuroanatomical changes
of LLD. MRI exposes the brain to pulsatile magnetic fields utilizing large magnets. Protons within water molecules of brain tissue are excited by this magnetic field. Excited protons return to an equilibrium state in multiple ways (relaxations), each of which emits energy. This energy is detected by the MRI scanner and used for anatomic 3-D reconstruction with high spatial resolution. Different MRI pulse sequences exploit different relaxations in order to acquire images with contrast specific for the tissues of interest. The time required to complete these relaxations is characterized by the time constants, $T_1$ and $T_2$. $T_1$-weighted images have excellent gray-white matter contrast. $T_2$-weighted images have high white matter contrast and are used to detect white matter lesions in the brain. Diffusion tensor imaging (DTI) measures the directionality of water diffusion to assess myelin integrity, quantified as fractional anisotropy (FA).

### Structural MRI associations with LLD: regional atrophy

A review of the literature comparing nondemented adults with LLD to controls has shown widespread regions of atrophy have been repeatedly observed in LLD (*Table I*). A recent meta-analysis\(^6\) assessed ob-

| Author (year) | Sample: size, age, description | Findings: regional volume associations with LLD |
|---------------|---------------------------------|-----------------------------------------------|
| Andreescu (2008)\(^8\) | 71 depressed patients (72.2±6.2) - 32 control subjects (71.0±6.7) | LLD was associated with smaller volumes of frontal lobe areas (superior orbital, orbital, inferior, superior medial, and gyrus rectus), temporal lobe areas (superior, middle, inferior, and pole), parietal inferior area, limbic areas (insula, hippocampus, parahippocampal area, amygdala), basal ganglia (putamen, pallidum) and thalamus, compared with controls. |
| Ballmaier (2008)\(^8\) | 46 depressed patients (71.1±7.0) - 24 early-onset (68.00±5.83) - 24 late-onset (74.5±8.09) - 34 control subjects (72.38±6.93) | LLD was associated with smaller volumes of hippocampus and hippocampal subfields CA1-CA3, compared with controls. |
| Bell-McGinty (2002)\(^7\) | 30 depressed patients (69.3±5.7) - 47 control subjects (66.9±7.3) | LLD was associated with smaller volumes of right hippocampal GM, bilateral middle frontal gyri GM, left ACC WM, and right middle frontal gyrus WM, compared with controls. Volume of hippocampal-entorhinal cortex inversely associated with duration since first onset of depression. |
| Burke (2011)\(^8\) | 30 depressed patients (67.7±6.25) - 54 early -onset (66.1±6.0) - 37 late-onset (70.1±6.6) - 47 control subjects (68.8±6.0) | LLD (both early- and late-onset) was associated with smaller volumes of the bilateral amygdala, compared with controls. |
| Chang (2011)\(^6\) | 88 depressed patients (69.1±5.7) - 35 control subjects (74.5±6.5) | LLD was associated with smaller volumes of bilateral dlPFC GM, compared with controls. |
| Disabato (2014)\(^7\) | 126 depressed patients (70.3±6.9) - 60 early-onset (69.4±6.48) - 66 late-onset (71.1±7.35) - 50 control subjects (age not reported) | LLD (both early- and late-onset) was associated with smaller volumes of frontal lobe areas (frontal pole, superior frontal gyrus, middle frontal gyrus) and limbic areas (amygdala, hippocampus, anterior cingulate), compared with controls. |
| Egger (2008)\(^7\) | 14 depressed patients (71.4±7.4) - 20 control subjects (72.3±7.77) | LLD was associated with smaller volumes of GM in frontal areas (bilateral medial orbitofrontal cortex) and limbic areas (right rostral hippocampus, right amygdala), compared with controls. |
| Janssen (2004)\(^7\) | 14 depressed patients (64.0±10.90) - 20 control subjects (62.37±11.38) - women only | LLD was associated with smaller volumes of right hippocampus, compared with controls. |

*Table I.* Structural MRI associations with late-life depression (LLD): regional atrophy. CA, cornu ammonis; GM, gray matter; ACC, anterior cingulate cortex; WM, white matter; dlPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex
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Observations of atrophy in the various regions associated with LLD. Significant atrophy was found within the orbitofrontal cortex (OFC), hippocampus, putamen, and thalamus. Atrophy of the caudate presented a trend toward significance. In spite of variability within the literature, the most frequently observed regions of atrophy in LLD are the frontal lobe, limbic system, basal ganglia, and thalamus.

Within the frontal lobe, atrophy has been observed in the OFC, and the anterior cingulate cortex (ACC). Volumetric decreases of the dorsolateral prefrontal cortex (dLPFC) and subregions of the dLPFC have been also been observed. An intricate frontal subregion analysis by Andreescu specifically associated volume loss in specific regions of the frontal lobe, including the dLPFC (frontal superior and superior middle areas), with duration of depression.

In limbic structures, hippocampal atrophy has been most frequently observed. Hippocampal subfields specifically affected include CA1–CA3, dentate gyrus, and subiculum. Atrophy of the amygdala has also been observed. Basal ganglia atrophy has been described within the caudate, putamen, and pallidus.

Structural MRI associations with LLD: hyperintensities

WMLs are markers of cerebrovascular burden associated with aging, hypertension, cardiovascular dysautonomia, ischemia, oligemia, and diabetes. WMLs are identified on T2-weighted MRI as WMHs and are a hallmark of vascular depression.

| Study          | Subjects                                      | Results                                                                 |
|---------------|-----------------------------------------------|-------------------------------------------------------------------------|
| Krishnan (1993) | 25 depressed patients (74.1±6.6) 20 control subjects (72.5±3.6) | LLD was associated with smaller volumes within the basal ganglia (caudate and putamen), compared with controls. |
| Lavretsky (2007) | 43 depressed subjects (70.67±7.7) 41 control subjects (72.19±7.27) | LLD was associated with smaller volumes within the GM of the bilateral orbitofrontal cortex and the WM of the left orbitofrontal cortex, compared with controls. |
| Lehmbeck (2008) | 21 depressed patients (66.05±6.3) - women only 13 control subjects (65.15±3.2) - women only | LDD was associated with less density in subgenual ACC, compared with controls. |
| Lloyd (2004)   | 51 depressed patients (74.0±6.3) - 23 early-onset (72.7±6.7) - 28 late-onset (75.1±5.8) 39 control subjects (73.1±6.7) | Late-onset LLD was associated with smaller volumes of bilateral hippocampi, compared with controls. |
| Sheline (1996) | 10 depressed patients (68.5±10.4) 10 control subjects (68.0±9.5) | LLD was associated with smaller volumes of bilateral hippocampi, compared with controls. Hippocampal volume was negatively correlated with duration of depression. |
| Smith (2009)   | 16 depressed patients (65.3±9.1) 13 control subjects (67.4±7.4) | LLD was associated with smaller GM volumes of the bilateral caudate, right thalamus, left precuneus, left supramarginal gyrus, and left cuneus, compared with controls. |
| Taylor (2007)  | 226 depressed patients (70.0±7.4) 144 control subjects (70.3±6.5) | LLD was associated with smaller volumes of bilateral OFC, compared with controls. |
| Zhao (2008)    | 61 depressed (65.8±5.5) - 37 non-remitted (65.1±5.3) - 24 remitted (66.9±5.7) 43 control subjects (69.0±5.5) | Non-remitted LLD was associated with smaller volume in the left hippocampus, compared with both controls and subjects with remitted LLD. Although changes could not be pinpointed to specific hippocampal subfields, non-remitted LLD was roughly associated with contraction in CA1, and CA2, while both remitted and non-remitted LLD was roughly associated with contraction of the dentate gyrus and expansion of the subiculum and CA2-3, compared with controls. |

Table I. Continued.
associated with greater hyperintensity volume (Table II). A meta-analysis observed that older adults with depression (onset at any age) had 2.15 and 1.92 greater odds of periventricular WMH (PVWMH) and deep WMH (DWMH), respectively, when compared with healthy age-matched controls. The odds were steeper in adults with late-onset depression, whose odds of PVWMH and DWMH were 2.57 and 4.51 times greater, respectively. Similarly, PVWMH and DWMH have also been associated with cognitive decline in older adults.56 More recent studies of LLD have found WMH in specific tracts connecting the frontal lobe with limbic structures and the basal ganglia, including the cingulum bundle, uncinate fasciculus, and superior longitudinal fasciculus.

**Structural MRI associations with LLD: white matter integrity**

DTI quantifies myelin tract integrity as functional FA. Decreased FA implies loss of myelin integrity, which may be mediated by inflammatory, immune, or cerebrovascular processes.101 FA deficits in LLD have been found in fronto-subcortical and fronto-limbic tracts, including the uncinate fasciculus, anterior thalamic radiation, superior longitudinal fasciculus, and PCC (Table III). These deficits are congruent with pathways implicated in the depression-executive dysfunction syndrome of LLD.45,46

**Structural MRI association with LLD treatment outcomes: regional atrophy**

In addition to investigating potential neuroimaging biomarkers specific to LLD, studies have sought structural MRI predictors of antidepressant treatment response. Smaller hippocampal volumes have been associated with poor therapeutic outcomes in LLD (Table IV). Indeed, smaller hippocampal volumes at baseline predicted treatment resistance among 60 depressed older adults after 12 weeks of protocolized pharmacotherapy.106 Similarly, of 92 depressed older adults receiving 2 years of protocolized pharmacotherapy, nonremitters were found to have smaller hippocampi at 2 years than at baseline.107 In that same study, a positive correlation was observed between the rate of hippocampal atrophy and Montgomery-Åsberg Depression Rating Scale (MADRS) scores.107 Additionally, lower baseline gray matter volume in the dorsal and rostral ACC were associated with nonremission after 12 weeks of escitalopram in a cohort of 41 depressed older adults.108

| Author (year) | Sample: size, age, description | Findings: hyperintensity associations with LLD |
|---------------|--------------------------------|-----------------------------------------------|
| Dalby (2010)10 | 22 depressed patients (57.4±4.6) 22 control subjects (59.2±7.3) | LLD with WMHs was associated with greater WMH density in the left superior longitudinal fasciculus and the right frontal projections of the corpus callosum, compared with controls with WMHs. |
| Greenwald (1996)91 | 48 depressed patients (74.6±6.1) 39 control subjects (72.6±6.4) | LLD was associated with greater subcortical gray matter hyperintensities, compared with controls. |
| Kumar (2000)92 | 51 depressed patients (74.3±6.56) 30 control subjects (69.43±6.09) | LLD was associated with greater whole brain hyperintensity volume, compared with controls. |
| Sheline (2008)98 | 83 depressed patients (68.7±7.6) 32 control subjects (69.7±6.0) | LLD was associated with greater hyperintensities in white matter tracts, including the superior longitudinal fasciculus, fronto-occipital fasciculus, uncinate fasciculus, extreme capsule, and inferior longitudinal fasciculus, compared with controls. Hyperintensity volumes in the superior longitudinal fasciculus, fronto-occipital fasciculus, and uncinate fasciculus were negatively correlated with executive function in depressed patients, but not in controls. |
| Taylor (2005)90 | 253 depressed patients (70.48±6.23) 146 control subjects (69.85±7.54) | LLD was associated with greater total bilateral hemispheric white and grey matter hyperintensities. |
| Taylor (2011)97 | 54 depressed patients (68.9±5.6) 37 control subjects (73.8±5.8) | LLD was associated with greater hyperintensities in the left upper cingulum near the cingulate gyrus, compared with controls. |

Table II. Structural MRI associations with late-life depression (LLD). WMH, white matter hyperintensities.
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Structural MRI association with LLD treatment outcomes: hyperintensities

In accordance with the vascular hypothesis, WMH burden is associated with poor therapeutic outcomes in LLD (Table V). Total brain WMH burden at baseline was associated with treatment resistance in two studies of 42 and 30 depressed older adults, who received 12 weeks of antidepressant pharmacotherapy. Nonremitters at baseline were found to have greater severity of DWMH, PVWMH, and subcortical nuclei WMH when compared with remitters after 12 weeks of treatment. More-

| Author (year) | Sample: size, age, description | Findings: FA associations with LLD |
|--------------|--------------------------------|-----------------------------------|
| Dalby (2010) | 22 depressed patients (57.4±4.6) - Late-onset only (onset after 50 years of age) 22 control subjects (59.2±7.3) | LLD severity was positively associated with the intersection of WM tracts by DWMH in the opercular part of the left superior longitudinal fasciculus and the temporal projections of the right uncinate fasciculus. In turn, FA of WM tracts was lower when intersected by WMHs, when compared with WM tracts without WMHs. |
| Sexton (2012) | 36 depressed-remitted patients (71.83±7.71) 25 control subjects (71.16±7.30) | Remitted LLD was associated with lower FA in the anterior thalamic radiation, corticospinal tract, splenium of the corpus callosum, superior longitudinal fasciculus, and uncinate fasciculus, compared with controls. |
| Alves (2012) | 17 depressed-remitted patients (65.53±5.46) 18 control subjects (66.4±3.47) | LLD was associated with lower FA in the right PCC, compared with controls. FA in the right PCC was positively correlated with performance in verbal naming task in depressed patients, but not in controls. |
| Taylor (2007) | 18 depressed patients (70.8±3.1) - 10 early-onset (69.6±2.8) - 28 mid-to-late-onset (72.2±3.4) 19 control subjects (72.2±3.8) | Early-onset depression was associated with lower FA in the left uncinate fasciculus, compared with both controls and patients with mid-to-late-onset LLD. |

Table III. Structural MRI associations with late-life depression (LLD): white matter integrity. WM, white matter; DWMH, deep white matter hyperintensities; FA, fractional anisotropy; WMH, white matter hyperintensities; PCC, posterior cingulate cortex

| Author (year) | Sample: size, age, description | Treatment/definition of remission | Findings: cerebral volume associations with response or remission |
|--------------|--------------------------------|---------------------------------|---------------------------------------------------------------|
| Gunning (2009) | 41 depressed patients - 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-IVTR and HDRS (24-item) | Pretreatment, nonremitters demonstrated smaller dorsal and rostral anterior cingulate GM volumes, compared with remitters. |
| Hsieh (2002) | 60 depressed patients - 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 ≤10 | Pretreatment, subjects in the lowest quartile of right and total hippocampal volumes were less likely to achieve remission than those in the upper three quartiles. |
| Taylor (2013) | 92 depressed patients - 47 remitters (69.3±6.5) - 18 relapsed (70±6.1) - 27 nonremitters (72.1±7.3) 70 control subjects (69.7±6.2) | Patient specific pharmacotherapy based on institutionally developed guidelines for 2 years - Remission: MADRS ≤5 for two consecutive assessments | Decreases in hippocampal volume between pre- and post-treatment were greater in nonremitters, compared with remitters. Rate of hippocampal atrophy was positively correlated with depression severity (MADRS scores). |

Table IV. Structural MRI associations with late-life depression (LLD) treatment outcomes: regional atrophy. SCID-IV-TR, Structured Clinical Interview of DSM-IV Text Revision; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; GM, gray matter
over, greater total brain, deep white matter, periventricular white matter, and subcortical hyperintensities at baseline correlated with nonresponse. Nevertheless, WMH predictions of nonresponse/nonremission were not found in all studies. Janssen et al found no difference between remitters and nonremitters with regards to the burden of subcortical and periventricular hyperintensities at the onset of antidepressant therapy.

### Structural MRI association with LLD treatment outcomes: white matter integrity

Two studies in 48 and 13 older adults with depression found diminished white matter FA at baseline among nonremitting participants relative to participants that remitted after a 12-week course with an SSRI (Table VI). Regions of significance included rostral

| Author (year) | Sample: size, age, description | Treatment/definition of remission | Findings: WMH associations with response or remission |
|---------------|--------------------------------|----------------------------------|-----------------------------------------------------|
| Bella (2010)  | 89 depressed patients - 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 | Pretreatment, nonremitters demonstrated significantly greater deep WMH, compared with remitters. |
| Gunning-Dixon (2010) | 42 depressed patients - 22 remitters (69.61±4.71) - 20 nonremitters (71.18±6.95) 25 control subjects (70.68±5.82) | 12-week course of escitalopram - Remission: no longer meeting criteria for depression on SCID-IVTR and HDRS (24-item) score <7 for 2 consecutive weeks | Post-treatment, nonremitters demonstrated significantly greater total hyperintensity burden, compared with both remitters and controls. Hyperintensity burden did not differ between remitters and controls. |
| Hickie (1995)  | 32 depressed inpatients (64.4, range 28-86) - 20 depressed inpatients age > 50 | Patient specific treatment throughout inpatient admission of 15.8±11.6 weeks. Included pharmacotherapy and/or ECT. - Remission not defined | Pretreatment, the extent of PVWMH, DWMH, and total WMH in depressed inpatients was negatively correlated with treatment response. PVWMH were most negatively correlated for those receiving ECT. DWMH and total WMH were most negatively correlated with those receiving pharmacotherapy. |
| Janssen (2007) | 42 depressed patients - 19 responders (68.0±4.7) - 23 non-responders (72.4±7.5) | Randomized to 12-week course of either venlafaxine or nortriptyline - Response: reduction of at least 50% of MADRS score or a final MADRS score ≤10 | Post-treatment, no differences were demonstrated in the volumes of cerebral GM, cerebral WM, OFC, hippocampi, and total WMHs between responders and nonresponders. |
| Sheline (2010) | 190 depressed patients - 72 responders (69.2±7.7) - 118 non-responders (67.6±6.7) | 12-week course of sertraline - Remission: MADRS score <7 after 8 weeks | Pretreatment, patients with greater WMH burden predicted lower MADRS scores over a 12-week course of pharmacotherapy. Remitters and nonremitters did not differ in WMH burden at onset of treatment. |
| Simpson (1998) | 75 depressed patients (75.7±5.7) 24 control subjects (74.9±6.3) | 12-week course of non-uniform pharmacologic monotherapy - Response: MADRS features of depression, and CGI score ≥ 4 | Early in treatment (between weeks 2 and 4 from onset of treatment), patients with hyperintensities in DWM, basal ganglia, pontine reticular formation were more likely to remit. |
| Sneed (2011) | 38 depressed patients - 10 remitters (64.7±6.5) - 28 nonremitters (66.5±7.9) | Randomized to 12-week treatment course of either: sertraline, nortriptyline - Remission: HDRS (24-item) score <7 for 2 consecutive observations | Pretreatment, patients with high DWMH, PVH, and total hyperintensity volumes were more likely to remit. |

Table V. Structural MRI associations with LLD treatment outcomes: hyperintensities. HDRS, Hamilton Depression Rating Scale; SCID-IV-TR, Structured Clinical Interview of DSM-IV Text Revision; ECT, electroconvulsive therapy; MADRS, Montgomery-Asberg Depression Rating Scale; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders III; WMH, white matter hyperintensities; PVWMH, paraventricular white matter hyperintensities; DWMH, deep white matter hyperintensities; GM, gray matter; DWM, deep white matter WM, white matter; PVH, paraventricular hyperintensities; HDRS, Hamilton Depression Rating Scale; SCID-IV-TR, Structured Clinical Interview of DSM-IV Text Revision; ECT, electroconvulsive therapy; MADRS, Montgomery-Asberg Depression Rating Scale; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders III; WMH, white matter hyperintensities; PVWMH, paraventricular white matter hyperintensities; DWMH, deep white matter hyperintensities; GM, gray matter; DWM, deep white matter WM, white matter; PVH, paraventricular hyperintensities.
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and dorsal ACC, dLPFC, genu of the corpus callosum, parahippocampal white matter, posterior cingulate cortical white matter, and insular white matter. A subsequent study by Taylor et al in 74 subjects with LLD found opposite results. Specifically, nonremitters at baseline had higher FA in the superior frontal gyri and ACC. A possible explanation for this contradiction is that Taylor avoided areas of WMH when choosing regions of interest. Alexopoulos made no reference to avoiding WMH. Areas of WMH have lower FA than unaffected white matter, potentially explaining the discrepancy.

**Functional MRI: description**

Functional MRI is capable of identifying pharmacologic challenges in real time. As such, fMRI has the potential to prognosticate early interventional efficacy (as early as minutes after initiation of pharmacotherapy). Functional MRI can be subdivided into task-based and resting-state modalities. Task fMRI uses blood-oxygen level dependent (BOLD) signal to identify areas of increased synaptic activity. Regions with increased BOLD signal during a predefined task are considered to have functional associations with the performance of the task. Task fMRI can also identify areas of functional connectivity (FC). Distinct regions of the brain are said to be functionally connected if their activations display temporal synchronicity. Resting fMRI, in turn, assesses the activity and FC of resting state networks, such as the default mode network (DMN). Resting state networks are suspended during goal-directed behavior.

**Functional MRI associations with LLD: resting-state fMRI**

Resting-state fMRI has highlighted changes within the DMN and cognitive control network (CCN) in LLD (Table VII). Relative to healthy controls, adults with LLD were observed to have low resting FC within the CCN and high resting FC within the DMN. Regions within the CCN noted for decreased FC were the dorsal ACC (dACC) with the dLPFC. Regions within the DMN with increased FC were the precuneus, subgenual ACC, and ventromedial prefrontal cortex (vmPFC). Alexopoulos et al found FC alterations in the CCN and DMN are congruent with LLD symptomatology. The CCN is thought to mediate goal-directed behavior and inhibition of negative biases, both of which are deficient in LLD. The DMN is thought to mediate self-referential thinking, which is susceptible to negativity bias in LLD.

| Author (year) | Sample: size, age, description | Treatment/definition of remission | Findings: FA associations with response or remission |
|---------------|-------------------------------|----------------------------------|---------------------------------|
| Alexopoulos (2008) | 48 depressed patients - 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 | Pretreatment, eventual nonremitters demonstrated lower FA in multiple frontal limbic brain areas, including the rostral and dorsal anterior cingulate, dLPFC, genu of the corpus callosum, white matter adjacent to the hippocampus, multiple posterior cingulate regions, and insular white matter, compared with eventual remitters. |
| Alexopoulos (2002) | 13 depressed patients (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 | Pretreatment, eventual nonremitters demonstrated lower FA in the frontal white matter above the AC-PC line, compared with eventual remitters. |
| Taylor (2008) | 74 depressed patients - 37 remitters (65.8±5.7) - 37 nonremitters (70.5±8.0) | 12-week course of sertraline - Remission: MADRS score <10 at any assessment | Within 2 weeks of starting treatment, eventual nonremitters demonstrated higher FA within the anterior cingulate and superior frontal gyrus, compared with eventual remitters. |

*Table VI. Structural MRI associations with late-life depression (LLD) treatment outcomes: white matter integrity. DSM-IV, Diagnostic and Statistical Manual of Mental Disorders IV; FA, functional anisotropy; dLPFC, dorsolateral prefrontal cortex; HDRS, Hamilton Depression Rating Scale; AC, anterior commissure; PC, posterior commissure; MADRS, Montgomery-Asberg Depression Rating Scale.*
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Function MRI associations with LLD: task-based fMRI

Task-based fMRI findings complement those of resting-state fMRI. Aizenstein et al used a “preparing to overcome” prepotency task (a variation of the Stroop task specific for the dACC and dLPFC within the CCN) to identify hypoactivity within the dLPFC, and lower FC between dLPFC and dACC in LLD (Table VIII). These findings are congruent with the observation by Alexopoulos et al of diminished resting-state FC within the CCN in LLD. Using an emotional oddball task meant to investigate the relationship between emotional and attentional processing, Wang et al observed task-based differences in DMN activity between acutely depressed, remitted, and healthy older adults. Acute and remitted LLD was associated with lower activation of the ACC, anterior portion of the posterior cingulate cortex (PCC), and inferior parietal areas, compared with controls. Acute LLD had increased deactivation of the posterior PCC and decreased activation of the middle frontal gyrus, when compared with both remitters and healthy controls. Task-based MRI has been further used to substantiate a link between cerebrovascular pathology and functional brain activity in LLD. Specifically, WMH burden was correlated with limbic hyperactivation in an affective reactivity task.

Functional MRI associations with LLD treatment-outcomes: task-based fMRI

Research into the use of resting-state and task-based fMRI to predict and assess therapeutic efficacy in LLD is sparse relative to research of fMRI in mid-life depression (Table IX). Aizenstein et al described the potential utility of task-based fMRI of the prefrontal cortex (PFC) to prognosticate treatment response in LLD. Prior to treatment with an SSRI, 13 participants with LLD had diminished task-based (“preparing to overcome” prepotency task) activity in the dLPFC relative to controls. After a 12-week trial of an SSRI, all 13 participants with LLD experienced symptomatic improvement in aggregate. Moreover, post-treatment task-based activity in the dLPFC increased (ie “normalized”) toward

| Author (year) | Sample: size, age, description | Task | Findings: activity and FC associations with LLD |
|---------------|--------------------------------|------|-----------------------------------------------|
| Aizenstein (2009) | 13 depressed patients (69.1±5.5), 13 control subjects (68.8±5.79) | Preparing to Overcome Prepotency task (specific for the cognitive control network) | Depressed subjects demonstrated decreased activity in dLPFC and lower FC between dLPFC and dACC, relative to controls. |
| Aizenstein (2011) | 33 depressed patients (67.7±5.2), 27 control subjects (71.6±7.5) | Faces and shapes task (shown to activate limbic structures) | Depressed subjects demonstrated increased activation in the subgenual component of the rostral cingulate (BA 25). |
| Wang (2008) | 12 depressed patients (69.1±6.0), 15 remitted patients (70.8±5.5), 20 control subjects (73.1±5.3) | Emotional Oddball task - Patients respond to infrequent attentional targets with sad and neutral pictures as distractors | Subjects with acute LLD and remitted LLD demonstrated decreased activation in the anterior PCC and inferior parietal areas, compared with controls. Acutely depressed subjects demonstrated decreased activity in the right middle frontal gyrus and the posterior PCC, compared with both controls and patients with remitted LLD. |

Table VIII. Functional MRI associations with late-life depression (LLD): task-based fMRI. dACC, dorsal anterior cingulate cortex; dLPFC, dorsolateral prefrontal cortex; FC, functional connectivity; dACC, dorsal anterior cingulate cortex; PCC, posterior cingulate cortex; LLD, late-life depression; BA, Brodmann area

| Author (year) | Sample: size, age, description | Treatment/definition of remission | Findings: FC associations with LLD |
|---------------|--------------------------------|---------------------------------|----------------------------------|
| Alexopoulos (2012) | 16 depressed patients - 8 remitters (69.7±4.7) - 8 nonremitters (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 | Pretreatment, LLD was associated with low resting-state FC in the CCN and high FC in the DMN, compared with controls. |

Table VII. Functional MRI associations with late-life depression (LLD): resting-state fMRI. FC, functional connectivity; CCN, cognitive control network; DMN, default mode network
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dLPFC activity levels of healthy controls.124 Brassen et al also observed the potential prognosticating power of task-based fMRI of the PFC with a similar pre- and postpharmacotherapy study.128 When participants with LLD were asked to evaluate emotional words at baseline, negative words resulted in hypoactivity of the vmPFC relative to positive words. At 7-month follow-up, at which point the majority of subjects experienced symptomatic improvement, the difference in task-based activation between negative and positive words had significantly diminished in magnitude.128 The importance of the PFC was further demonstrated by Wang et al by looking at acute LLD, remitted LLD, and controls using an emotional oddball task. Diminished activation of the middle frontal gyrus was specific to acute LLD, when compared with subjects with remitted LLD and controls.126 Taken together, task-based fMRI studies suggest that LLD is associated with hypoactivity in the PFC, which can diminish the inhibitory influence over associated limbic structures.128,129 Furthermore, “normalization” of PFC hypoactivity (ie, increased activity) is associated with treatment response.

Functional MRI associations with LLD treatment outcomes: resting-state fMRI

A resting-state fMRI study by Alexopoulos et al observed that low FC in the CCN at baseline predicted treatment resistance122 (Table X). A second study by Andreescu et al described how FC within the DMN might predict treatment response in LLD. Specifically, prior to 12 weeks of antidepressant pharmacotherapy, eventual nonresponders had increased FC between the PCC and dACC and cuneus, and decreased FC between the PCC and medial PFC and precuneus, when compared with eventual treatment responders.130 Moreover, increased FC in the left striatum over the course of antidepressant therapy was associated with treatment resistance.130

Mechanisms of psychopathology observed with MRI

Depression in late life is the cumulative expression of multiple etiologies associated with aging.131 For example, the inflammation and immune hypotheses co-exist within a vascular depression framework. Aging induces immune dysregulation,132 which in turn results in a proinflammatory state. Immune dysregulation and chronic inflammation can directly mediate depressive symptoms, cognitive deficits,133,134 and cerebrovascular disease.43 Structural and functional associations with LLD presented in this review support the idea of a depression-executive dysfunction syndrome as a clinical manifestation of vascular depression.

This review of neuroimaging in LLD links hyperintensity burden to structural and functional MRI findings in older adults with depression. LLD is associated with cerebral atrophy, loss of myelin integrity, and cerebrovascular changes observed as WMH burden, which is a hallmark of vascular depression.40,100 WMHs were found along tracts connecting frontal and limbic structures,97-99 which in turn were found to have diminished

| Author (year) | Sample: size, age, description | Treatment/definition of remission | Findings: FC associations with response or remission |
|---------------|---------------------------------|----------------------------------|-----------------------------------------------|
| Alexopoulos (2012)132 | 16 depressed patients - 8 remitters (67.9±4.7) - 8 nonremitters (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 | Pretreatment, low resting FC in the CCN predicted treatment resistance. |
| Andreescu (2013)130 | 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 | Pretreatment, nonresponders demonstrated lower FC between PCC and medial PFC and precuneus, as well as increased FC between PCC and dorsal ACC and cuneus, compared with responders. During treatment and post-treatment, non-response was associated with increased FC in the left striatum, compared with responders. |

Table IX. Functional MRI associations with late-life depression (LLD) treatment outcomes: resting-state fMRI. MADRS, Montgomery-Asberg Depression Rating Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders IV; FC, functional connectivity; CCN, cognitive control network; HDRS, Hamilton Depression Rating Scale; PCC, posterior cingulate cortex; PFC, prefrontal cortex; ACC, anterior cingulate cortex;
myelin integrity. Areas of gray matter connected by these white matter tracts, specifically frontostriatal and limbic areas, were found to have significant atrophy. Resting-state fMRI further outlined the effects of WMH with the observation of diminished FC within frontostriatal-limbic areas that make part of the CCN. Task-based fMRI was able to correlate limbic hyperactivation with WMH burden during an affective reactivity task.

Mechanisms of treatment resistance and response observed with MRI

Pretreatment structural and functional correlates of treatment resistance (atrophy, WMH, FC) appear to associate the heaviest initial burden of pathology with the smallest likelihood for remission. Smaller hippocampal volumes and greater WMH burdens at baseline were associated with eventual treatment resistance, while increased rate of hippocampal atrophy was associated with worsening symptoms of LLD. Whole brain WMHs, PVWMHs, and DWMHs at baseline were associated with treatment resistance. Resting-state fMRI studies found that low FC in the CCN and high FC in the DMN predicted treatment resistance. Task-based fMRI has the potential to be useful in the longitudinal assessment of therapeutic efficacy. Those treated effectively for LLD may have task-based fMRI activity that approaches the activity patterns of healthy controls over time. One could consider this an effective “normalization” of brain activity, or a reversal of depression pathology. An example of this was the association of treatment response with the “normalization” of dLPFC activity in response to an overcoming-prepotency task. That is, at baseline, those with LLD had low task-based activity in the dLPFC relative to healthy controls. Increases in dLPFC activity during the course of therapy was associated with symptomatic improvement.

Sources of variability among studies

MRI studies of LLD are burdened by significant variability. Research methods are one culprit. Among the most variable aspects of experimental design are the following: age cutoffs used to define late-life, subjective symptom inventories, remission criteria, types of antidepressants administered, and tasks used in task-based fMRI.

Cerebrovascular burden: a treatment-resistant etiology of LLD

The most variable factor in the study of LLD is LLD itself. This disease is heterogeneous in its presentation, clinical response, and etiology. The presentation of LLD represents the cumulative burden of various risk-

| Author (year) | Sample: size, age, description | Treatment/definition of remission | Task | Findings: activity and FC Associations with response or remission |
|---------------|--------------------------------|----------------------------------|------|---------------------------------------------------------------|
| Aizenstein (2009) | 13 depressed patients (69.1±5.5), 13 control subjects (68.8±5.79) | 12 weeks of paroxetine - Remission not defined - Depressed group experienced aggregate decrease in symptom severity. (Pretreatment HDRS: 19.7. Post-treatment HDRS: 7.5) | Preparing to Overcome Pre-potency task (specific for the cognitive control network) | Increased activity in the dLPFC between pre- and post-treatment was associated with symptomatic improvement in depressed patients. |
| Brassen (2008) | 13 depressed patients (66.4±6.1), 13 control subjects (65.6±6.1) | Patient specific treatment, including: pharmacotherapy (6 patients), behavioral therapy (2 patients), none (5 patients) - Remission not defined - Symptom severity improved in 12 of 13 depressed subjects. | Emotional evaluation of positive, negative, and neutral words | Pretreatment, depressed patients demonstrated decreased activity in vmPFC during evaluation of negative words compared with positive words. Post-treatment, depressed subjects demonstrated similar activity in vmPFC during evaluation of both positive and negative words. |

Table X. Functional MRI associations with late-life depression (LLD) treatment outcomes: task-based fMRI. HDRS, Hamilton Depression Rating Scale; dLPFC, dorsolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex.
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Nevertheless, the neuroimaging determinants of treatment-resistant LLD were predominantly associated with frontostriatal and limbic areas. Cerebrovascular findings in these specific areas are the hallmark of vascular depression, and help explain the common presentation of older adults with executive dysfunction-depression syndrome. The neuroimaging determinants of treatment resistance may be more than prognostic biomarkers. They may also identify those individuals whose LLD is heavily mediated by cerebrovascular burden. In contrast, those more likely to remit may possess a LLD less reliant on cerebrovascular burden and more heavily mediated by reversible pathogenic processes. The cumulative irreversible burden of cerebrovascular insults may be responsible for treatment resistance for many with LLD.

Potential clinical applications of MRI for LLD

The translation of neuroimaging for clinical use in LLD requires further research. Potential applications of such translational research include the following:

- Identification of the best initial treatment modality: LLD is mediated by the cumulative effect of various pathogenic processes. A potential clinical application of neuroimaging can be to identify structural or functional biomarkers associated with likelihood of response to different types of pharmacotherapy. This may expedite the identification of optimal patient-specific treatment modalities.

- Optimization of initial antidepressant dose: functional MRI can identify changes within the brain within seconds. Dose-dependent amygdala activation responses to IV citalopram have been observed within seconds. It may be possible to use fMRI to identify neuroimaging biomarkers associated with an optimal therapeutic state within the first few hours or minutes after initiating antidepressant therapy.

- Earlier measures of therapeutic efficacy: further clinical research may help translate structural and functional MRI for clinical practice, in order to create individualized “brain maps” for each patient with LLD. Follow-up scans after commencement of therapy (eg, SSRI) can be used to look for “normalization” of the most pathogenic features of a patient’s “brain map.” These iterative scans could then justify early alterations in the course of treatment, and expedite the arrival at optimal therapy.

Novel targets based on vascular depression and executive dysfunction-depression syndrome

The frontostriatal-limbic distribution seen in vascular LLD lends itself to therapeutic agents targeted at unconventional receptors. Specifically, dopamine D3 receptors, kappa-opiate receptors, and mu-opiate receptors may be promising targets.

Aripiprazole: partial D3 receptor agonist

The involvement of the frontostriatal-limbic pathways in vascular LLD has been well documented, as have been the associated symptoms of depression and executive dysfunction. The atypical antipsychotic, aripiprazole, is currently not a first-line intervention for LLD. Neuroimaging results, however, support the potential therapeutic utility of expanding the role of a D3 partial agonist, like aripiprazole. Those with predominantly vascular depression may have the most to gain, since MRI studies have shown atrophy, diminished functional connectivity, heavy WMH burden, and task-based fMRI hypoactivity within frontostriatal and limbic areas in LLD. These regions appear to be crucial for vascular depression, and are replete with D3 receptors. Those with executive dysfunction-depression syndrome in late life are more often resistant to first-line therapies, and may benefit from interventions targeting D3 receptors. Animal studies have shown that D3 receptor agonists reduce depressive symptoms. Moreover, an open-label pilot study found aripiprazole effective at treating TRLLD. Further evaluation with a randomized control trial has recently been completed by the authors, suggesting the efficacy and safety of aripiprazole in older adults, whose episodes of major depression did not respond fully to venlafaxine.

Buprenorphine: kappa-opiate receptor antagonist and mu-opiate receptor partial agonist

Neuroimaging findings in LLD also support the potential use of buprenorphine for those with vascular depression and TRLLD. Buprenorphine is a kappa-opioid receptor antagonist and mu-opioid receptor partial agonist. Frontostriatal and limbic findings in LLD support mu and kappa receptors as therapeutic targets,
as kappa receptors have been found throughout frontostriatal and limbic structures.139,140 Mu receptors are also plentiful in limbic regions of the rhesus monkey, including the globus pallidus, cingulate cortex, insula, caudate, and putamen.142 Agonism of kappa receptors have been found to induce depressive symptoms in rats, while antagonism reduces depressive symptoms in forced swim tasks.142 Although venlafaxine induces antidepressant effects in mice, this effect is diminished in mu-receptor knockout mice.143 Furthermore, paroxetine, an SSRI, increases mu-receptor density in mice, suggesting a connection between mu-opiate receptors and the antidepressant effects of SSRIs.144 The therapeutic potential of buprenorphine in LLD is further supported by the observed decrease in mu-receptor density with age.145,146 A recent open-label trial in older adults found buprenorphine to be safe and effective in the treatment of LLD.147 Further evaluation with randomized control trials are warranted to generate the evidence base required for clinical application of this novel approach.

Proposed steps for translation of neuroimaging into clinical practice

Other neuroimaging modalities: magnetic resonance spectroscopy and positron-emission tomography

This review only summarizes structural and functional MRI findings in LLD. Nevertheless, other imaging modalities have been applied in the research of LLD: positron emission tomography (PET) and magnetic resonance spectroscopy (MRS). PET is used to make dynamic measurements of neurotransmitter receptor occupancy and other potential molecular mediators of LLD. In-vivo MRS can measure the relative quantities of molecules in specific regions of the brain, including membrane-bound molecules, intracellular molecules, lipids, enzymes, amino acids, and neurotransmitters. These imaging modalities can serve to further refine our understanding of the etiological mechanisms of LLD.148-150

Improved technology

Technological innovation is accelerating. Most studies of depression have used magnets that are 3 Tesla or smaller. As more powerful magnets become the new standard, spatial resolution, temporal resolution, and image contrast will improve. Innovations in image processing algorithms will further improve signal-to-noise ratios. The advancement of technology will reduce data variability, and allow for more precise observations of disease processes.

Neuroimaging as a clinical tool for optimizing any clinical intervention

The studies in this review overwhelmingly use SSRIs or SNRIs (at predominantly serotonergic doses) for treatment of LLD. As such, the neuroimaging findings in this review primarily support the use of MRI as a clinical tool for optimizing serotonergic pharmacotherapy. MRI can potentially identify the best initial dose of an SSRI or SNRI. Follow-up scans could then inform whether a starting dose is sufficient, or whether changes in a person’s brain are associated with a trajectory toward treatment response. Nevertheless, this paradigm may be applied to other therapeutic modalities. Proper research can identify neuroimaging biomarkers associated with the likelihood of treatment response for other medications such as aripiprazole or buprenorphine. In order to translate neuroimaging into clinical practice, randomized controlled trials are needed to test how well neuroimaging biomarkers can inform treatment selection and modification.

Acknowledgments: Supported in part by P30 MH90333, R01 MH076079, R34 MH101371, T32 MH19986, U1L TR000005, and the UPMC Endowment in Geriatric Psychiatry.

REFERENCES

1. Ferrari AJ, Charlson FJ, Norman RE, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. PLoS Med. 2013;10(11):e1001547.
2. Luppia M, Sikorski C, Motzek T, Konnopka A, Konig HH, Riedel-Heller SG. Health service utilization and costs of depressive symptoms in late life - a systematic review. Curr Pharm Des. 2012;18(36):5936-5957.
3. Stevens JA, Hasibrook L, Durant TM, et al. Surveillance for injuries and violence among older adults. MMWR CDC Survell Summ. 1999;48(8):27-50.
4. Charney DS, Reynolds CF, 3rd, Lewis L, et al. Depression and Bipolar Support Alliance consensus statement on the unmet needs in diagnosis and treatment of mood disorders in late life. Arch Gen Psychiatry. 2003;60(7):664-672.
5. Bruce ML, Ten Have TR, Reynolds CF 3rd, et al. Reducing suicidal ideation and depressive symptoms in depressed older primary care patients: a randomized controlled trial. JAMA. 2004;291(9):1081-1091.
6. Snowden M, Steinman L, Frederick J. Peer reviewed: treating depression in older adults: challenges to implementing the recommendations of an expert panel. Prev Chronic Dis. 2008;5(1):A26.
### Clinical research

| Application de la resonancia magnética para el tratamiento de la depresión resistente en la edad avanzada | Applications de l’imagerie par résonance magnétique dans la dépression du sujet âgé résistante au traitement |
|---|---|
| La depresión en la edad avanzada (DEA) es una preocupación creciente de salud general y pública, con diversas manifestaciones clínicas y etiologías. Este artículo revisa de manera resumida los hallazgos de las neuroimágenes asociados con la depresión en adultos mayores y la variabilidad de la respuesta terapéutica. La DEA se ha asociado con atrofia cerebral, disminución de la integridad de la mielina y lesiones cerebrales en las regiones limbicas-frontoestriatales. Estas asociaciones ayudan a explicar el síndrome de disfunción ejecutiva de la depresión observado en la DEA y apoyan la carga cerebrovascular como un mecanismo patogénico. Este artículo sugiere además que los hallazgos esenciales de las neuroimágenes de la resistencia al tratamiento también reflejan la carga cerebrovascular. Entre las teorías etiológicas de la DEA, la carga cerebrovascular puede mediar la resistencia al tratamiento. Esta revisión propone que las neuroimágenes tienen un potencial en la traslación clínica. Los ensayos controlados pueden identificar biomarcadores de neuroimágenes que orienten el tratamiento al identificar adultos con depresión que probablemente remitirán con farmacoterapia, identificar dosis terapéuticas individualizadas y facilitar las mediciones de respuesta terapéutica precoz. Las neuroimágenes también tienen el potencial de orientar de manera similar la variabilidad de la respuesta terapéutica del tratamiento con aripiprazol (modulador dopaminérgico) y con buprenorfina (modulador opiáceo). | La dépression du sujet âgé est un problème croissant de santé publique et mondiale dont l’étiologie et les manifestations cliniques sont variées. Cette revue de la littérature résume les résultats de neuro-imagerie associés à la dépression chez les personnes âgées ainsi que la variabilité de la réponse au traitement. La dépression du sujet âgé s’associe à une atrophie cérébrale, à une perte d’intégrité de la myéline et à des lésions cérébrales dans les régions fronto-striato-limbiques. Ces associations permettent d’expliquer le syndrome de dysfonction exécutive observé dans la dépression du sujet âgé et sont en faveur d’une charge cérébrovasculaire comme mécanisme pathogène. De plus, d’après cet article, les facteurs de la résistance au traitement en neuro-imagerie reflètent aussi cette charge. Selon les études théoriques de la dépression du sujet âgé, cette charge cérébrovasculaire jouerait un rôle de médiateur dans la résistance au traitement. Cet article propose que la neuro-imagerie en soit la traduction clinique. Des études surveillées peuvent déterminer des biomarqueurs de neuro-imagerie qui renseigneraient le traitement en identifiant les adultes déprimés susceptibles de guérir avec un traitement médicamenteux, en précisant la dose thérapeutique personnalisée et en facilitant les mesures précoces de réponse au traitement. La neuro-imagerie peut également informer de la même façon sur la variabilité de la réponse au traitement avec l’aripiprazole (modulateur de la dopamine) et avec la buprénorphine (modulateur opiacé). |

7. Nelson JC, Clary CM, Leon AC, Schneider LS. Symptoms of late-life depression: frequency and change during treatment. Am J Geriatr Psychiatry. 2005;13(6):520-526.
8. Butters MA, Whyte EM, Nebes RD, et al. The nature and determinants of neuropsychological functioning in late-life depression. Arch Gen Psychiatry. 2004;61(6):587-595.
9. Reynolds CF, Hoch CC, Buyssse DJ, Monk TH, Houck PR, Kupfer DJ. Symposium: Normal and abnormal REM sleep regulation: REM sleep in successful, usual, and pathological aging: the Pittsburgh experience 1980-1993. J Sleep Res. 1993;2(4):205-210.
10. Dew MA, Reynolds CF, 3rd, Houck PR, et al. Temporal profiles of the course of depression during treatment. Predictors of pathways toward recovery in the elderly. Arch Gen Psychiatry. 1997;54(11):1016-1024.
11. Bhalla RK, Butters MA, Mulsant BH, et al. Persistence of neuropsychologic deficits in the remitted state of late-life depression. Am J Geriatr Psychiatry. 2006;14(5):419-427.
12. Butters MA, Young JB, Lopez O, et al. Pathways linking late-life depression to persistent cognitive impairment and dementia. Dialogues Clin Neurosci. 2008;10(3):345-357.
13. Nebes RD, Butters MA, Mulsant BH, et al. Decreased working memory and processing speed mediate cognitive impairment in geriatric depression. Psychol Med. 2000;30(3):679-691.
14. Web-based Injury Statistics Query and Reporting System (WISQARS): Leading Causes of Death Reports. Centers for Disease Control and Prevention, 2009. Available at: www.cdc.gov/injury/wisqars. Accessed July 24, 2014.
15. Dombrovski AY, Butters MA, Reynolds CF 3rd, et al. Cognitive performance in suicidal depressed elderly: preliminary report. Am J Geriatr Psychiatry. 2008;16(2):109-115.
16. Robinson RG, Price TR. Post-stroke depressive disorders: a follow-up study of 103 patients. Stroke. 1982;13(5):635-641.
17. Dam H. Depression in stroke patients 7 years following stroke. Acta Psychiatr Scand. 2001;103(4):287-293.
18. Ellis C, Zhao Y, Egede LE. Depression and increased risk of death in adults with stroke. J Psychosom Res. 2010;68(6):545-551.
19. Magaziner J, Simonisck EM, Kasher TM, Hebel JR, Kenzora JE. Predictors of functional recovery one year following hospital discharge for hip fracture: a prospective study. J Gerontol. 1990;45(3):M101-107.
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20. Haentjens P, Autier P, Barette M, Boonen S. Belgian Hip Fracture Study Group. Predictors of functional outcome following intracapsular hip fracture in elderly women. A one-year prospective cohort study. Injury. 2005;36(7):842-850.

21. Blazer DG, Moody-Ayers S, Craft-Morgan J, Burchett B. Depression in diabetes and obesity: racial/ethnic/gender issues in older adults. J Psychosom Res. 2002;53(4):913-916.

22. Romanelli J, Fauerbach JA, Bush DE, Ziegelstein RC. The significance of depression in older patients after myocardial infarction. J Am Geriatr Soc. 2002;50(5):817-822.

23. Klap R, Unroe KT, Unutzer J. Caring for mental illness in the United States: a focus on older adults. Am J Geriatr Psychiatry. 2003;11(5):517-524.

24. Conner KO, Copeland VC, Grote NK, et al. Mental health treatment seeking among older adults with depression: the impact of stigma and race. J Am Geriatr Soc. 2010;18(6):531-543.

25. Barley EA, Murray J, Walters P, Tylee A. Managing depression in primary care: A meta-synthesis of qualitative and quantitative research from the UK to identify barriers and facilitators. BMC Fam Pract. 2011;12:47.

26. Rattan PL, Rao S, Vaze A. Do primary care physicians have particular difficulty identifying late-life depression? A meta-analysis stratified by age. Psychother Psychosom. 2010;79(5):285-294.

27. Reynolds CF, 3rd, Miller MD, Pasternak RE, et al. Treatment of depressed mood in major depressive episodes in later life: a controlled study of acute and continuation treatment with nortriptyline and interpersonal psychotherapy. Am J Psychiatry. 1999;156(2):202-208.

28. Maldent R, Livingston G, Katona C. Just keep taking the tablets: adherence to antidepressant treatment in older people in primary care. Int J Geriatr Psychiatry. 2002;17(8):752-757.

29. Hall CA, Reynolds-III CF. Late-life depression in the primary care setting: challenges, collaborative care, and prevention. Maturitas. 2014;79(2):147-152.

30. Bruce ML. Psychosocial risk factors for depressive disorders in late life. Biol Psychiatry. 2002;52(3):175-184.

31. Arean PA, Reynolds CF, 3rd. The impact of psychosocial factors on late-life depression. Biol Psychiatry. 2005;58(4):277-282.

32. Aizenstein HJ, Khalaf A, Walker SE, Andreescu C. Magnetic resonance imaging predictors of treatment response in late-life depression. J Geriatr Psychiatry Neurol. 2014;27(1):24-32.

33. Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry. 1965;122(5):509-522.

34. Germain A, Kuper DJ. Circadian rhythm disturbances in depression. Hum Psychopharmacol. 2008;23(7):571-585.

35. Gibbons JL. Cortisol secretion rate in depressive illness. Arch Gen Psychiatry. 1999;3(1):298-306.

36. Smith RS. The macrophage theory of depression. CNS Drugs. 1995;20(4):111-116.

37. Shinitani F, Kanba S, Nakaki T, et al. Interleukin-1 beta augments reactivation of late-life depression. J Neurosci. 1993;13(8):3574-3581.

38. Maes M, Bosmans E, Meltzer HY, Scharpe S, Suy E. Interleukin-1beta: a putative mediator of HPA axis hyperactivity in major depression? J Psych Res. 1993;150(8):1189-1193.

39. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig DA. “Cerebral depression” hypothesis. Arch Gen Psychiatry. 1997;54(10):915-922.

40. Alonso JT. Sleep duration is associated with all-cause and cause-specific mortality in older adults: the Northern Manhattan Study. J Sleep Res. 2014;23(5):524-530.

41. Winsaweger O. Die Abgrenzung der allgemeinen progressiven Paralyse. Berl KlinWschr. 1894;31:1180-1186.

42. Stollberger C, Finsterer J. Role of infectious and immune factors in coronary and cerebrovascular arteriosclerosis. Clin Diag Lab Immunol. 2002;9(2):207-215.

43. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. Mol Psychiatry. 2013;18(9):963-974.

44. Fujikawa T, Yamawaki S, Touhoudy Y. Background factors and clinical symptoms of major depression with silent cerebral infarction. Stroke. 1994;25(4):798-801.

45. Alexopoulos GS. “The depression-executive dysfunction syndrome of late life”: a specific target for D3 agonists? Am J Geriatr Psychiatry. 2001;9(1):22-29.

46. Alexopoulos GS, Katz IR, Reynolds CF, 3rd, Carpenter D, Docherty JP, Ross RW. Pharmacotherapy of depression in older patients: a summary of the expert consensus guidelines. J Clin Psychiat. 2001;76:361-376.

47. Associaation AP. Practice Guideline for the Treatment of Patients with Major Depressive Disorder. Arlington, VA:American Psychiatric Association; 2010.

48. Trivedi RB, Nieuwma JH, Williams JW Jr. Examination of the utility of psychotherapy for patients with treatment resistant depression: a systematic review. J Gen Intern Med. 2011;26(6):843-850.

49. Shear MK. Clinical practice. Complicated grief. N Engl J Med. 2015;372(2):153-160.

50. Barrett MS, Chuja WJ, Crits-Christoph P, Gibbons MB, Casiano D, Thompson D. Early withdrawal from mental health treatment: implications for psychotherapy practice. Psychotherapy (Chic). 2008;45(2):247-267.

51. Sheltan RC, Ousoktonu O, Heinloth AN, Corya SA. Therapeutic options for treatment-resistant depression. CNS Drugs. 2010;24(2):131-161.

52. 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, viii-iii.

53. Shrefflin M, Driscoll HP, Lenze EJ, et al. Getting to remission: use of aripiprazole for incomplete response in late-life depression. J Clin Psychopharmacol. 2009;30(2):208-213.

54. Corrigan MH, Denahan AQ, Wright CE, Ragul RJ, Evans DL. Comparision of pramipexole, fluoxetine, and placebo in patients with major depression. Depress Anxiety. 2000;11(2):58-65.

55. Lavretsky H, Park S, Siddarth P, Kumar A, Reynolds CF 3rd. Methylphenidate-enhanced antidepressant response to citralopram in the elderly: a double-blind, placebo-controlled pilot trial. Am J Geriatr Psychiatry. 2006;14(2):181-185.

56. Kok RM, Nolen WA, Heeren TJ. Outcome of late-life depression after 3 years of sequential treatment. Acta Psychiatr Scand. 2009;119(4):274-281.

57. Unutzer J. Clinical practice. Late-life depression. N Engl J Med. 2007;357(22):2269-2276.

58. Kujala I, Rosenwine B, Bekkelund SI. Clinical outcome and adverse effects of electroconvulsive therapy in elderly psychiatric patients. J Geriatr Psychiatry Neurol. 2002;15(2):73-76.

59. O’Leary D, Gill D, Gregory S, Shawcross C. The effectiveness of real versus simulated electroconvulsive therapy in depressed elderly patients. Int J Geriatr Psychiatry. 1994;9(7):567-571.

60. Sexton CE, Mackay CE, Elmeire KP. A systematic review and meta-analysis of magnetic resonance imaging studies in late-life depression. Am J Geriatr Psychiatry. 2013;21(2):184-195.

61. Andreescu C, Butters MA, Begley A, et al. Gray matter changes in late-life depression--a structural MRI analysis. Neuropsychopharmacology. 2008;33(1):2566-2572.

62. Smith GS, Kramer E, Ma Y, et al. The functional neuroanatomy of geriatric depression. Int J Geriatr Psychiatry. 2009;24(8):798-808.

63. Bell-McGinty S, Butters MA, Meltzer CC, Greer PJ, Reynolds CF 3rd, Becker JT. Brain morphometric abnormalities in geriatric depression: long-term neurobiological effects of illness duration. Am J Psychiatry. 2002;159(2):1424-1427.
Clinical research

71. Lavretsky H, Ballmaier M, Pham D, Toga A, Kumar A. Neuroanatomical characteristics of geriatric apathy and depression: a magnetic resonance imaging study. Am J Geriatr Psychiatry. 2007;15(5):386-394.

72. Taylor WD, Macfall JR, Payne ME, et al. Orbitofrontal cortex volume in late life depression: influence of hyperintense lesions and genetic polymorphisms. Psychol Med. 2007;37(12):1763-1773.

73. Egger K, Schocke M, Weiss E, et al. Pattern of brain atrophy in elderly patients with depression revealed by voxel-based morphometry. Psychiatry Res. 2008;163(2):237-244.

74. Disabato BM, Morris C, Hranilovic J, et al. Comparison of brain structural variables, neuropsychological factors, and treatment outcome in early-onset versus late-onset late-life depression. Am J Geriatr Psychiatry. 2014;22(10):1039-1046.

75. Lehmenkamp JT, Brassen S, Braus DF, Weber-Fahr W. Subgenual anterior cingulate cortex alterations in late-onset depression are related to “pessimism parameters”. Neuropsychopharmacology. 2009;34(11):2481-2490.

76. Chang CC, Yu SC, McQuoid DR, et al. Reduction of dorsolateral prefrontal cortex gray matter in late-life depression. Psychiatry Res. 2011;193(1):1-6.

77. Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci U S A. 1996;93(9):3908-3913.

78. Lloyd AJ, Ferrier IN, Barber R, Ghoklar A, Young AH, O'Brien JT. Hippocampal volume change in depression: late- and early-onset illness compared. Br J Psychiatry. 2004;184(6):488-495.

79. Janssen J, Hulshoff Pol HE, Lampe IK, et al. Hippocampal change and white matter lesions in elderly patients with major depression. Biol Psychiatry. 2004;56(11):821-831.

80. Zhao Z, Taylor WD, Stynier M, Steffens DC, Krishnan KR, MacFall JR. Hippocampus shape analysis and depression. PLoS One. 2008;3(3):e1837.

81. Ballmaier M, Narr KL, Toga AW, et al. Hippocampal morphology and distinguishing late-onset from early-onset elderly depression. Am J Psychiatry. 2008;165(2):229-237.

82. Burke J, McQuoid DR, Payne ME, Steffens DC, Krishnan RR, Taylor WD. Amygdala volume in late-life depression: relationship with age of onset. Am J Geriatr Psychiatry. 2011;19(9):771-776.

83. Krishnan KR, McDonald WM, Doraiswamy PM, et al. Neuroanatomical substrates of depression in the elderly. Eur Arch Psychiatry Clin Neurosci. 1993;243(1):41-46.

84. Awad IA, Johnson PC, Spetzler RF, Hodak JA. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly. II. Postmortem pathological correlations. Stroke. 1986;17(6):1090-1097.

85. Longstreth WT, Jr, Manolio TA, Arnold A, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. Stroke. 1996;27(8):1274-1282.

86. Taylor WD, MacFall JR, Provenzale JM, et al. Serial MR imaging of volumes of hyperintense white matter lesions in elderly patients: correlates with vascular risk factors. Am J Roentgenol. 2003;181(2):571-576.

87. Dufouil C, de Kercourt-Gilly A, Besancon V, et al. Longitudinal study of blood pressure and white matter hyperintensities: the EVA MRI Cohort. Neurology. 2001;57(6):921-926.

88. Vaseevey A, O'Brien JT, Tan MF, Parry SW, Thomas AJ. A study of orthostatic hypotension, heart rate variability and baroreflex sensitivity in late-life depressives. J Affect Disord. 2011;131(1-3):374-378.

89. Thomas AJ, Perry R, Barber R, Kalaria RN, O'Brien JT. Pathologies and pathological mechanisms for white matter hyperintensities in depression. Ann N Y Acad Sci. 2002;977(1):333-339.

90. Taylor WD, MacFall JR, Payne ME, et al. Greater MRI lesion volumes in elderly depressed subjects than in control subjects. Brain. 2005;128(5):1105-1116.

91. Greenwald BS, Kramer-Ginsberg E, Krishnan RR, Ashtari M, Aupperme PM, Patel M. MRI signal hyperintensities in geriatric depression. Am J Psychiatry. 1996;153(9):1212-1215.

92. Kumar A, Bilker W, Jin Z, Udupa J. Atrophy and high intensity lesions: complementary neurobiological mechanisms in late-life major depression. Neuropsychopharmacology. 2000;22(3):264-274.

93. Herrmann LL, Le Masurier M, Ebmeier KP. White matter hyperintensities in late life depression: a systematic review. J Neural Neurosurg Psychiatry. 2008;79(6):619-624.

94. De Groot JC, De Leeuw FE, Oudkerk M, et al. Periventricular cerebral white matter lesions predict rate of cognitive decline. Ann Neurol. 2002;52(3):335-341.

95. van den Heuvel DM, ten Dam VH, de Craen AJ, et al. Increase in periventricular white matter hyperintensities parallels decline in mental processing speed in a non-demented elderly population. J Neural Neurosurg Psychiatry. 2006;77(2):149-153.

96. Debette S, Bombois S, Bruandet A, et al. Subcortical hyperintensities are associated with cognitive decline in patients with mild cognitive impairment. Stroke. 2007;38(11):2924-2930.

97. Taylor WD, MacFall JR, Boyd B, et al. One-year change in anterior cingulate cortex white matter microstructure: relationship with late-life depression outcomes. Am J Geriatr Psychiatry. 2011;19(1):43-52.

98. De Groot JC, De Leeuw FE, Price JL, Vaishnavi SN, et al. Regional white matter hyperintensity burden in automated segmentation distinguishes late-life depressed subjects from comparison subjects matched for vascular risk factors. Am J Psychiatry. 2008;165(4):524-532.

99. Dalby RB, Chakravarty MM, Ahadian I, et al. Localization of white matter lesions and effect of vascular risk factors in late-onset major depression. Psychol Med. 2010;40(8):1389-1399.

100. Vu NQ, Alizenstein HJ. Depression in the elderly: brain correlates, neuropsychological findings, and role of vascular lesion load. Curr Opin Neurol. 2013;26(6):656-661.

101. Taylor WD, MacFall JR, Gerig G, Krishnan RR. Structural integrity of the uncinate fasciculus in geriatric depression: Relationship with age of onset. Neuropsychiatr Dis Treat. 2007;3(5):669-674.

102. Dalby RB, Frandsen J, Chakravarty MM, et al. Depression severity is correlated to the integrity of white matter fiber tracts in late-onset major depression. Psychiatry Res. 2010;184(1):38-48.

103. Sexton CE, Allan CL, Le Masurier M, et al. Magnetic resonance imaging in late-life depression: multimodal examination of network disruption. Arch Gen Psychiatry. 2012;69(7):680-689.

104. Sexton CE, Le Masurier M, Allan CL, et al. Magnetic resonance imaging in late-life depression: vascular and glucocorticoid cascade hypotheses. Br J Psychiatry. 2012;201(1):46-51.

105. Alves GS, Karakaya T, Fussier F, et al. Association of microstructural white matter abnormalities with cognitive dysfunction in geriatric patients with major depression. Psychiatry Res. 2012;203(2-3):194-200.

106. Hsieh MH, McQuoid DR, Levy RM, Payne ME, MacFall JR, Steffens DC. Hippocampal volume and antipsychotic response in geriatric depression. Int J Geriatr Psychiatry. 2002;17(6):519-525.

107. Taylor WD, McQuoid DR, Payne ME, Zannas AS, MacFall JR, Steffens DC. Hippocampal atrophy and the longitudinal course of late-life depression. Am J Geriatr Psychiatry. 2014;22(12):1504-1512.

108. 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.

109. 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.

110. Sneed JR, Culfang-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.

111. 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.

112. 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.

113. Simpson S, Baldwin R, Jackson A, Burns A. Is subcortical disease associated with a poor response to antidepressants? Neurological, neuropsychological and neuroradiological findings in late-life depression. Psychol Med. 1998;28(05):1015-1026.

114. Sheline YI, Pieper CF, Barch DM, et al. Support for the vascular hypothesis of depression. J Neurol Neurosurg Psychiatry. 2008;79(6):619-624.
115. 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.

116. 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(1):1929-1932.

117. 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.

118. 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.

119. Taylor WD, Bae JN, MacFall JR, et al. Widespread effects of hyperintense lesions on cerebral white matter structure. AJR Am J Roentgenol. 2007;188(6):1695-1704.

120. Bigos KL, Pollock BG, Alzienstein HJ, Fisher PM, Bies RR, Hariri AR. Acute 5-HT reuptake blockade potentiates human amygdala reactivity. Neuropsychopharmacology. 2008;33(13):3221-3225.

121. Tadayonnejad R, Ajilore O. Brain network dysfunction in late-life depression: a literature review. J Geriatr Psychiatry Neurol. 2014;27(1):5-12.

122. Alexopoulos GS, Hopftman 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.

123. MacDonald AW, 3rd, Cohen JD, Stenger VA, Carter CS. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science. 2000;288(5472):1835-1838.

124. Alzienstein 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.

125. Fichtenholtz HM, Dean HL, Dillon DG, Yamaski H, McCarthy G, LaBar KS. Emotion-attention network interactions during a visual oddball task. Brain Res Cogn Brain Res. 2004;20(1):67-80.

126. 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.

127. Alzienstein HJ, Andreeus C, Edelman KL, et al. fMRI correlates of white matter hyperintensities in late-life depression. Am J Psychiatry. 2011;168(10):1075-1082.

128. Braass S, Kalsch R, Weber-Fahr W, Braus DF, Buchel 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.

129. Carmichael ST, Price JL. Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. J Comp Neurol. 1995;363(4):615-641.

130. Andreeus C, Tudorascu DL, Butters MA, et al. Resting state functional connectivity and treatment response in late-life depression. Psychiatry Res. 2013;214(3):313-321.

131. Alexopoulos GS. Depression in the elderly. Lancet. 2005;365(9475):1961-1970.

132. Gruver AL, Hudson LL, Sempowski GD. Immunosenescence of ageing. J Pathol. 2007;211(2):144-156.

133. Raison CL, Demetradilli M, Capuron L, Miller AH. Neuropsychiatric adverse effects of interferon-alpha: recognition and management. CNS Drugs. 2005;19(2):105-123.

134. Alexopoulos GS, Morimoto SS. The inflammation hypothesis in geriatric depression. Int J Geriatr Psychiatry. 2011;26(11):1109-1118.

135. Gurevich EV, Joyce JN. Distribution of dopamine D3 receptor expressing neurons in the human forebrain: comparison with D2 receptor expressing neurons. Neuropsychopharmacology. 1999;20(1):60-80.

136. Wilner P, Lappas S, Cheeta S, Muscat R. Reversal of stress-induced anhedonia by the dopamine receptor agonist, pramipexole. Psychopharmacology (Berl). 1994;115(4):454-462.

137. Hitchcock PK, Bonardi CM, Phillips GD. Enhanced stimulus-reward learning by intra-amygdala administration of a D3 dopamine receptor agonist. Psychopharmacology (Berl). 1997;133(3):240-248.

138. Maj J, Rogoz Z, Skuzu G, Kolodziejczyk K. Antidepressant effects of pramipexole, a novel dopamine receptor agonist. J Neural Transm. 1997;104(4-5):525-533.

139. Vogt BA, Wiley RG, Jensen EL. Localization of Mu and delta opioid receptors to anterior cingulate afferents and projection neurons and input/output model of Mu regulation. Exp Neurol. 1995;135(2):83-92.

140. Zubieta J-K, Ketter TA, Bueller JA, et al. Regulation of human affective responses by anterior cingulate and limbic µ-opioid neurotransmission. Arch Gen Psychiatry. 2003;60(11):1145-1153.

141. Zheng MQ, Kim SJ, Holden D, et al. An improved antagonist radiotracer for the kappa-opioid receptor: synthesis and characterization of 11C-LY2459989. J Nucl Med. 2014;55(7):1185-1191.

142. Reindl JD, Rowan K, Carey AN, Peng X, Neumeyer JL, McLaughlin JP. Antidepressant-like effects of the novel kappa opioid antagonist MCL-1488 in the forced-swim test. Pharmacology. 2008;81(3):229-235.

143. Ide S, Fujiwara S, Fijiwara M, et al. Antidepressant-like effect of venlafaxine is abolished in µ-opioid receptor knockout mice. J Pharmacol Sci. 2010;114(1):107-110.

144. Vilipoux C, Carpentier P, Leroux-Nicollet I, Naudon L, Costentin J. Differential effects of chronic antidepressant treatments on µ and δ-opioid receptors in rat brain. Eur J Pharmacol. 2002;443(1):85-93.

145. Gambert SR, Garbetha TL, Pontzer CH, Hagen TC. Age-related changes in central nervous system beta-endorphin and ACTH. Neuroendocrinology. 1980;31(4):252-255.

146. Wang ZP, Man SY, Tang F. Age-related changes in the contents of neuropeptides in the rat brain and pituitary. Neurobl Aging. 1993;14(6):529-534.

147. Karp JF, Butters MA, Begley AE, et al. Safety, tolerability, and clinical effect of low-dose buprenorphine for treatment-resistant depression in midlife and older adults. J Clin Psychiatry. 2014;75(8):778-783.

148. Hiroa K, Smith GS. PFCinjection tomography molecular imaging in late-life depression. J Geriatr Psychiatry Neurol. 2014;27(1):13-23.

149. Benjamin S, Steffens DC. Structural neuroimaging of geriatric depression. Psychiatr Clin North Am. 2011;34(2):423-435, ix.

150. Dager SR, Oskin N, Richards TL, Posse S. Research applications of magnetic resonance spectroscopy (MRS) to investigate psychiatric disorders. Top Magn Reson Imaging. 2008;19(2):81-96.