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Recent Advances in Neuroimaging Biomarkers in Geriatric Psychiatry

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Abstract Neuroimaging, both structural and functional, serve as useful adjuncts to clinical assessment, and can provide objective, reliable means of assessing disease presence and process in the aging population. In the following review we briefly explain current imaging methodologies. Then, we analyze recent developments in developing neuroimaging biomarkers for two highly prevalent disorders in the elderly population- Alzheimer's disease (AD) and late-life depression (LLD). In AD, efforts are focused on early diagnosis through in vivo visualization of disease pathophysiology. In LLD, recent imaging evidence supports the role of white matter ischemic changes in the pathogenesis of depression in the elderly, the "vascular hypothesis." Finally, we discuss potential roles for neuroimaging biomarkers in geriatric psychiatry in the future.

Keywords Geriatric · Psychiatry · Neuroimaging · Biomarkers · Dementia · Alzheimer's disease (AD) · Late-life depression (LLD) · MRI · DTI · fMRI · PET · FDG-PET · Pittsburgh Compound B (PiB) · White matter lesions (WML) · Resting-state network · Vascular hypothesis

Introduction

The increasingly aged population of the United States brings with it myriad public health concerns. Nowhere is this more evident than within geriatric psychiatry, where individuals who would have previously passed away from now-preventable or modifiable causes of disease, are now living to develop diseases of high morbidity, such as Alzheimer's disease (AD) and late-life depression (LLD). Such disorders have devastating emotional and cognitive effects on both patients and their families; however the absence of effective therapies in the former, and the treatment refractory nature of the latter, have increased the need for ways to diagnose such disorders earlier, to begin disease-modifying therapies; and to develop tools to assess new diagnostic and therapeutic approaches, such as pharmaceutical compounds.

A term often used in the field is biomarker. But what exactly is a biomarker? A biomarker is a physiologic, biochemical, or anatomic parameter that can be objectively measured as an indicator of normal biologic processes, pathologic processes, or responses to a therapeutic intervention [1]. Biomarkers are not mechanisms. They do not necessarily explain underlying disease pathophysiology, in the same way that body temperature is a biomarker of fever, but does not in itself explain the inflammatory process underlying fever. However, in geriatric psychiatry biomarkers can offer a more objective, reliable means of assessing both disease presence and process in geriatric psychiatry. In the following article, we present a general review of recent advances in neuroimaging biomarkers in geriatric psychiatry.

Currently in the clinical evaluation of mood disorders, neuroimaging is primarily used to rule out acute or gross sources of insult, such as hematoma or mass lesions. In mood disorders research, however, neuroimaging has long been used, with findings being shown to associate both with depression subtypes and treatment response. However, neuroimaging biomarkers still remain within the academic realm, with disease guidelines for geriatric mood disorders still focusing primarily on interview-based diagnoses by human clinicians. In addition, while qualitative neuroimaging is often used in the clinical evaluation of dementia,

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quantitative imaging biomarkers (for example, hippocampal volume) are still primarily research tools and are yet to be integrated into clinical practice. In research studies neuroimaging is also increasingly being used as a surrogate outcomes measure, its lower variance leading to lower sample size.

Introduction to Neuroimaging

Neuroimaging can be divided into two basic types: structural and functional.

Structural Imaging

Computed tomography, or CT scan, uses X-rays that produce a series of images showing slices of an organ, such as the brain, which can then be reconstructed into 3-D images. Commonly available in most medical centers, CT is useful in determining the presence of surgically treatable or modifiable causes of brain disease, such as mass lesions, hydrocephalus, or intracranial hematoma, as well as gross changes in grey/white matter such as stroke. However, CT is less sensitive in detecting subtle grey matter atrophy, or early diffuse cerebrovascular disease in white matter. Thus, for disorders such as Alzheimer's and late-life depression, which involve often-subtle and widespread neuroanatomical changes, magnetic resonance imaging (MRI) is the structural modality of choice. MRI utilizes a large stationary magnet, and electromagnetic changes in protons in water molecules in brain tissue for anatomic 3-D reconstruction with high spatial resolution. Different MRI pulse sequences can be used to acquire images with contrast specific for the tissues of interest, e.g., T1-weighted imaging has excellent grey-white contrast, T2-weighted can detect ischemic changes in the white matter. Of particular note, diffusion tensor imaging (DTI) in MR measures the restricted diffusion of water through white matter tracts, and thus can detect pathologic changes in myelination. Other recently developed methodologies include magnetization transfer ratio (MTR) imaging, which improves image contrast in MRI based on the application of off-resonance radio-frequency pulses and their effects on MR signal intensity; this has been used as a complement to DTI in assessing myelin integrity. In addition, magnetic resonance spectroscopy (MRS) can measure concentrations of widespread compounds like amino acids or membrane lipids by utilizing their unique MR spectra, and thus provide quantitative biochemical data on geriatric disorders.

Functional Imaging

Functional imaging studies have mainly used functional MRI or PET. Functional MRI (fMRI) can be subdivided into either task-based or resting-state fMRI. Task-based fMRI is based on detection temporal fluctuations in blood oxygen level-dependent, or BOLD, signal intensity across areas of the brain during a defined task (e.g., a cognitive, emotional, or motor task). Areas with increased synaptic activity have corresponding increased increase in local blood, leading to an increase in the ratio of oxygenate/de-oxygenated hemoglobin. This change in the hemoglobin ratio leads to an increase in the T2* MRI contrast; this is the BOLD fMRI signal. Thus the regional increase in synaptic can be localized by comparing the BOLD signal acquired during an experimental condition the task with the images acquired during a control condition: the subtraction of the control condition from the experimental condition give the activation map. The temporal synchronicity between anatomically distinct regions can be analyzed to infer functionally connected networks. Comparison of these functional networks between control and disease subjects can thus provide useful insights into the neuroanatomical substrates underlying performance on the specific experimental task. An alternative to task-based functional imaging is task-free, or resting-state functional MRI. As first described by Raichle and colleagues in 2007 [2], there exists an organized, baseline default mode of brain function that is suspended during specific goal-directed behaviors. Analysis of this network, and other resting state networks, provides insight into the functional activation differences between individuals, even without the in-scanner performance of a task. This has particular advantage with geriatric patients where severe cognitive deficits can interfere with task performance.

Positron emission tomography (PET) is another brain imaging system used for studying brain function. PET scans produce 3D images of the brain by detecting pairs of gamma rays emitted indirectly by a positron-emitting isotope radionuclide carried in a biologically active molecule. Regional brain activation is usually measured in PET, using 18 F 2-fluorodeoxy-D-glucose (FDG), a glucose analogue. FDG-PET reflects regional brain metabolic activity defined by the tissue uptake of glucose. A non-contrast brain CT obtained concurrently defines the 3D images of tracer concentration. In addition to FDG, radiotracers have also been developed for other compounds, such as ligands for specific neurotransmitter systems, like serotonin transporters, or disease-specific pathologies, like amyloid in Alzheimer's, thus permitting visualization of specific neuroreceptor pools or disease pathologies. Thus, the utility of PET has been extended through the further development of pertinent radiotracers.

Alzheimer's Disease

Of all geriatric disorders, dementia- a syndrome marked by persistent, often irreversible cognitive decline- is the most feared. While not a normal part of aging, aging is the single

greatest risk factor- after 65 years of age, the lifetime risk of developing dementia is 17-20 percent. Alzheimer's disease, the most common form of dementia (70 % of dementia cases) , affects more than 5.4 million Americans, and that number is expected to more than triple by 2050 [3]. A transitional stage between normal cognition and AD exists, called mild cognitive impairment (MCI); each year, 10-15 % of MCI patients progress to AD. As AD costs the US over $200 billion in direct medical costs annually, and no current treatments exist to reverse or even halt disease progression, neuroimaging biomarkers are urgently needed to better define diagnosis, progression, and treatment effect.

A discussion of neuroimaging biomarkers in Alzheimer's disease must begin with a brief overview of neuropathology, as imaging research strives to replicate and anticipate in vivo the well-known cellular markers found postmortem, namely extracellular beta-amyloid plaques and intracellular neurofibrillary tangles [4]. Amyloid, a normal transmembrane protein, is broken down into a beta fragment, which then abnormally accumulates in beta-pleated sheets and forms neurotoxic beta-amyloid (AB) plaques within the brain, thought to be the first observable pathology in Alzheimer's disease. Tau, a component of cytoskeletal microtubules, becomes hyperphosphorylated in AD, dissociating and forming insoluble neurofibrillary tangles inside neurons. As found by Braak and Braak [5], these neurofibrillary tangles proliferate and progress in characteristic stages, from the entorhinal cortex to hippocampus to neocortex, with clinical evidence of dementia starting at neocortical stages 3-4. Braak staging correlates well with cognitive impairment, and results in neuronal dysfunction, synaptic loss, and cell death, with progressive atrophy starting in the medial temporal lobes.

Structural imaging has thus endeavored to find antemortem biomarkers of these well-known pathologic findings. Structural MRI, with its ability to detect subtle changes in grey and white matter, has focused on visualizing atrophy within AD brains. The topographic distribution of atrophy on MRI has been found to map well with Braak staging in subjects who underwent both antemortem MRI and postmortem staging [6, 7]. Also, in recent years, MRI research in Alzheimer's disease has progressed from qualitative visual assessment, to manual hippocampal volumetry (with inherent operator variability), to automated software like Harvard's Freesurfer (http://surfer.nmr.mgh.harvard.edu), utilizing voxel-based and region-based methods, including measures of cortical thickness. Using one such automated method, tensor-based morphometry (TBM), Hua and colleagues [8] found that rates of brain atrophy, vs. simply atrophy volume, correlated with rates of concurrent cognitive decline. In addition, research has expanded beyond grey matter analysis to white matter tracts, via DTI. DTI has been used to differentiate AD from FTLD and DLB [9, 10], and white matter changes in DTI correlate with both regional cortical atrophy and cognitive function [11].

However, given that atrophy is thought to occur later in the disease process than beta-amyloid plaques, effort has focused on the visualization of these plaques, and possible relationships between amyloid deposition and disease severity and progression. PET, with its ability to utilize targeted radiotracers, such as toward beta-amyloid, provides an important means of developing early neuroimaging biomarkers. The first amyloid-imaging tracer, Pittsburgh Compound-B (PiB), labeled with carbon 11, was developed almost a decade ago [12] and was shown to have marked retention in brain areas containing amyloid deposition postmortem. PiB remains very frequently used for research studies of amyloid deposition. However, given its half-life of only 20.4 minutes, PiB use is limited to a minority of PET centers that can produce it on-site. Recently, two new PET AB-binding agents, (flutemetamol and florbetapir) have been developed that utilize the fluorine 18 isotope, with a greatly increased half-life of 109.8 minutes, allowing effective distribution within a 2-4 hour radius and greatly widening its availability (and commercial viability) [13]. Since their development, many studies have verified the sensitivity and specificity of 18-F tracers for amyloid plaques in AD antemortem [14–17] at postmortem autopsy [18••, 19] and had high comparability to PiB results, even within the same brain [20]. As a result, the FDA recently approved Florbetapir for clinical use in April 2012.

In functional neuroimaging, work on Alzheimer's has focused on finding early functional biomarkers in Alzheimer's, particularly in at-risk asymptomatic or MCI subjects. For example, most investigators have found decreased activation in task-based fMRI in AD subjects vs. age-matched controls, logically consistent with a clinical picture of cognitive decline. However, research has also shown increased activation strength in subjects with MCI, particularly in the hippocampus [21–24]. One explanation for increased activation in at-risk subjects is compensation in the face of progressive neurodegeneration; others believe that hyperactivation may represent a pathological state in and of itself contributing to future disease. Further work in MCI hyperactivation may help provide another early neuroimaging biomarker before the onset of clinical Alzheimer's.

Another exciting area of recent research is resting state fMRI. Buckner [25] initially found that posterior cortical areas active in the resting state coincide with areas known to be susceptible to amyloid deposition and depressed glucose metabolism in AD; since then, disruption of resting state network connectivity has been shown in cognitively normal subjects with high amyloid burden [26–28]. Both increases [29], decreases [30], and a mixed pattern [15, 31] in resting network connectivity have been described in MCI and asymptomatic at-risk subjects. Whether resting state fMRI

overall decreases, increases, or shows a mixed pattern is a subject for further clarification in its development as a neuroimaging biomarker.

FDG-PET studies in Alzheimer's reflect brain metabolism, and so synaptic activity during mental processes. Decreased FDG uptake thus is an indicator of impaired synaptic function. Both MCI and mildly affected AD subjects show a decrease in FDG uptake in comparison to controls [32]. FDG-PET shows promise in early diagnosis of transition from MCI to AD, particularly in combination with other modalities [33].

Given the increasing prevalence of Alzheimer's disease in the population, and the continued high costs of advanced neuroimaging modalities, several studies have also investigated the potential use of other biomarkers, such as cerebrospinal fluid (CSF) measures of amyloid-beta [42] (AB42). AB42 has been shown to be reliably decreased in Alzheimer's disease; and unlike expensive neuroimaging modalities, CSF can be quickly and relatively cheaply obtained. Recent studies have shown that CSF amyloid reliably and inversely correlates with PET PiB imaging [13, 34, 35•]. Thus, in the future CSF biomarkers may serve as a reliable and sensitive early measure of detecting disease, to be followed up with more involved neuroimaging studies.

Currently there are no approved disease modifying therapies for Alzheimer's disease; existing treatments provide symptomatic improvement, but fail to reverse or even halt disease progress [36]. A current focus of research involves early identification of individuals at risk, accurate differential diagnosis, and early treatment initiation to potentially prevent progression to dementia. Indeed, a recent paper by Jack and colleagues [37••] proposed a model relating disease stage (from asymptomatic to AD) with biomarkers (including neuroimaging), in which amyloid biomarkers become abnormal first, before neurodegenerative MRI biomarkers and cognitive symptoms, these changes correlating with clinical symptom severity [1]. Recently revised guidelines for Alzheimer's disease from the National Institute on Aging and Alzheimer's Association, while still focusing on clinical criteria, have begun incorporating biomarkers, including neuroimaging biomarkers via MRI and PET, into the diagnostic process [38••]. These revisions only serve to highlight the increasingly large role neuroimaging is playing in clinical practice as well as research.

Late-life Depression

Depression is the most common psychiatric disorder (non-dementia) in the elderly, affecting over 6.5 million Americans over age [39, 65]. Late-life depression is not a clinically separate entity from major depressive disorder (MDD). Indeed, the very definition of geriatric depression as either late-life depression (LLD)- MDD in older patients- vs. late-onset depression (LOD)- new onset of depression at an older age- remains a subject of debate. However, it is increasingly recognized that geriatric depression has distinct features from MDD in younger patients, including detrimental cognitive effects and treatment resistance. Thus, neuroimaging biomarkers serve a crucial role, in delineating the neuroanatomcal substrates of LLD, distinguishing between MDD in younger vs. older patients, and determining treatment efficacy in LLD.

Structural neuroimaging provides both qualitative and quantitative information on underlying neuroanatomical changes in LLD, both in grey matter regions of interest (ROI) and white matter ischemic lesions.

Several laboratories have found reduced grey matter volume in the cortico-striato-limbic circuit reduced in LLD. Multiple studies have shown various combinations of reduced volumes in the prefrontal cortex [40–43] , caudate [44], amygdala [45] and hippocampus [40, 46] variations in findings can be ascribed to differences in study methodologies. For example, studies showing no change in hippocampal volume [41, 42] utilized self-report for depressive symptoms, while those showing hippocampal reduction [40, 46] defined depression by clinical diagnosis.

Some laboratories have pursued a reductionist approach, by examining subdivisions of the above area to further localize specific structural differences in LLD. For example, Chang [43] extended reduced prefrontal volumes in geriatric depression to include the dorsolateral prefrontal cortex. Other studies have focused on the temporal aspect of structural changes, to further delineate a neuroanatomical difference between early-onset LLD (i.e., the first episode of depression started in mid-life or earlier) general) depression and late-onset depression. Andreescu [40] found that volume reductions in multiple areas across the frontal, temporal, and parietal lobes correlated with a later age of onset. Another very recent study [47] compared elderly subjects with early-onset vs. late-onset depression, and found that late-onset correlated with a greater rate of hippocampal volume loss, as well as greater cognitive decline.

Lastly, longitudinal studies have focused on the complex relationship between late-life depression, cognitive decline, and associated grey matter structural changes over progression of the disorder. As has been discussed, dementia is well-known to be associated with grey matter structural changes; however, as late-life depression has been shown to be associated with cognitive impairment, as well as being a risk factor for dementia, it is difficult to dissociate the specific grey matter pathophysiologic changes specific to late-life depression, and not dementia (or prodromal dementia). However, two recent studies of depressed non-demented older adults vs. non-depressed non-demented controls [48, 49] found late-life

depression (nondemented) was associated with greater hippocampal volume over several years, and that hippocampal atrophy was associated with subsequent decline in mini-mental status exam (MMSE) scores among the depressed group. Thus, even outside of the dementia population, grey matter volume reductions have been linked in late-life depression with greater risk of cognitive decline. It is important to note, however, that further studies are needed to determine what grey matter volumetric changes, as potential biomarkers for late-life depression, actually represent: changes in neuropil, alterations in glial cell density or synaptic density, or changes in the density and size of neurons.

Beyond grey matter, a large body of work has revolved around changes in white matter tracts, and their relationship to late-life depression and associated cognitive decline. White matter lesions (WMLs) represent areas of hyperintensity on T2-weighted and FLAIR MRI images; while the precise etiology of WMLs remains unclear, it is likely that they reflect underlying cerebrovascular disease, including small vessel ischemic change [50]. A series of seminal studies in the 1990s found important correlations between such lesions and LLD generally, and more specifically to LOD [51, 52]. This ultimately led to the vascular depression hypothesis [53], which posited that cerebrovascular disease contributes to geriatric depression by affected subcortical white matter structures involved in mood regulation.

Structural neuroimaging studies have further elaborated the potential role of WML as a biomarker of late-life depression. Recently, the severity of WML in elderly depressed was shown in a large European multi-center MRI study to predict both depressive episodes and depressive symptoms [54]. WML burden has also served to differentiate the neuropathology associated with late-onset versus early-onset late life depression, as LOD subjects have been shown to have significantly greater WML burden than both early-onset depressed elders and elderly controls [55]. MRI WML has also been shown in elderly depressed patients to correlate negatively with performance on neuropsychological tests, as well as predict poor outcome after antidepressant therapy [56]. In a similar vein, WML volume was found to be higher in depressed nonresponders to antidepressant treatment vs. depressed responders [57], as well as negatively correlate with treatment remission [58]. The application of newer methodologies, namely MTR and DTI, have further clarified the extent to which WML burden affects LLD to the microstructural level. A study by Gunning-Dixon and colleagues [59] demonstrated lower MTR of white matter in specific fronto-striatal and limbic circuits, which was interpreted as reduced myelin integrity. Another study by Shimony et al. [60], which purposely excluded WMLs from DTI analysis by segmentation techniques, found that even outside frank WMLs, fractional anisotropy was reduced in LLD vs. controls. Thus, even "normal appearing" white matter displays diffuse microstructural damage in LLD.

The location of WML may also serve as a biomarker for LLD. Dalby [61] found no significant differences between LOD subjects and controls in number or volume of MRI WMLs, but LOD subjects did display a higher lesion density in specific white matter tracts underlying cognitive and emotional functions, namely the left superior longitudinal fasciculus and the right frontal projections of the corpus callosum. Further support for lesion location playing a part also comes from DTI, where fractional anisotropy (FA) serves as a measure of myelin integrity. Elderly subjects with MDD were shown to have reduced FA (i.e., decreased myelin integrity) in the right posterior cingulate cluster vs. controls, which correlated with poorer performance on cognitive tasks [62]. Interestingly, FA was shown to correlate with Framington Stroke Risk Profile (FSRP), a well-validated risk-prediction algorithm, in specific white matter tracts (namely the corpus callosum), providing further support for the vascular hypothesis of depression via particular cortico-limbic tracts [63]. The outstanding issue still remains, however, whether lesion volume or lesion location (or a combination thereof) determines the role of WML in LLD etiology. Once again, differences may stem from differences in methodologies, metrics, and definition of geriatric depression.

Finally, apart from grey matter and white matter changes, MRS has found abnormalities at the metabolite level in LLD. One MRS study found decreased phosphate metabolites and increased pH in older depressed subjects vs. age-matched controls, which changed significantly toward baseline with sertraline treatment [64]. However, another study found that remitted LLD subjects still showed alterations in amino acid levels, suggesting that significant effects in brain metabolism occur even in clinically improved LLD [65]. Regardless, given the handful of available MRS studies, further work is needed in the development of MRS-based biomarkers.

It has long been recognized that LLD, like early-onset depression (EOD), is marked not only by affective changes, but also neuropsychological deficits. Functional studies, such as fMRI and PET, provide dynamic neuroanatomical correlates for these cognitive changes.

Few task-based fMRI studies have focused on depression in elderly subjects. However, these have provided important insights into functional circuits underlying both emotional and cognitive changes specific to LLD, and LOD in particular. For example, while LOD subjects showed no performance difference from controls on an emotional evaluation task, the depressed group showed decreased activation in the ventromedial PFC in response to negative words, compared to positive stimuli [66]. Other recent studies have expanded

the scope of fMRI beyond the traditional realm of the PFC, to study posterior frontal and parietal regions of these functional networks. Examining executive function in LOD, Wang [67] found decreased activation in prefrontal, cingulate and inferior parietal areas relative to controls. Recently, our lab [68] has been studying the relationship between WML and functional neuroanatomy in geriatric depression. We found not only greater activity in the subgenual cingulate in depressed elderly compared to healthy controls in response to a facial expression affective reactivity task, but that task-related activity positively correlated with WML burden. As the depressed group also showed greater interaction between WML and fMRI activity, this further supports the idea that WML underlies LLD by disrupting key regions in emotional and cognitive networks.

Resting fMRI is a new frontier in LLD research, with even fewer studies in the literature than task-based fMRI. However, such studies shed further light on the pathophysiology underlying LLD, by showing differences even at rest in the LLD brain compared to elderly controls. For example, depressed subjects pretreatment had decreased connectivity in the subgenual anterior cingulate cortex and increased connectivity in the dorsomedial prefrontal cortex and the orbito-frontal cortex, which significantly correlated with WML burden [69]. Alexopoulos [70] recently extended resting-state findings to include both the default mode network and cognitive networks, by showing a double dissociation of low resting functional connectivity within cognitive control networks and high resting functional connectivity within the default mode network in depressed vs. healthy elderly subjects. Additionally, they showed that low functional connectivity within the cognitive control network, but not default mode network, predicted low remission rate and persistence of emotional and cognitive symptoms after antidepressant treatment, suggesting that resting fMRI may prove a powerful new tool in charting functional neuroanatomical response to treatment.

PET studies utilizing fluorodeoxyglucose (FDG) provide further understanding of general changes in LLD brain activation, by measuring cerebral glucose metabolism. In geriatric depressed subjects, Smith [71] found hypermetabolism in frontal and parietal lobe regions which showed atrophy on accompanying MRI; in addition regions of FDG-PET hypermetabolism positively correlated with depressive symptoms; this was thought to be a compensatory response. Since then, several FDG-PET studies have examined the efficacy of various treatment paradigms via alterations in functional networks. For example, Diaconescu [72] explored the effects of citalopram treatment in LLD on functional networks associated with affective and cognitive improvement. Functional connectivity analyses revealed two distinct networks, one associated with treatment-related improvement in affect, the other with cognitive improvement. Major advances in the use of radioligands have also allowed for direct investigation of neurotransmitter systems long thought to be involved in depression, and their particular patterns of dysfunction in LLD. A combined serotonin transporter (SERT) and FDG-PET study by Smith [73] found that SERT occupancy correlated with cortical and limbic areas showing changes in glucose metabolism, suggesting that SERT occupancy in specific cortico-limbic circuits underly the changes in cerebral glucose metabolism seen with antidepressants.

In recent years, greater interest in structural and functional neuroanatomical changes specific to geriatric depression have produced a wealth of potential new imaging biomarkers for late-life depression. To be sure, several issues and controversies remain in the field, related to study design. Researchers must be aware that findings are influenced by differences in size; the increasing use of multi-center studies and large populations will hopefully yield more powerful imaging findings. Whether depression is determined by clinical diagnosis vs. self-report must also be taken into account. The very definition of elderly- 50 years, 60, 65- varies considerably between laboratories, as does the fundamental difference between LLD, late-life depression and LOD, late-onset depression. Finally, depending on the aims of one's study, cognitive studies in geriatric depression may be enhanced or confounded by coincidence of dementia, for which geriatric depression has long been a recognized risk factor.

Conclusions

Neuroimaging biomarkers show great potential in current academic, and future clinical use in geriatric psychiatry. However, several limitations currently hamper their effectiveness in eventual clinical practice.

The largest issue remains that of standardization. Classically, assessment of neuroimaging findings was a qualitative enterprise; however, the clinical disorders discussed are now thought to exist on a continuous, and so require by necessity continuous biomarkers to adequately describe both risk of disease incipience, and degree of disease progression. Thus, efforts continue to be exerted in transforming qualitative biomarkers, such as the presence of hippocampal atrophy, into quantitative measurements for statistical analysis. However, even quantitative measurement of regions of interest will vary based on individual and manual definitions of regions of interest. Thus, further work is also being done in automatically parcellating grey matter density or the thickness of cortical surfaces into regions of interest, thus obviating the need for manual intervention. Finally, findings must be able to be compared against a population-sized database of neuroimaging data, to both generalize future findings as well as further define

diagnostic classification criteria. Similar standardization work in blood pressure, serum glucose, and serum lipids has already been done and have proven crucial for hypertension, diabetes, and heart disease, respectively.

In the future, neuroimaging may be used for prediction of future clinical course in asymptomatic or mildly affected individuals, as well as longitudinal measure of disease progression. Neuroimaging may also continue to develop its utility in clinical trials for new therapeutic options, by offering a means of assessing treatment effects apart from self-report and clinical evaluation.

Conflict of Interest Abhisek C. Khandai declares that he has no conflict of interest.

Howard J. Aizenstein declares that he has no conflict of interest.

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- • Of importance
- •• Of major importance

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