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Positron Emission Tomography Molecular Imaging in Late-Life Depression

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Abstract

Molecular imaging represents a bridge between basic and clinical neuroscience observations and provides many opportunities for translation and identifying mechanisms that may inform prevention and intervention strategies in late-life depression (LLD). Substantial advances in instrumentation and radiotracer chemistry have resulted in improved sensitivity and spatial resolution and the ability to study in vivo an increasing number of neurotransmitters, neuromodulators, and, importantly, neuropathological processes. Molecular brain imaging studies in LLD will be reviewed, with a primary focus on positron emission tomography. Future directions for the field of molecular imaging in LLD will be discussed, including integrating molecular imaging with genetic, neuropsychiatric, and cognitive outcomes and multimodality neuroimaging.

Keywords

positron emission tomography; molecular imaging; serotonin; dopamine; acetylcholine; depression

Introduction

The development of molecular brain imaging methods over the past 3 decades has had a significant influence on our ability to test neurobiological hypotheses of neuropsychiatric disorders based on an integration of clinical observations, preclinical data (including animal models), and postmortem data in the living human brain. Advances in instrumentation have improved spatial resolution, while advances in radiotracer chemistry have made possible the visualization of an increasing number of neurotransmitters, neuromodulators, and neuropathological processes. This article will review molecular brain imaging studies in late-life depression (LLD), with a primary focus on positron emission tomography (PET). Studies using single photon emission computed tomography are referenced for mechanisms

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and/or applications not yet investigated with PET. A brief introduction to PET imaging will be presented, followed by a section describing considerations in the design of molecular imaging studies and interpretation of molecular imaging data. The studies that have applied molecular imaging to LLD will be presented. The article concludes with a discussion of future directions for the field of molecular imaging in LLD.

Overview of PET Methodology

Positron emission tomography is an in vivo imaging technique that provides quantitative measures of physiological processes. A PET scan involves the detection of γ radioactivity from the intravenous administration of a radiotracer, which is a position-emitting isotope that is labeled to a pharmacologic agent as a tracer (subphysiological dose). The details of the PET method have been reviewed extensively.[1–3] The initial focus of radiochemistry development was on radiotracers to measure global neural activity, specifically the cerebral metabolic rate of glucose and regional cerebral blood flow (rCBF; [^{18}F]-2-deoxy-2-fluoro-D-glucose and [^{15}O]-water, respectively). The application of these radiotracers resulted in the initial observations of the functional neuroanatomy of the “resting state” and of the changes associated with behavioral activation in normal individuals as well as abnormalities observed in a range of neuropsychiatric diseases (eg, schizophrenia, depression, obsessive–compulsive disorder, and Alzheimer disease [AD]).[4–9] At the same time, selective radiotracers for transporters and receptors of neurotransmitter were being developed, with an initial focus on the dopamine (D2) receptor.[10,11] The development of these radiotracers for specific neurochemical targets made it possible to directly investigate neurochemical changes in neuropsychiatric disorders as well as relationships between drug dose, plasma concentrations, drug occupancy, and clinical response and have had a substantial impact on drug development.[12,13] Over the past 3 decades, radiotracer development has made possible the visualization of enzymes, neurotransmitter synthesis/metabolism, transporters, and receptor sites for a variety of neurotransmitter and neuromodulatory systems (including second messengers and neuropeptides, as reviewed by Sacher and Smith).[14] A major focus of radiochemistry development over the past decade is on the development of radiotracers to image neuropathological mechanisms that have been associated with neurodegenerative diseases. Such mechanisms include inflammation (radiotracers for the peripheral benzodiazepine receptor that bind to activated microglia), β-amyloid deposition (the Pittsburgh B compound and other radiotracers developed subsequently), tau (τ)-protein, and alpha (α)-synuclein.[15–18]

In parallel to advances in radiotracer chemistry, developments in instrumentation have resulted in substantial improvements in PET spatial resolution. The highest resolution PET scanner is the high-resolution research tomograph, a dedicated human brain PET scanner with a resolution of 2.3 to 3.4 mm.[19] Another major innovation in instrumentation has been the development of dual modality imaging. Positron emission tomography/computed tomography scanners were developed and are widely used in both clinical and research applications, followed by the recent development of PET/magnetic resonance (MR) scanners.[20,21] Simultaneous PET/MR imaging (MRI) will have important implications for understanding the relationship between changes in neural circuitry associated with drug interventions/cognitive paradigms and specific neurochemical and molecular processes.

Considerations Regarding the Design and Interpretation of PET Molecular Imaging Studies

The clinical and methodological aspects involved in the design, analysis, and interpretation of molecular imaging studies will be reviewed briefly. Although a majority of PET studies have examined patients and demographically matched controls in a cross-sectional manner, serial PET studies using within-patient designs are highly informative but logistically challenging. The repeated study of patients during the course of treatment provides important information to understand trait versus state-related effects as well as to evaluate the neurobiological substrates of treatment response and treatment resistance.

Clinical Considerations

Previous medication exposure, the duration of the unmedicated interval prior to scanning, and treatment response history may introduce variability into the results obtained. The majority of neurochemical imaging studies in neuropsychiatric disorders such as schizophrenia, major depression, and AD are conducted in patients who have never been treated or who have undergone a medication-free interval. The selection of such patients represents a challenge to patient recruitment and has also limited the ability to conduct neurochemical imaging studies in severely symptomatic patients (eg, mania and psychotic depression). In studies involving repeated imaging before and during the treatment, the primary considerations are whether the treatment interval for the medication being studied is sufficient to observe a consistent response (either response or non-response) and whether the duration between last medication dose and time of scan was controlled and drug concentrations prior to and after the scan were obtained.

Psychiatric and medical comorbidities are major issues in the design and interpretation of molecular imaging studies, particularly in the elderly patients. For example, given the high comorbidity of depression with anxiety disorders and with substance use disorders, samples that exclude such patients may not be representative of the population. At the same time, comorbid diagnoses may contribute variance into the results and should be considered in data analyses. Medical comorbidity is another major issue in studies of geriatric patients. For example, cerebrovascular disease is commonly observed in the elderly patients and findings such as white matter hyperintensities or strokes can be quantified using structural imaging (eg, MRI). In designing studies in the elderly patients, there is tension whether to enroll a highly selected sample of patients or to exclude the patients who are often those who present challenges in clinical management to obtain a more “homogeneous sample.” The limitation of studying highly selected patients is that the sample may not be representative of the population and may not capture severely ill or treatment-resistant patients for whom the neuroimaging data may be most informative as mentioned in the previous section. There are a number of considerations for selecting a comparison (control) group, including whether family history of psychiatric or neurological conditions should be excluded, should the controls be “matched” with the patient group in medical comorbidities, and should the controls be free of symptoms such as subjective cognitive complaints, subsyndromal anxiety, or depression that are common in the elderly patients.

Some of the most informative molecular imaging studies have explained within- and between-group variability based on correlations with affective or cognitive symptoms, personality traits, or genetic polymorphisms, even in the absence of between group differences. The primary limiting factor for this type of investigation is sample size. Most molecular imaging studies have relatively limited sample sizes, while studies to evaluate the functional correlates of genetic polymorphisms or correlations with clinical variables require larger sample sizes. The preselection of patients to enroll in neuroimaging studies based on genotype is an approach that could be implemented to make sure that the polymorphisms of interest are represented in the sample.

Methodological Considerations

By the time a radiotracer is approved for human use, the radio-tracer would have typically undergone rigorous evaluation in rodents, nonhuman primates, and humans, including "blocking" studies to determine the extent of specific binding to the target of interest versus nonspecific binding or binding to other targets to which the compound may bind based on the pharmacologic profile. Other aspects of radiotracer evaluation include measuring the temporal course of binding, specifically whether the half-life of the isotope is long enough to be able to image the molecular process of interest. Considerations for determining the suitability of a radiotracer include (1) how selective is the binding of the radiotracer to the target of interest; (2) how high are the ratios of specific to nonspecific binding; (3) do radiolabeled metabolites of the radiotracer enter the brain and are the metabolites found in high enough amounts to hinder quantification of specific binding; and (4) are the kinetics of the radiotracer such that the radiotracer reaches equilibrium and washes out within several half-lives of the radiotracer and in a reasonable amount of time so that duration of scanning is not too burdensome to the patients. In applying radiotracers to study patients, additional considerations include potential effects of the disease or acute/chronic intervention studied (1) on ligand delivery (particularly with respect to high affinity ligands whose binding is more blood flow dependent than lower affinity ligands), (2) on the rate of metabolism of the radiotracer, and (3) on endogenous neurotransmitter concentrations (if the radiotracer is sensitive to alterations in neurotransmitter concentrations). The ability to interpret the data obtained is largely determined by the degree to which the radiotracer has been characterized in terms of its binding profile and sensitivity to its endogenous competitor (eg, endogenous dopamine concentrations for D1 or D2 receptor). The quantification method used is another consideration, specifically whether or not the quantification method involved obtaining venous or arterial blood to measure radioactivity/metabolite concentrations or whether a reference region approach was used that involves deriving an input function from a region in the PET image that is devoid of or has low concentrations of the transporter or receptor of interest (eg, the cerebellum for D1 or D2 receptor or for β-amyloid imaging studies).

With respect to image processing, corrections for partial volume effects (imaging of less brain volume in a region of interest (ROI) due to cerebral atrophy) and correction for head movement during the scans are 2 challenging issues. Correction methods for both issues have been proposed and implemented.[22–25] Partial volume effects can result in a signal loss and can be observed as spillover of radioactivity between regions. This phenomenon occurs when the size of the region is similar to or smaller than the point spread function, being

attributed to the limited spatial resolution of the scanner. Head movement can occur, especially given the long scan protocols for some radiotracers (60–90 minutes or longer), and may be a more critical issue when studying symptomatic patients rather than treated patients.

Considerations with respect to data analyses include (1) whether structural brain scans are used for anatomical definition and correction for the effects of cerebral atrophy; (2) whether the tracer kinetic model has been validated; (3) whether a hypothesis-driven, ROI approach or a data-driven, voxel-wise approach is used (eg, statistical parametric mapping); and (4) the statistical procedures used (eg, analysis of variance, correction for multiple comparisons, and network analysis methods including principal component analysis).

Late-Life Depression

Cerebral Metabolism and rCBF

Positron emission tomography neuroimaging studies in affective disorders have focused on the characterization of rCBF and glucose metabolic alterations in mid-life patients with primary, unipolar depression and secondary depression in stroke, dementia, and movement disorders (Huntington and Parkinson disease). The effects of antidepressant interventions have been studied to evaluate the neural circuitry associated with treatment response and resistance. These results have been reviewed extensively.[14,26–28] Fewer studies comparing patients with LLD to controls or evaluating treatment effects in older patients have been performed.[29–34] The initial studies of rCBF and metabolism in LLD reported decreased cortical metabolism in patients relative to controls. Kumar et al reported widespread reductions in regional cerebral glucose metabolism in neocortical (frontal, temporal, parietal, and sensory motor), subcortical (caudate, lenticular nuclei, and right cerebellum), and paralimbic regions (anterior cingulate, posterior cingulate, and orbitofrontal) in patients with LLD compared to matched controls that may have the pathophysiological implications.[29] Similarly, Nobler et al reported that elderly patients with depression had reduced rCBF in frontal cortex compared with matched controls at baseline. After electroconvulsive treatment, responders showed further reductions in perfusion in frontal regions.[30] Subsequent studies observed increased cerebral glucose metabolism in patients with LLD in anterior (right and left superior frontal gyrus) and posterior (precuneus and inferior parietal lobule) cortical regions relative to normal controls.[34] The metabolic increases were correlated with greater depression and anxiety symptoms and were observed in regions that demonstrated cerebral atrophy. These increases in metabolism were observed in contrast to decreased metabolism observed in normal aging and neurodegenerative conditions such as AD. With respect to changes in cerebral metabolism associated with treatment, studies in patients with LLD observed decreased anterior cortical and limbic metabolism and increases in posterior cortical regions and cerebellum with antidepressant treatment (including selective serotonin reuptake inhibitors [SSRIs] and total sleep deprivation).[32,33,35,36] Further, the cerebral metabolic response to a single, intravenous dose of citalopram, specifically greater reductions in anterior cortical regions and increases in posterior cortical regions, was associated with greater clinical improvement after a 12-week trial of the oral medication.[37] Although changes in neural circuitry with antidepressant treatment have been observed in

patients with mid-life depression and LLD, the relationship to improvement in domains of symptoms is not well understood. Functional connectivity methods have identified neural networks associated with improvement in affective and cognitive symptoms in patients with LLD who underwent PET glucose metabolism studies prior to and during a course of citalopram treatment.[36] The partial least squares method identified that a subcortical–limbic–frontal network was associated with improvement in affective symptoms (mood and anxiety), while a medial temporal–parietal–frontal network was associated with improvement in cognition symptoms (immediate verbal learning/memory and verbal fluency). 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 dementia and may reflect neuronal vulnerability to neurodegenerative processes, such as β-amyloid deposition.[38] Studies to test these hypotheses are ongoing. 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.

Molecular Imaging

The initial application of neurochemical imaging methods to affective disorders was to test the hypothesis of decreased mono-aminergic function (norepinephrine, dopamine, and, in particular, serotonin) in depression.[39,40] The majority of the studies have been performed in patients with mid-life depression. The subsequent review will summarize the results of the mid-life studies and discuss studies performed in patients with LLD.

The Dopamine System

Several lines of evidence support dopamine hypofunction in mid-life depression.[41,42] The data include improvement in depressive symptoms with dopamine agonists, the induction of a depressive relapse by pharmacologic depletion of dopamine, low cerebrospinal fluid homovanillic acid levels in patients with depression compared to controls, and postmortem data showing a loss of dopamine transporters and receptors. In postmortem studies, reduced dopamine transporter concentrations were found in the central and basal nuclei of the amygdala in major depression.[43] Bowden et al reported no differences in the number or affinity of D1 or D2 receptors in caudate, putamen, and nucleus accumbens between suicides that had been free of antidepressants for at least 3 months prior to death and age-matched controls. However, increased number of binding sites and decreased affinity of D2 receptors were found in each brain region of antidepressant-treated suicides.[44]

The available molecular imaging data suggest modest decreases or no change in dopamine metabolism, dopamine transporter, and D1 and D2 receptors.[45–47] Dopamine transporters were reduced in patients with depression relative to controls.[46] With respect to the D1 receptor, decreased D1 receptors were observed in the left middle caudate in 1 report.[48] Several studies of striatal and extrastriatal D2 receptors have not shown differences between patients and controls, including studies in medication naive patients.[49–52] Greater psychomotor slowing has been associated with increased striatal D2 receptors, indicating that differences may be observed in subgroups of patients with depression.[53] No differences

in amphetamine-induced striatal dopamine release ([^{11}C]-raclopride) have been observed in patients with either euthymic bipolar or euthymic unipolar depression.[50,54] Several lines of evidence suggest that dopamine dysfunction may play a more prominent role in LLD. A substantial age-related decline in dopamine transporters and receptors is observed by Volkow et al.[55,56] Furthermore, the evidence for the augmentation of the antidepressant response by psychostimulants, such as methylphenidate, supports the further investigation of the dopamine system in LLD.[55–57] A better understanding of the nature of the dopaminergic deficits in LLD would lead to targeted treatments that would potentially be more effective, especially for symptoms such as apathy and psychomotor slowing.

The Serotonin System

The evidence for serotonin hypofunction in major depression, based on changes in symptoms with acute pharmacologic interventions of the serotonin system, neuroendocrine challenge studies, measurements of serotonin metabolites in cerebrospinal fluid, and plasma and post-mortem studies supported PET neuroimaging studies of the serotonin system in patients with depression.[58,59] The majority of studies have been performed in younger patients with depression. McKeith et al reported a nonsignificant increase in 5-hydroxytryptamine (5-HT) 2 receptors in the prefrontal cortex (BA10) in patients with affective disorders (the sample included patients with unipolar, bipolar, and dysthymic disorders) compared to controls.[60] Further, Arango et al reported an increase in 5-HT2 receptor binding to the prefrontal cortex in patients who committed suicide compared to controls.[61] Stockmeier et al reported increased 5-HT1A binding to the midbrain dorsal raphe of suicide victims with major depression compared to controls.[62] Thomas et al reported no difference in serotonin transporters in older patients with depression as compared to controls.[63]

Neurochemical imaging studies have evaluated serotonin synthesis, serotonin transporters (the initial target site of action of the SSRIs), as well as 5-HT1A and 5-HT2A receptors. Reduced cortical serotonin synthesis in mid-life depression has been observed in several studies using the radiotracers [^{11}C]-5-hydroxytryptophan and α-[^{11}C]methyl-L-tryptophan.[64,65] Serotonin synthesis was reduced in anterior cingulate gyrus (bilaterally in females and left hemisphere in males) and left medial temporal cortex in patients with unmedicated depression.[65] Studies have evaluated serotonin transporters, 5-HT1A, and 5-HT2A receptors in patients with mid-life unipolar and bipolar depression. Increased serotonin transporters,[66,67] decreased serotonin transporters,[68–70] or no difference in serotonin transporters has been reported in patients with mid-life, unmedicated, recovered, or current depression.[71,72] Although the direction of the results across studies is different, the regions implicated are remarkably consistent (eg, cingulate gyrus, frontal cortex, insula, thalamus, and striatum). The factors that may contribute to differences across studies include differences in sample characteristics or the radiotracers used [^{11}C]-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)benzonitrile vs [^{11}C]-(+)-6-[4-(methylsulfanyl)phenyl]-1,2,3,5,6,10β-hexahydr opyrrolo[2,1-a]isoquinoline. Two studies have reported that higher baseline serotonin transporters predicted remission to acute fluoxetine treatment as well as remission at 1 year.[69,73] Serotonin transporter occupancy by SSRIs has been evaluated in patients with mid-life depression and LLD. Studies in patients

with mid-life depression treated for 4 weeks with either paroxetine or citalopram have reported significant serotonin transporter occupancy in caudate, putamen, and thalamus in addition to prefrontal and anterior cingulate cortices. The magnitude occupancy for both compounds was similar, ranging from 65% to 87% across regions.[74] The magnitude of occupancy and the relationship between brain occupancy and plasma concentrations is consistent with that observed in elderly patients with depression treated with the citalopram at steady state doses.[75] Significant overlap between regions of serotonin transporter occupancy that were correlated with improvement in depressive symptoms and regions of cerebral metabolic alterations by citalopram was observed (eg, anterior cingulate gyrus, middle frontal gyrus, precuneus, inferior parietal lobule, and cuneus).[32,36,76] Importantly, positive correlations were observed between the improvement in depressive symptoms and greater serotonin transporter occupancy in the anterior cingulate gyrus (bilaterally), left middle and inferior frontal gyrus, right superior and middle temporal gyrus, right precuneus, left inferior parietal lobule, parahippocampal gyrus (bilaterally), and left cuneus. The findings suggest that cortical and limbic serotonin transporter occupancy may be an underlying mechanism for the regional cerebral metabolic effects of citalopram in LLD. Furthermore, serotonin transporter occupancy in cortical and limbic regions is associated with treatment response, a finding that has not yet been reported in patients with mid-life depression. Studies of the 5-HT1A receptor have either shown decreased[77–79] or increased receptors.[80] A correlation between higher baseline 5-HT1A receptors and poorer treatment response has been reported.[81,82] One study of patients with LLD observed decreased 5-HT1A receptors in the dorsal raphe as well as in the middle temporal cortex and hippocampus.[83] Alterations in 5-HT1A receptors following SSRI treatment have not been observed in human neuroimaging studies.[78,82] This finding is unexpected as animal studies show 5-HT1A desensitization induced by SSRI treatment, and a decrease in receptors in the human studies would be expected.[84] 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 change with treatment may be observed in high-affinity sites. The 5-HT2A receptors have been reported to be unchanged in patients with both mid-life depression and LLD.[85,86] Decreases have been observed in one study in orbitofrontal cortex[87] and in hippocampus in a second study.[88] Some studies observed increased receptors.[89,90] Antidepressant treatment studies have shown either a decrease[85,91] or an increase in 5-HT2A receptors.[92,93] The discrepancy between studies may be due to differences in antidepressant drugs or radiotracers used. At the present time, there are no published studies on the effects of antidepressant treatment on the 5-HT1A or 5-HT2A receptors in LLD.

Other Neurochemical Systems

Other neurobiological mechanisms and therapeutic targets have been evaluated in younger patients with depression and may have implications for patients with LLD. Regarding the muscarinic (M2) receptor, Cannon et al found that M2 receptors were decreased in the anterior cingulate cortex of patients with bipolar disorder compared with major depression and healthy controls using [^{18}F](3-(3-(3-fluoropropyl)thio)-1,2,5-thiadiazol-4-yl)-1,2,5,6-tetrahydro-1-methylpyridine.[94] Administration of the muscarinic receptor antagonist scopolamine has been associated with a rapid onset of antidepressant effects as reviewed by Drevets et al.[95] Clinical and preclinical evidence suggests glutamatergic hyperactivity in

depression. Recently, the metabotropic glutamate receptor subtype 5 (mGluR5) has been proposed as a potential target for novel therapeutic approaches to depression.[96–98] Positron emission tomography studies have demonstrated lower mGluR5 receptors in prefrontal cortex, cingulate cortex, insula, thalamus, and hippocampus in patients with mid-life depression relative to controls. Greater depression severity was correlated with lower mGluR5 receptors in hippocampus.[99] With respect to the N-methyl-D-aspartate (NMDA) receptor subtype, studies have shown that the NMDA antagonist ketamine is associated with a rapid onset of antidepressant effects. The mechanism of action of ketamine is an active area of investigation as well as other molecular imaging studies are performed to better elucidate the glutamatergic deficit in LLD.[100] γ-Aminobutyric acid (GABA) is the main inhibitory transmitter in the central nervous system, and several preclinical and clinical studies have implicated GABA involvement in the neurobiological processes behind mood regulation.[101,102] However, the precise mechanistic action behind its role remains unclear. In a postmortem study, Khundakar et al reported a significant reduction in parvalbumin-containing GABAergic neurons selectively in layer 6 of the dorsolateral prefrontal cortex in patients with LLD compared to controls.[103] In the cases of the treatments targeted at the M2 muscarinic receptor, the glutamate and GABA receptor subtypes, direct evidence of dysfunction of these systems in LLD and the evaluation of whether the nature of the deficits are the same as younger patients with depression would be needed before initiating treatment. This is particularly important since the medications discussed might be associated with greater side effects, including delirium in the elderly patients (eg, scopolamine and ketamine).[104]

Neuropathology

There are several postmortem studies in LLD. Sweet et al observed that patients with LLD having evidence of dementia prior to death had significant amounts of AD pathology. Neuritic plaque concentrations were high in the entorhinal cortex, middle frontal gyrus, inferior parietal cortex, and superior temporal gyrus. Neurofibrillary tangles were observed in high concentrations in the entorhinal cortex, and Lewy body pathology was observed in high concentrations in the nucleus basalis of Meynert in half of the patients.[105] On the other hand, Tsopelas et al reported that patients with LLD who had no premorbid dementia had Lewy bodies in the substantia nigra and the locus ceruleus and neuronal loss in the hippocampus and in subcortical structures (nucleus basalis, substantia nigra, and raphe nucleus). Depression was not associated with cerebrovascular or Alzheimer pathology (neurofibrillary tangles) in cortical and subcortical areas.[106] Thus, in patients with LLD with and without cognitive impairment prior to death, Lewy bodies in subcortical monoaminergic nuclei is a consistent finding. Postmortem cellular morphometry studies can be informative in the identification of discrete changes in brain microstructure in depression. There are varying degrees and types of neuronal and glial cell pathology in depression from young to late life, which may suggest a different pathophysiological basis for depression, with vascular factors (eg, microvascular lesions and postischemic inflammatory changes) playing a potentially greater role in late life as reviewed by Khundakar and Thomas.[107]

In the initial study of β-amyloid deposition in LLD evaluated, patients with LLD who met criteria for amnestic mild cognitive impairment (MCI) demonstrated greater β-amyloid

deposition than those with nonamnestic MCI and participants who were cognitively normal.[108] These results are consistent with that of nondepressed participants with cognitive impairment. In a study of patients with LLD who did not meet criteria for MCI, greater β-amyloid deposition relative to controls was observed in the anterior cingulate gyrus, superior and middle frontal gyrus, left orbitofrontal gyrus, precuneus, bilateral insula, and left parahippocampal gyrus.[109] Kumar et al reported that 2-(1-(6-[(2-[^{18}F]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene)malononitrile ([^{18}F]-FDDNP) binding was significantly higher in the posterior cingulate and lateral temporal regions in patients with LLD compared with controls, which may reflect either greater concentrations of β-amyloid or τ-protein.[110] Interestingly, in patients with MCI and cognitively normal controls, greater depression and higher anxiety symptoms were associated with higher [^{18}F]-FDDNP binding.[111] These studies suggest that normal controls with depressive symptoms and patients with depression without cognitive impairment may demonstrate AD neuropathology.

Inflammation may be a common underlying mechanism for depression and cognitive impairment, as well as cardiovascular disease, diabetes, and cancer, and may be more relevant to LLD, given the increasing medical comorbidity in late life.[28,112–114] Hannestad et al reported that there was no significant differences in translocator protein (TSPO) binding between major depression and controls (using the TSPO radiotracer [^{11}C]PBR28). Future studies are needed to determine whether individuals with depression who have elevated levels of systemic inflammation or cerebrovascular disease measured by MRI might demonstrate higher TSPO binding than controls.[115] For example, MRI studies suggest that white matter lesions in frontostriatal pathways in patients with depression may be vascular in origin. Patients with such lesions may have higher TSPO binding.[116]

Conclusion

Positron emission tomography studies in patients with LLD, thus far, have focused on elucidating the functional neuroanatomy and neural circuitry associated with treatment response. The studies using radiotracers for specific neurotransmitters or neuropathological processes in patients with LLD are limited. 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 β-amyloid deposition in LLD as a mechanism underlying cognitive impairment that might be related to the increased risk of AD in patients with depression. There are several other potentially relevant molecular targets for which radiotracers are in development and/or promising new radiotracers are available. With respect to other monoaminergic targets, radiotracers for other serotonin receptors are being evaluated which may elucidate the role of serotonin in affective and cognitive symptoms, including 5-HT1b,[117] 5-HT4,[118] and 5-HT6 receptors.[119] The development of radiotracers for the noradrenergic system has been challenging due to the lack of pharmacologically selective agent and the low signal-to-noise levels of binding in the brain. Recently developed radiotracers for the norepinephrine transporter have been developed and look promising.[120] The reports of rapid antidepressant effects of ketamine and scopolamine have renewed interested in the glutamatergic and muscarinic systems.[121,122] These systems may be especially relevant to cognitive impairment in LLD

and may represent a pathophysiological link to AD.[123] Finally, inflammation may be a common underlying mechanism for depression and neurodegeneration and may be more relevant to LLD given the increasing medical comorbidity in late life.[112,124] Thus, future studies can test hypotheses using these radiotracers and mechanisms identified to understand the neurobiology of treatment resistance and of cognitive impairment in both late-life unipolar and bipolar depression. The use of molecular imaging to understand the mechanisms underlying the increased risk of dementia associated with depression is critical to developing strategies for prevention and intervention.

Future Directions

The present review focused on molecular imaging studies in LLD to identify alterations in neural circuitry, neurochemical, and neuropathological mechanisms. In reflecting on the studies presented, the importance of further investigation of mood symptoms in the normal aging process to potentially identify the earliest mechanisms of risk of psychiatric and neurodegenerative diseases cannot be overstated. This is particularly important as many neurodegenerative diseases first present with mood or other neuropsychiatric symptoms. Important areas of focus for future studies in LLD include further studies to investigate neurobiological mechanisms of risk genes for mood disorders identified in neuropsychiatric diseases, multimodality imaging studies to understand changes in neural circuitry for mood, reward, and cognition relative to changes in neurochemistry and to neuropathology, and combined radiotracer studies to evaluate alterations in neurotransmitter interactions (eg, dopamine and serotonin modulation of other monoamines, acetylcholine, and glutamate) would be an important and unique opportunity to inform the development of treatment strategies. Similar considerations and priorities apply to studying secondary depression in neurodegenerative diseases such as MCI, AD, and Parkinson disease.

With respect to identifying targets for more effective treatments, possible mechanisms include neuroreceptor modulators other than the approved psychotropic medications (eg, 5-HT4 partial agonists and monoamine stabilizers)[125–127] as well as neural circuitry-based interventions such as transcranial magnetic stimulation.

It is important to note that other neuropsychiatric disorders of late life are associated with cognitive impairment and disability and have not been a major focus of molecular imaging studies. Among the most important conditions are late-life schizophrenia, bipolar disorder, posttraumatic stress disorders, and generalized anxiety disorders. There are fundamental issues of clinical management in such patients as the medications that are effective in younger patients are not as effective in older patients and are associated with greater side effects in the elderly patients (eg, antipsychotics, mood stabilizers, and benzodiazepines), as well as medical comorbidities, cognitive deficits, and motor symptoms. Molecular imaging in these conditions is important to identify whether the neural circuitry and neurobiological mechanisms are same or different between young and older patients, to evaluate drug occupancy, dosing, and symptom/side effect relationships to determine whether lower doses of the medications are equally effective and safe, to determine whether the neurobiological mechanisms of cognitive impairment are same or different from neurodegenerative diseases, and to determine whether different medications or more careful monitoring is needed in

patients who have evidence of neuropathology (eg, β-amyloid deposition, τ protein, or neuroinflammation). Thus, studies performed during the course of treatment that are designed to understand the neurobiological mechanisms of treatment response, the role of drug occupancy in treatment response, as well as multimodality imaging studies to evaluate molecular mechanisms relative to structural brain changes or cerebrovascular disease (PET and MR) or multiple PET tracers to evaluate the impact of neuropathology on neurochemical mechanisms.

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