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FUNCTIONAL NEUROIMAGING IN GERIATRIC DEPRESSION

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Synopsis

Abnormalities in specific cerebral networks likely confer vulnerability that increases the susceptibility for development of geriatric depression and impact the course of symptoms. Functional neuroimaging enables the *in vivo* identification of alterations in cerebral function that not only characterize disease vulnerability, but also may contribute to variability in depressive symptoms and antidepressant response. Judicious use of functional neuroimaging tools can advance pathophysiological models of geriatric depression. Furthermore, due to the age-related vulnerability of specific brain systems that have been implicated in mood disorders, geriatric depression provides a logical context within which to study the role of specific functional abnormalities in both antidepressant response and key behavioral and cognitive abnormalities of mood disorders.

Keywords

geriatric depression; PET; fMRI; spectroscopy

Overview

Geriatric depression is a complex syndrome that is associated with a high degree of inter-individual variability and determined by multiple biological and environmental factors. Among these, abnormalities in specific cerebral functions likely confer vulnerability that increases the susceptibility for development of geriatric depression and impact the course of symptoms. Functional neuroimaging makes possible the identification of alterations in cerebral function that not only characterize disease vulnerability, but may also be responsible for variability in mood and cognitive responses to treatment. Thus, thoughtful use of functional neuroimaging approaches can inform conceptual models of late-life depression and guide treatment developments.

The present articles reviews several techniques - regional cerebral blood flow (rCBF) and cerebral metabolism studies, molecular imaging, blood oxygenation level dependent (BOLD) imaging, magnetic resonance spectroscopy (MRS) - that have been used to examine abnormalities in brain function, with a focus on the pattern of results obtained by each method as well as recommendations for future research.

The authors have nothing to disclose.

The Functional Neuroanatomy of Geriatric Depression and Treatment

PET Cerebral Glucose Metabolism Studies—The major focus of PET neuroimaging studies in affective disorders has been the characterization of rCBF and glucose metabolic alterations in mid-life patients with primary, unipolar depression, secondary depression in stroke or movement disorders (Huntington's and Parkinson's Disease), as well as the effects of antidepressant interventions (see 1–3 for review). Fewer studies comparing geriatric depressed patients to controls or evaluating treatment effects have been performed (2, 4–8). As cerebral glucose metabolism is the final common pathway of neurochemical activity, these studies identify the neural circuitry of pathophysiology and treatment response to inform the design of mechanistic studies within the pathways identified.

These rCBF and cerebral metabolism studies, in addition to preclinical and post-mortem data, have been integrated to develop a functional neuroanatomic model of depression and of antidepressant effects in mid-life depressed patients. This model involves increased metabolism in dorsal structures and decreased metabolism in ventral structures (1). Many of the brain regions that comprise this model have been implicated in a recent meta-analysis of neuroimaging studies in major depression (3). The regions that are hypoactive at rest, show a lack of activation during negative mood states and increase with SSRI treatment include the dorsal pregenual cingulate gyrus, middle and dorsolateral prefrontal cortex (DLPFC), insula and superior temporal gyrus. A second network identified was a cortical-limbic network including the medial and inferior frontal cortex and basal ganglia, structures that were overactive at rest and during induction of negative mood states and reduced in activity with antidepressant treatment. The amygdala and thalamus were also implicated in the network in some studies. Other regions highlighted in the meta-analysis included the cerebellum (which showed increased activity at rest), posterior cingulate and medial temporal lobe (including the parahippocampal gyrus), all of which show abnormal activation in mood induction paradigms. The applicability of this model to geriatric patients can be tested, given that such data have become available recently (9–11).

Comparison of the neural circuitry of depression across the lifespan— Differences between the functional neuroanatomical alterations in older depressed patients compared to younger patients have been observed (10). Relative to younger patients, geriatric depressed patient demonstrate increased glucose metabolism in a more extensive network of both anterior cortical regions, as well as posterior cortical regions (10). In younger depressed patients, antidepressant treatment increased anterior cortical metabolism and decreased limbic metabolism. Within the cingulate gyrus, effects are observed in rostral areas (BA 24, 25) in mid-life depressed patients (1). In contrast, studies in older depressed patients (8,9, 11,12) observe decreased anterior cortical and limbic metabolism and increases in posterior cortical regions and cerebellum with antidepressant treatment (including SSRIs and total sleep deprivation). With respect to the cingulate gyrus, effects are observed in caudal sub-regions of the cingulate gyrus (BA 32) with acute treatment and in rostral sub-regions (BA24) with chronic treatment in geriatric depression. The regional differences in metabolic response to antidepressant medications between younger and older depressed patients may be attributable to differences in depression phenomenology, as well as differential compensatory processes in the aging brain.

Mood and cognitive networks of treatment response in geriatric depression— Functional connectivity methods have identified neural networks associated with improvement of affective and cognitive symptoms in geriatric depressed patients who underwent PET glucose metabolism studies prior to and during a course of treatment with the antidepressant citalopram (9). The partial least squares (PLS) method identified a subcortical-limbic-frontal network was associated with improvement in affect (mood and

anxiety), while a medial temporal-parieto-frontal network was associated with improvement in cognition (immediate verbal learning/memory and verbal fluency). The network of regions that correlated with the left anterior cingulate (ACC; BA 24) seed and with improved affect was comprised of the left amygdala, frontal regions [right orbitofrontal cortex (BA 11), bilateral medial frontal gyrus (BA 10), bilateral middle frontal gyrus (BA 46), bilateral superior frontal gyrus (BA 6), and right inferior frontal gyrus (BA 45)], right ACC (BA 24), the bilateral insula (BA13), and left midbrain. The network of regions that correlated with the right parahippocampal gyrus (PHG) seed and with improved scores in the California Verbal Learning Test (CVLT; sum of the first 5 trials) and Controlled Oral Word Association Test (COWAT) included the left hippocampus, frontal [bilateral middle frontal gyrus (BA 46), bilateral orbitofrontal cortex (BA 11), and left inferior frontal gyrus (BA 47)], temporal regions [left inferior temporal gyrus (BA 20), bilateral middle temporal gyrus (BA 21), and right superior temporal gyrus (BA 22)], parietal regions [left inferior parietal lobule (BA 40) and right post-central gyrus (BA 2)], and the bilateral cerebellum. In contrast, the bilateral insula and occipital areas [bilateral lateral occipital gyrus (BA 19), right superior occipital gyrus (BA 39), and right fusiform gyrus (BA 37)] showed increased metabolism and also correlated with improvements in the two cognitive measures. The underlying mechanisms of the midbrain-limbic-frontal affective network may involve interactions between monoaminergic and glutamatergic systems. The regions involved in the medial temporal- parietal-frontal cognitive network, overlap with the regions affected in Alzheimer's dementia and may reflect neuronal vulnerability to a neurodegenerative processes (such as *beta*-amyloid deposition, 13). Thus, an understanding of the cerebral metabolic networks associated with the affective and cognitive responses to antidepressant treatment is critical to the design of future mechanistic studies.

In summary, PET cerebral glucose metabolism measures have provided a fundamental understanding of the functional neuroanatomic pathways underlying depressive symptomatology and treatment response. This information is critical to inform the design of studies to evaluate specific neurochemical substrates with molecular imaging methods.

Molecular Imaging in Depression

The initial application of neurochemical imaging methods was to test the hypothesis of decreased monoaminergic function (norepinephrine, dopamine, and in particular, serotonin (14–16) in depression. The majority of the studies have been performed in mid-life depressed patients. Advances in radiotracer chemistry over the last decade have made possible the ability to image neuropathological processes that may be relevant to understanding neurodegenerative and cerebrovascular mechanisms involved in geriatric depression. The monoamine imaging data in depression will be reviewed in this section with a focus on the serotonin and dopamine systems, the major areas of investigation. The amyloid imaging data will be reviewed next, followed by a discussion of future directions that is based on new developments in radiotracer chemistry and recent data that implicates the role of therapeutic mechanisms beyond the monoamine systems

The Serotonin System

The evidence supporting serotonin hypofunction in major depression includes 1) alterations in serotonin transporter binding, 5HT1A and 5-HT2A receptor binding in post-mortem and *in vivo* studies; 2) a blunted neuroendocrine response to acute pharmacologic interventions of the serotonin system and 3) alterations in mood in depressed patients by pharmacologic manipulations of serotonin system (improvement in mood with increased serotonin and worsening of mood with reduced serotonin concentrations) (17–19). Neurochemical imaging studies have evaluated serotonin synthesis, SERT binding, the initial target site of action of

the SSRIs, as well as 5-HT1A and 5-HT2A binding. Radiotracers for other relevant serotonin receptor sites are being evaluated 5-HT1b (20), 5-HT4 (21), 5-HT6 (22).

Reduced serotonin synthesis in depression has been observed in several studies. Agren and colleagues (23) reported lower uptake of [11C]-5-hydroxytryptophan, a radiolabeled precursor for serotonin synthesis, in depressed patients. Serotonin synthesis as measured by trapping of the radiotracer alpha-[11C] methyl-L-tryptophan was shown to be reduced in ACC (bilaterally in females, left hemisphere in males) and left medial temporal cortex in unmedicated depressed patients (24).

Several studies have evaluated SERT binding in midlife unipolar and bipolar depressed patients. The results include increased SERT (25, 26), decreased SERT (27–31) or no difference in unmedicated, recovered patients or unmedicated patients (32,33). While the direction of the results across studies is different, the regions implicated are remarkably consistent (e.g. cingulate gyrus, frontal cortex, insula, thalamus and striatum). The factors that may contribute to differences across studies include differences in the radiotracers used ([11C]-DASB versus [11C]-McN5652) and sample characteristics. At this time, there do not appear to be any published studies of SERT in geriatric depression. Preliminary studies in two samples of geriatric depression patients suggest decreased SERT relative to controls in the ACC (BA 24), middle temporal gyrus, parahippocampal gyrus, amygdala, caudate and thalamus (34). Two studies have reported that higher baseline SERT binding predicted remission to acute fluoxetine treatment, as well as remission at one year (35,36).

SERT occupancy by SSRIs has been evaluated in mid-life depressed patients. Studies in mid-life depressed patients treated for four weeks with either paroxetine or citalopram have reported significant SERT occupancy in caudate, putamen, thalamus, in addition to prefrontal and anterior cingulate cortices. The magnitude occupancy for both compounds was similar (ranging from 65–87% across regions; 37). The magnitude of occupancy and the relationship between brain occupancy and plasma concentrations is consistent with that observed in elderly depressed patients treated with the citalopram at steady state doses (2). There was a remarkable degree of similarity between regions of SERT occupancy that were correlated with improvement in depressive symptoms and regions of cerebral metabolic alterations by citalopram (e.g. ACC, middle frontal gyrus, precuneus, inferior parietal lobule, cuneus; 2,9). These data suggest that a serotonergic mechanism (decreased serotonin function in cortico-limbic pathways) may underlie observations of altered cerebral blood flow and metabolism associated with the antidepressant response and that voxel-wise analyses of the neurochemical imaging data may be informative to detecting changes in brain regions relevant to the antidepressant response that have lower concentrations of the transporters/receptors of interest. While the data concerning SERT binding in the baseline, unmedicated state in unipolar depressed patients are controversial, there is consistency between studies to show the predictive value of baseline SERT binding with respect to treatment outcome and remission, as well as occupancy by antidepressant medications. The available data suggest that striatal and thalamic occupancy (70% or greater) is necessary to observe an antidepressant response, however less occupancy of cortical and limbic SERT may be associated with treatment resistance.

Studies of the 5-HT1A receptor have either shown decreased (38,39) or increased (40) binding. In a study by Parsey and colleagues (40), antidepressant naive subjects and subjects homozygous for the functional 5-HT (1A) G (−1019) allele of the promoter polymorphism demonstrated higher 5-HT1A binding. A correlation between higher baseline 5-HT1A binding and poorer treatment response has been reported (41,42). The one study of geriatric depressed patients observed decreased 5-HT1A binding in the dorsal raphe, as well as in the middle temporal cortex and hippocampus (43). A similar, selective reduction in 5-HT1A

binding in temporal cortex has also been observed in AD patients (44), which might suggest that decreased serotonin modulation of temporal cortical regions may be associated with affective or cognitive deficits similar to depression and AD.

Alterations in 5-HT1A binding following SSRI treatment has not been observed in human neuroimaging studies (39,42), a finding that is not expected based on animal studies showing 5-HT1A desensitization induced by SSRI treatment (45). One of the explanations for the lack of an observed effect is that the 5-HT1A antagonist radiotracers bind to low affinity sites, whereas the changes with treatment may be observed in high affinity sites. To test this hypothesis, a promising 5-HT1A agonist radiotracer has been developed (46).

5-HT2A receptor binding has reported to be unchanged in both mid and late life depressed patients, (37,47,48), decreased in orbitofrontal cortex in one report (49) or increased (50). Treatment studies have shown either a decrease (51,52) or increase in 5-HT2A binding (53,54). The discrepancy between studies may be that in the Yatham et al. (52) study, desipramine was administered, which binds directly to the 5-HT2A receptors, whereas SSRIs were used in the other studies. In addition, different radiotracers were used across studies [18F]-setopertone versus the spiperone derivative radiotracer, [18F]-FESP).

In summary, studies of SERT and the 5-HT1A and 5-HT2A receptor have been performed in mainly in mid-life unipolar depressed patients. The within group variability obtained in transporter or receptor binding has been explained in some studies by correlations with affective or cognitive symptoms or particular genetic polymorphisms related to the transporters or receptors of interest (e.g. 33,40)).

The Dopamine System

The role of the dopamine system in depression has been reviewed in detail (55,56). There are several lines of evidence to support dopamine dysfunction in depression, including: improvement in depressive symptoms with dopamine agonists, the induction of a depressive relapse by pharmacologic depletion of dopamine and low cerebrospinal fluid homovanillic acid levels in depressed patients compared to controls. The available imaging data suggests modest decreases or no change in dopamine metabolism, dopamine transporter and D1 and D2 receptor binding (57–59). Dopamine transporter binding was reduced in MDD relative to controls (58). Several studies of striatal and extrastriatal D2 receptor availability have not shown differences between patients and controls, including studies in medication naive patients (60–62). Greater psychomotor slowing has been associated with increased striatal D2 receptor binding, indicating that perhaps differences may be observed in sub-groups of depressed patients (63). With respect to the D1 receptor, decreased binding was observed in the left middle caudate in one report (64). In addition, no differences in amphetamine-induced striatal dopamine release have been observed in either euthymic bipolar patients or patients with unipolar depression (61, 65).

In summary, the available dopamine neuroimaging data suggest a pre-synaptic deficit in the dopamine system, as the post-synaptic receptors are not significantly altered, except in patients with psychomotor slowing. Several lines of evidence suggest that that dopamine dysfunction may play a more prominent role in geriatric depression, including the substantial age related decline in dopamine transporters and receptors, as well as the evidence for the augmentation of the antidepressant response by psychostimulants (such as methylphenidate; 66,67). A better understanding of the nature of the dopaminergic deficits in geriatric depression would lead to targeted treatments that would potentially be more effective.

Beta Amyloid Imaging

The development of radiotracers to image beta-amyloid deposition, one of the pathological hallmarks of AD (in addition to hyperphosphorylated tau), represents a significant advance in neuroimaging studies of neurodegenerative disease. Several PET radiotracers for beta amyloid have been evaluated in human subjects and show good diagnostic sensitivity between normals, MCI and AD ([18F]-FDDNP, [11C]-SB13, [11C]-PIB;68–73). [11C]-PIB is the best characterized and most commonly used radiotracer [11C]-PIB has a high binding affinity and specificity to amyloid in AD brain (70, 74,75).

Several lines of evidence suggest that [11C]-PIB measures are sensitive to subtle cognitive impairment and may predict subsequent cognitive decline. Higher cortical PIB concentrations is associated with cognitive impairment in healthy controls, as well as cognitive impairment and cognitive decline in subjects with mild cognitive impairment (MCI; 73, 76–78).

The initial study of [11C]-PIB in geriatric depression was recently published (79). Nine remitted, depressed patients underwent cognitive testing, MR and [11C]-PIB scanning. Subjects who met criteria for amnestic MCI demonstrated greater binding than those with non-amnestic MCI and subjects who were cognitively normal. These results are consistent with that of non-depressed subjects with cognitive impairment. In a recent study of geriatric depressed patients who do not meet criteria for MCI, greater beta-amyloid deposition relative to controls was observed in the ACC, superior and middle frontal gyrus, left orbito-frontal gyrus, precuneus bilateral insula, and left parahippocampal gyrus (80). In patients with MCI and cognitively normal controls, greater depression and anxiety symptoms were associated with higher [^{18}F]-FDDNP binding (81). These studies suggest that depressive symptoms in normal control subjects and depressed patients without cognitive impairment are associated with AD neuropathology. Beta-amyloid deposition may underlie the cognitive impairment that persists after mood symptom remission.

Future Directions for Molecular Imaging Studies

As reviewed in the previous sections, the serotonin and dopamine systems have been the major focus of neurochemical imaging studies in depression, the majority of studies have been performed in younger patients. Recent studies have focused on imaging beta-amyloid deposition in geriatric depression as a mechanism underlying cognitive impairment that might be related to the increased risk of AD in depressed patients. There are several other potentially relevant molecular targets for which radiotracers are in development and/or promising new radiotracers are available. These important future directions for molecular imaging studies, of particular relevance to geriatric patients will be reviewed.

Radiotracer development for the noradrenergic system (including the norepinephrine transporter and beta-adrenergic receptors) has been challenging due to the lack of pharmacologically selective agents, the low signal to noise levels of binding in the brain (as reviewed by 82,83). Given the role of the norepinephrine transporter in the mechanism of action of antidepressant agents, a suitable radiotracer would permit drug occupancy studies, as well as studies of pathophysiology. Such studies would be especially critical in older patients, given the side effects associated with noradrenergic agents (84).

The recent evidence for the antidepressant effects of the n-methyl-d-aspartate (NMDA) antagonist, ketamine, and the genetic data implicating glutamate receptor polymorphisms in the response to SSRI's has stimulated research to evaluate the role of glutamate in depression (85). Several radiotracers have been evaluated for the NMDA receptor (86–88) and do not have suitable imaging properties for human studies. The recent emphasis and

greatest success for glutamate radiotracer development has been the metabotropic glutamate subtype 5 (MgluR5) receptor (89). Given the role of glutamate in neurotoxicity as shown in preclinical studies (90), glutamatergic dysfunction in geriatric depression may be associated with subsequent neurodegenerative processes and cognitive decline.

The antidepressant effects of cholinergic agents, such as muscarinic antagonists and nicotinic agonists, highlight a possible primary or secondary role of the cholinergic system in depression (91,92). For the cholinergic system, radiotracers have been developed for the vesicular acetylcholine transporter, acetylcholinesterase, nicotinic and muscarinic receptors. These radiotracers have not been studied extensively in mood disorders. One study using a muscarinic receptor (M2 subtype selective) radiotracer, [18F]FP-FTZP, observed reduced muscarinic receptor binding in the ACC in bipolar depressed patients relative to MDD patients and controls (93). The reduction in receptor binding was negatively correlated with depressive symptoms. The further investigator of muscarinic and nicotinic mechanisms in geriatric depression would be of potential mechanistic and therapeutic relevance for mood symptoms and cognitive deficits.

Inflammation may be a common underlying mechanism for depression, as well as cardiovascular disease, diabetes, and cancer, and may be more relevant to geriatric depression given the increasing medical co-morbidity in late life (as reviewed by 94). A recent focus in radiotracer chemistry is the development of is peripheral benzodiazepine (PBR) radiotracers that bind with high affinity to translocator protein (TSPO). TSPO is upregulated in activated microglia and represents a marker of neuroinflammation. A number of radiotracers have been developed and evaluated in human subjects (95–97) and offer promise for the evaluation of the role of inflammation in the pathophysiology of geriatric depression.

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) is a noninvasive imaging tool that can provide a quantitative measure of biochemical concentration data in the brains of elderly depressed patients. Different molecules have unique MR spectra that can be quantified by taking the area under the signal curve. In most cases, the values are not absolute, so it is customary to take ratios of the measure of interest to some standard metabolite, for example choline. MRS measures complement PET imaging methods and permit the noninvasive evaluation of concentrations of amino acids (GABA, glutamate) and membrane lipids in the brain that are found in high concentrations that are difficult to image with PET due to high non-specific binding of radiotracers.

Kumar and colleagues(98) used MRS to examine biochemical abnormalities in left frontal WM and bilateral anterior cingulate gray matter of elderly depressed patients. They observed higher choline to creatine as well as myo-inositol to creatine ratios in the white matter of patents relative to age-matched comparison subjects. In a follow-up study using 2D MRS, they detected a significant difference in the overall pattern of associations between the measured metabolites (choline, myo-inositol, creatine, phosphoethanolamine, phosphocholine) and verbal learning and processing speed in elderly depressed patients compared to elderly controls (99). The authors interpreted the weaker relationship between metabolites and specific cognitive domains in patients with late-life depression, as evidence that cognitive decline in geriatric depression may be associated with biochemical changes in frontolimbic circuitry. Further, in a recent study of elderly depressed patients and age-matched control subjects, MRS spectra were acquired from voxels that were placed in the left frontal white matter, left periventricular white matter, and left basal ganglia. Elderly depressed patients had significantly lower NAA/creatine ratio in the left frontal white

matter, and higher Cho/creatine and myo-inositol/creatine ratios in the left basal ganglia when compared with the control subjects. Furthermore, the myo-inositol correlated with global cognitive function among the patients(100). Taken together, these findings suggest that biochemical abnormalities not only are present in geriatric depression, but also are associated with the cognitive deficits that characterize the illness.

MRS and Course of Illness

Single-voxel (1)H (MRS) was used to examine biochemical abnormalities related to late-life depression in the medial prefrontal cortex and medial temporal lobe. Elderly, previously depressed individuals had significantly reduced concentrations of total N-acetyl aspartate (NAA), choline, and creatine in the medial prefrontal cortex, suggesting that reduced neuronal, phospholipid, and energy metabolism is present even in clinically improved depression (101). Furthermore, using a three-dimensional chemical shift imaging sequence, tissue specific differences in markers of energy metabolism, including high energy phosphate compounds (beta and total NTP, PCr) and pH, were examined in 13 older adults with major depression pre- and post- 12 weeks of treatment with sertraline and 10 age-matched controls. Relative to controls, total NTP was reduced in the white matter, but not in the gray matter, in the depressed group prior to treatment. In addition, intracellular pH was higher in the gray matter of subjects with pre-treatment depression but similar to levels of controls after treatment (102).

Most spectroscopy studies thus far have used single voxel acquisitions, with a high number of repetitions in order to get adequate signal to noise ratio. Other studies use chemical shift imaging to obtain spectroscopy data on an image slice or set of slices. The key limitation for chemical shift imaging is that the signal to noise ratio increases in magnitude as more voxels are acquired. Though there are only a handful of published reports that have used MRS to examine the neurochemical environment in geriatric depression, this appears to be a promising technique that, especially if used in combination with other measures of biochemistry, is likely to be a quite powerful tool to advance our understanding of the neurobiological underpinnings of late-life depression.

Functional MRI (fMRI) Studies

The most commonly used fMRI technique, blood oxygen level dependent, (BOLD), is a noninvasive, indirect measure of cerebral activity that enables functional imaging with a temporal resolution on the order of 100 milliseconds and a spatial resolution of 1–2 millimeters. Thus, BOLD fMRI is ideal for localizing activity in response to transient cognitive events, even in relatively small brain structures that have been implicated in late-life depression (e.g., the amygdala and brain stem nuclei). This section will begin with a brief overview of the initial task-based findings, then will focus on fMRI studies of two networks that appear to be critical to the pathophysiology of geriatric depression (i.e., the cognitive control network, the affective network) followed by some recommendations regarding two additional networks that we believe should be examined in late-life depression.

Functional neuroimaging studies in late-life depression reveal a pattern of abnormal activation of frontolimbic regions, generally characterized by hypoactivation of specific dorsal cortical regions including the DLPFC and the dorsal ACC. One of the first published reports of task-related activation in geriatric depression was a PET study that compared cerebral blood flow during a word activation task between elderly patients with severe depression and normal elders. During the word activation task, hypoactivation of the dorsal ACC and the hippocampus was detected (103). This finding of attenuated activation of the dorsal ACC during a verbal fluency task was later replicated by another group in an fMRI

study of older depressed individuals in remission who had experienced multiple previous episodes of depression (104). Furthermore, in depressed elderly patients, relative to age-matched controls, Aizenstein and colleagues (105) reported decreased DLPFC in addition to increased caudate activation in response to an explicit sequence learning task.

These initial task-based activation studies of late-life depression converge with emerging evidence from other clinical and cognitive neuroscience techniques that cognitive control systems are disrupted in late-life depression (106,107; see PET and MRS sections above). The cognitive control system of interest is comprised of the dorsal ACC, DLPFC, and select parietal regions, and enables efficient information processing by facilitating the adaptation to changing environmental demands and personal goals (108,109). A number of previous studies of mid-life depression have reported activation abnormalities during cognitive control tasks, mostly involving hypoactivation of the dorsal ACC and the DLPFC (110–112); with some evidence for abnormal functional connectivity within this network (113,114).

Cognitive control is of particular interest in geriatric depression because of the vulnerability of cognitive control structures to aging (115–117) and the potential of specific cognitive control dysfunctions to explain a number of the salient cognitive and other behavioral features of the illness, including the inability to ignore irrelevant, especially negative, stimuli. In elderly depressed patients, the DLPFC was observed to be hypoactive during the depressed state in response to a cognitive control paradigm along with reduced functional connectivity between the DLPFC and dorsal ACC (118). An fMRI study of elderly depressed patients that used an emotional oddball task reported that relative to healthy comparison subjects, the elderly depressed patients demonstrated attenuated activation in select frontolimbic regions, including the right middle frontal gyrus and the cingulate, as well as the inferior parietal cortex (119). In this sample, activation in the middle frontal gyrus appeared depressive state-related, whereas attenuated activation in the posterior cingulate and inferior parietal regions persisted in the remitted subjects, suggesting a state-related alteration in cognitive control systems.

Functional abnormalities in the affective network in depression, which includes the ventral ACC, the amygdala, and portions of the orbitofrontal cortex, were first observed using PET (for review see 1; see PET section above). Structures involved in the affective network typically demonstrate increased resting state metabolism during depressed states in mixed aged-depressed (1,7,120–22). Subsequent fMRI studies in young and middle aged adults with major depression have shown hyperactivation of ventral limbic regions most consistently, including the perigenual cingulate and amygdala, in response to emotional stimuli (111, 112, 123–127). In contrast to the pattern of hyperactivity in the affective network in mid-life depression, in an fMRI study that used an affective paradigm in elderly acutely depressed patients, relative to elderly control subjects, depressed patients exhibited hypoactivation of the ventromedial prefrontal cortex in response to the emotional evaluation of negatively-valenced relative to positively-valenced words (128).

Activation and Antidepressant Treatment in Mid-Life Depression

FMRI studies in mid-life depression on change in activation from baseline to post treatment suggest hyperactivity of the perigenual ACC (129–131) and amygdala (121,129,131) and hypoactivity of DLPFC (132) occurring during depressed states tends to resolve with antidepressant treatment. For example, fMRI studies conducted by Fales and colleagues (111,132) reported hypoactivity of the DLPFC and hyperactivity of the amygdala in depressed patients during a cognitive control task involving emotional interference. Hypoactivity of the DLPFC resolved following SSRI treatment (132). Furthermore, the studies in mid-life depression of the relationship of pretreatment fMRI activation to

antidepressant response suggest that in response to affective stimuli greater activity in the rostral ACC (134,135)and amygdala (134–137)prior to treatment may be associated with better clinical outcomes.

Activation, Antidepressant Treatment, and Geriatric Depression

There are only two published studies that report the relationship of fMRI activation to antidepressant response. In a study of the affective network that examined the relationship of cerebral activation to course of illness, acutely depressed patients exhibited hypoactivation of the ventromedial prefrontal cortex in response to the emotional evaluation of negatively-valenced relative to positively-valenced words. However, this hypoactivation normalized after several months of uncontrolled antidepressant treatment (128). Furthermore, in a controlled, antidepressant treatment trial, during a cognitive control task elderly depressed patients demonstrated hypoactivation in the DLPFC and diminished functional connectivity between the DLPFC and dorsal ACC prior to treatment (118). Although the hypoactivity in the right DLPFC subsided after successful antidepressant treatment, the reduced functional connectivity between the dorsal ACC and the DLPFC persisted.

Summary and Future Directions

Taken together, the functional neuoroimaging results indicate that abnormal frontolimbic activation is present in elderly depressed patients during the depressed state and some of the these abnormalities may normalize (e.g. hypoactivation of the DLPFC and hyperactivation of the amygdala), at least in part, in response to antidepressant treatment, whereas other abnormalities (i.e., reduced functional connectivity, abnormal activity in the posterior cingulate) may persist despite antidepressant treatment (118; 119). However, the bulk of the existent fMRI data are from mid-life depression and it is quite likely as more data become available that a different pattern of results may emerge in late life that can clarify conceptual models of the pathophysiology of geriatric depression.

Reward Systems—To date, the task-based activation studies in geriatric depression have concentrated on cognitive control and affective regions. However, there are other systems that have been shown to be central to the behavioral disturbances observed in geriatric depression. For example, reward functions are disrupted in depression (56) and these disruptions may be fundamental to the presentation of core symptoms of geriatric depression including anhedonia (137,138). FMRI studies of mid-life depression indicate hypoactivation of the brain's reward structures, including dopaminergically-mediated ascending mesolimbic projections areas such as the dorsal and ventral striata as well as the medial prefrontal cortex (137,139,140). However, despite the vulnerability of reward systems to aging (see above section on the dopamine system) (141), to our knowledge, there are no published reports that have examined task-related activation of reward systems in late life-depression, a syndrome for which anhedonia is especially problematic (142).

The Default Mode Network—Traditionally, fMRI studies have focused on regional activation, and more recently, network activation related to task-performance. However, there is a growing body of evidence that the resting brain is organized in a way that reflects interrelationships among structures with related functions and, therefore, resting state functional connectivity analysis can identify functionally integrated, biologically meaningful networks(143–5). These relationships can be examined using resting state functional connectivity, which refers to the temporal correlation of brain activity across disparate regions.

The default mode network is one of several functionally connected networks that have been identified under resting-state conditions. The default mode network overlaps with the

affective network and is comprised of a set of regions (posterior cingulate/precuneus, medial prefrontal cortex, ventral ACC, inferior lateral parietal lobes, and parts of the temporal lobe) that consistently decrease their activity during cognitive task performance (143,145). The default mode network is important in self-referential activities, including evaluating salience of internal and external cues, remembering the past, and planning the future (145,146). Resting state studies of mid-life depression suggest that the default network may demonstrate higher FC in depression than in controls (147,148). Furthermore, there is preliminary evidence that resting state FC in the subgenual ACC is correlated with the length of major depressive episode with higher FC found during longer episodes of depression (147). Given the influence of age on the functional connectivity of the default mode network (149), and the putative role of the default mode network in depression-related cognitive biases (150), future studies should focus on the characterization of the default mode network in geriatric depression and how this network may interact with other cerebral systems to produce the depressive syndrome in late life.

Conclusions and Future Directions

Thus far most of the functional neuroimaging data in late-life depression have focused on patterns of cerebral abnormalities that characterize the illness. As with many areas of study of psychiatric illnesses, functional neuroimaging observations are notable for the variability of findings between studies. However, when considering evidence from multiple functional neuroimaging modalities, a general pattern of findings has emerged. For example, studies that examine cerebral activity using either cerebral glucose metabolism or BOLD fMRI, generally yield a pattern of functional abnormalities in select aspects of cortico-limbic networks, as well as elements of the default network, although the direction of the activation abnormalities (hypo versus hyper) tends to vary across imaging modalities and across the lifespan. Furthermore, abnormal activation in these systems not only appears to normalize, at least in part, in response to antidepressant treatment, but we are beginning to be able to dissociate networks associated with changes in cognitive symptoms from those associated with changes in affective symptoms (e.g., 151). To date, few molecular imaging studies have been performed in elderly depressed patients. However, based on the data in mid-life depressed patients and age related neurochemical changes, studies of monoamergic and glutamatergic systems are a logical focus of future molecular imaging studies. Additionally, studies of beta-amyloid and neuroinflammation may advance our understanding of the neurobiological basis of the cognitive and affective symptoms of the illness, including the increased risk of dementia associated with depression.

We believe a critical next step in geriatric depression research is to use functional neuroimaging techniques to focus on dysfunctions in the networks that have been implicated in the pathophysiology of depression and relate these specific network dysfunctions to salient features of the illness, including the response of both cognitive and affective symptoms to treatments. In July, 2010 NIMH published the NIMH Research Domain Criteria (RDoC) Project (152) which called for a search for “clinically relevant models of circuitry-behavior relationships”. The RDoC mandates that investigators focus “*on neural circuitry, with a level of analysis progressing…upwards from measures of circuitry function to clinically relevant variation*”. Due to the age-related vulnerability of some of the brain systems that have been implicated in mood disorders (e.g., dopamine system, cognitive control system), geriatric depression is likely to be associated with more severe cerebral abnormalities than in mid-life depression. Thus, consistent with the RDoC mandate, geriatric depression provides a logical context within which to study the role of specific functional abnormalities in both antidepressant response and key behavioral and cognitive abnormalities of mood disorders.

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