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

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Late-life depression: a nefarious public health burden

Depression in late life is a worldwide public health concern, with important implications for brain health. Worldwide, depressive disorders rank second in years lost to disability (YLDs) and third in disability-adjusted life years. Aging of the global population accounted for a 10.4% increase in depression-induced YLDs between 1990 and 2010.[1] Health care costs of depressed older adults exceed their nondepressed counterparts by one third.[2] Late-life depression (LLD) is responsible for

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).

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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*

additional risks of suicide, dementia, and worsened medical comorbidity.[3-5] Insufficient implementation of recommended interventions and limited access to care[6] 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%).[7,8] Sleep disturbances independently predict poor response in LLD.[9,10] Cognitive deficits associated with LLD may be a prodrome of dementia, with cognitive impairment often persisting after remission of affective symptoms.[8,11,12] These cognitive impairments include deficits of information processing speed and executive functioning.[12,13] Suicide is more prevalent in older depressed individuals than in any other age group, and more so in those with cognitive impairment.[14,15] Comorbid depression frequently complicates medical conditions prevalent in older adults, such as stroke,[16-18] hip surgery,[19,20] diabetes, and obesity.[21] Depression also correlates with a fourfold higher rate of death following myocardial infarction.[22]

LLD: underdiagnosed and undertreated

Underdiagnosis worsens the burden of LLD.[4] The stigma of depression may reduce symptom reporting and discussions about emotional distress.[23-25] By default, primary care physicians (PCPs) are the first line of care.[4] PCPs often lack the training to identify the clinical heterogeneity of LLD.[26] 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.[27-29] Social isolation and disability from medical illness are significant psychosocial risk factors.[30,31] 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.[32]

Depression hypotheses: an iterative history

The mechanistic hypotheses of depression are diverse and representative of a multifactorial etiology. The monoamine hypothesis[33] 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.[34] The discovery of elevated cortisol in depressed persons[35] led to the hypothesis that dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may contribute to depression. The inflammation hypothesis[36,37] 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.[37-39] Depression in late life is likely a convergence of multiple etiologies. Indeed, the vascular hypothesis of LLD[40] accounts for the cumulative cardiovascular effects of inflammatory, immune, and sleep[41] 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.[42] The modern vascular depression hypothesis

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.[43] 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.[40,44] The imaging hallmark of vascular depression is white matter lesions (WMLs), seen on magnetic resonance imaging (MRI) as white matter hyperintensities (WMHs).[32,40,45] 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.[46] Cumulative damage by WMLs may disconnect frontostriatal and limbic circuits responsible for mood and executive functions.[44,47]

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.[48] Other medications used as first-line pharmacotherapies include: serotonin–norepinephrine reuptake inhibitors (SNRIs), mirtazapine, and bupropion.[49] 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.[27] A 2006 Cochrane review of pharmacotherapy for unipolar LLD reported no differences in acute efficacy between these different classes of antidepressants.[50]

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).[51] When remission is achieved after acute LLD, consensus recommends that therapy be continued for 6 to 12 months.[48] A study with paroxetine (an SSRI) found benefit of maintenance therapy of 2 years, including patients in their first lifetime episodes.[52]

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.[51] 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).[51]

Psychotherapy

Psychotherapy is effective and generally well-tolerated.[53] Expert consensus guidelines endorse psychotherapy along with antidepressant medication as the treatment of choice for LLD.[48,54] Specifically, cognitive behavioral therapy, problem-solving therapy, interpersonal psychotherapy, and supportive psychotherapy are first-line psychosocial interventions.[48] With mild depression and dysthymia, psychotherapy may be first-line treatment without pharmacotherapy.[48,53] 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,[55] it has been observed that the psychotherapy may reduce attrition and improve medication adherence, resulting in better clinical outcomes.[56,57]

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.[58] The second involves augmentation pharmacotherapy, if the first-line agent has led to partial response.[59] 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.[60] D3 agonists include aripiprazole and pramipexole.[61] Other commonly used augmentation agents include lithium, thyroid hormone, and methylphenidate.[58,62,63]

Treatment-resistant LLD: somatic interventions

Nonpharmacologic somatic interventions may also be used for TRLLD. Electroconvulsive therapy (ECT) is the most effective treatment for LLD,[53] successful in 60% to 80% of cases of treatment-resistant depression. ECT has an important role in depression with suicidality and psychosis.[64-66] Vagal nerve stimulation and transcranial magnetic stimulation are two other therapies for pharmacotherapy-resistant depression, FDA-approved in 2005 and 2008, respectively.[59]

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.[32,49]

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, T1 and T2. T1-weighted images have excellent gray-white matter contrast. T2-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[67] assessed ob-

Author (year)	Sample: size, age, description	Findings: regional volume associations with LLD
Andreescu (2008)[68]	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)[81]	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)[70]	30 depressed patients (69.3±5.7) 47 control subjects (66.9±7.3)	LLD associated with small 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)[82]	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)[76]	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)[74]	126 depressed patients (70.3±6.9) - 60 early-onset (69.42±6.48) - 66 late-onset (71.11±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, supeior frontal gyrus, middle frontal gyrus) and limbic areas (amygdala, hippocampus, anterior cingulate), compared with controls.
Egger (2008)[73]	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)[79]	14 depressed patients (64.04±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

servations 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.[67] 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.[68,69]

Within the frontal lobe, atrophy has been observed in the OFC,[68,70-74] and the anterior cingulate cortex (ACC).[74,75] Volumetric decreases of the dorsolateral prefrontal cortex (dLPFC) and subregions of the dLPFC have been also been observed.[68,76] 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.[68]

Within limbic structures, hippocampal atrophy has been most frequently observed.[68,70,73,74,77-81] Hippocampal subfields specifically affected include CA1–CA3, dentate gyrus, and subiculum.[74,80,81] Atrophy of the amygdala has also been observed.[68,73,74,82] Basal ganglia atrophy has been described within the caudate,[69,83] putamen,[68,83] and pallidus.[68]

Structural MRI associations with LLD: hyperintensities

WMLs are markers of cerebrovascular burden associated with aging,[84-86] hypertension,[85,87] cardiovascular dysautonomia,[88] ischemia,[85,89] oligemia,[89] and diabetes.[86] WMLs are identified on T2-weighted MRI as WMHs and are a hallmark of vascular depression.[40] LLD is asso-

Krishnan (1993)[83]	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)[71]	43 depressed subjects (70.67±7.76) 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)[75]	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)[78]	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)[77]	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)[69]	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)[72]	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)[80]	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.

ciated with greater hyperintensity volume[90-93] *(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.[93] Similarly, PVWMH and DWMH have also been associated with cognitive decline in older adults.[94-96] 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.[97-99]

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.[100] FA deficits in LLD have been found in fronto-subcortical and fronto-limbic tracts, including the uncinate fasciculus,[101-104] anterior thalamic radiation, superior longitudinal fasciculus,[102-104] and PCC[105] *(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)[99]	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.

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.[109,110] 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.[109-111] More-

Author (year)	Sample: size, age, description	Findings: FA associations with LLD
Dalby (2010)[99]	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)[103]	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)[105]	17 depressed-remitted patients (65.53±5.46) 18 control subjects (66.44±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)[101]	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)[108]	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)[106]	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 score <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)[107]	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.[110,112-114] 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.[115]

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[116,117] *(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)[111]	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)[109]	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)[112]	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)[115]	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 MADRES 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)[114]	190 depressed patients - 72 remitters (69.2±7.7) - 118 nonremitters (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)[113]	75 depressed patients (75.7±5.7) 24 control subjects (74.9±6.3)	12-week course of non-uniform pharmacologic monotherapy - Response: MADRS score <10, <5 *DSM-III-R* 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)[110]	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

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.[118] 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,[119] potentially explaining the discrepancy.

Functional MRI: description

Functional MRI is capable of identifying pharmacologic challenges in real time.[120] 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[121] *(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.[122] 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).[122] 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.[122] The DMN is thought to mediate self-referential thinking, which is susceptible to negativity bias in LLD.[122]

Author (year)	Sample: size, age, description	Treatment/definition of remission	Findings: FA associations with response or remission
Alexopoulos (2008)[117]	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)[116]	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)[118]	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

Functional 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[123]) to identify hypoactivity within the dLPFC, and lower FC between dLPFC and dACC in LLD[124] *(Table VIII)*. These findings are congruent with the observation by Alexopoulos et al of diminished resting-state FC within the CCN in LLD.[122] Using an emotional oddball task meant to investigate the relationship between emotional and attentional processing,[125] 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.[126] 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.[126] 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.[127]

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.[124] 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)[124]	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)[127]	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)[126]	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)[122]	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, 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

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 resistance[122] *(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 coexist 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)[122]	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 cuenus, 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.[67,101,102] Areas of gray matter connected by these white matter tracts, specifically frontostriatal and limbic areas, were found to have significant atrophy.[67-69] 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.[122] 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.[106,107] 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.[122,130] 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.[124]

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)[124]	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 Prepotency 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)[128]	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

factors crossing a pathologic threshold.[44] 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.[120] Dose-dependent amygdala activation responses to IV citalopram have been observed within seconds.[120] 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.[46] 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,[40,46] and are replete with D3 receptors.[135] 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.[136-138] 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.[141] 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. ❑

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Aplicaciones de la resonancia magnética para el tratamiento de la depresión resistente en la edad avanzada

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 límbicas-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).

Applications de l'imagerie par résonance magnétique dans la dépression du sujet âgé résistante au traitement

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 étiologies 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 contrôlées 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).

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