Molecular Neuroimaging in Vascular Cognitive Impairment

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ger-related cognitive impairment is arguably the greatest looming threat to aging populations in both the developed and developing world. Emerging evidence indicates that cerebral small vessel disease (SVD) is a major contributor to cognitive impairment, highlighting the importance of improved understanding of the molecular and physiological mechanisms leading to vascular brain injury. As a result, 2 of the 3 highest priority research areas for the next 5 to 10 years identified by National Institute of Neurological Disorders and Stroke’s (NINDS) Workgroup on Stroke Prevention Research in 2012 were focused on prevention of vascular cognitive impairment (VCI) and imaging biomarkers in stroke prevention. This important initiative of NINDS has further accelerated the neuroimaging research in VCI that was blossoming over the preceding 10 years. Novel magnetic resonance imaging (MRI) markers of ischemic and hemorrhagic tissue damage in the brain have been identified, and their associations with the underlying cerebrovascular pathologies and resulting cognitive changes are extensively studied. MRI-based studies yielded a large gamut of imaging markers that mediate vascular contributions to dementia. Silent infarcts, lacunes, white matter hyperintensities (WMH) on fluid-attenuated inversion recovery MRI, fractional anisotropy and mean diffusivity changes, and acute punctate infarcts on diffusion weighted MRI are examples of ischemic markers that have been increasingly studied during the past decade. Cerebral microbleeds (CMB) and cortical superficial siderosis are subtle hemorrhagic lesions visible on T2*-MRI, and they serve as key markers of the most common SVDs that contribute to VCI in elderly. Enlarged perivascular spaces (EPVS), identified on T1- and T2-weighted MRIs by radiologists for over 2 decades, are emerging as another VCI-related marker, especially because of their association with the type of SVD. Functional MRI provided measures of vascular dysfunction and resting-state functional connectivity, whereas diffusion tensor imaging can identify subtle but important changes in structural connectivity. The aforementioned structural and functional imaging techniques resulted in an unprecedented boom in VCI research, but a good understanding of disease mechanisms and development of therapeutic approaches rely on detection of molecular changes that occur during the pathological processes. Development of novel positron emission tomography (PET) tracers and advances in MRI allowed the use of cutting-edge molecular neuroimaging techniques in VCI research that make the focus of the current topical review. The information obtained from well-designed studies published within the past few years will be critically reviewed, and preliminary data from ongoing efforts will be presented.

Molecular Neuroimaging Studies in VCI

Rationale

Up until recently, the only way to estimate molecular changes in human brains was to perform histopathologic studies. Detailed postmortem histological studies are seen as gold standard, but it is obvious that their role is limited in identifying the initial changes in the brain and their progression, a process that might take decades to culminate in dementia. Understanding the early phases of such progression in dementia research is key to stop the pathological cascade before severe damage occurs. Histopathologic studies in humans are possible only in the context of a postmortem examination, at the tail end of the pathological evolution, and in rare instances where a brain biopsy was clinically needed/obtained in vivo (during evacuation of intracerebral hemorrhage (ICH) or a biopsy to look for an inflammatory condition). For these reasons, developing neuroimaging methods that can detect molecular alterations in living humans has been an important goal in dementia research. Brain amyloid imaging based on PET that was introduced a decade ago has revolutionized research into disease mechanisms in Alzheimer’s Disease (AD). It helped clarify the longitudinal associations of parenchymal amyloid with clinical and other imaging findings in patients with AD as well as healthy older adults. PET amyloid imaging also helped in assessing the efficacy of treatments targeting brain amyloid. PET and MRI-based molecular imaging methods have been gradually implemented in clinical research to uncover mechanisms of damage in the most common types of SVD. An overview of the PET and MRI-based methods that are currently available or under development can be found in the Table.

Main Contributors to VCI in Older Adults

VCI is indeed an umbrella term, and it encompasses contributions from both acute symptomatic strokes and more importantly accumulating damage from slowly progressive ischemic and hemorrhagic cerebral pathologies.
symptomatic ischemic strokes and ICHs will not be discussed per se because their effects on VCI are mostly related to their location, size, and related neurological deficits.13 Their etiologies and prevention methods are extensively discussed elsewhere. The focus in VCI research has been understandably on SVD in elderly, the 2 most common conditions being cerebral amyloid angiopathy (CAA) and perforating arteriosclerosis. CAA is caused by the accumulation of amyloid-β peptides (Aβ) in the walls of the cerebral small vessels, whereas arteriosclerosis is characterized by deposits of fibro-hyaline material, narrowing of the lumen, and thickening of the vessel wall in older adults with vascular risk factors (Figure 1).14 Epidemiological and clinical–pathological studies suggest that both types of SVDs are associated with nontraumatic ICH, a common cause of death and severe disability.15 The parenchymal lesions of SVD (leukoaraiosis, lacunes, microbleeds, EPVS) are also independently associated with cognitive decline in the elderly.15 The proposed mechanism mediating this clinical effect is vascular dysfunction and resulting ischemic brain injury for CAA (Figure 2).9,16–18 The relatively high prevalence of CAA (36% in autopsy series)19 and moderate–severe arteriosclerosis (40%) in the elderly20 make these conditions ideal models to study disease mechanisms for VCI. Not surprisingly, most of the molecular neuroimaging studies in VCI were performed in such cohorts.

### In Vivo Detection of Vascular Amyloid

#### Using Pittsburgh Compound B PET

An important advance in identification of brain amyloid load on PET was the development of the Pittsburgh Compound B (PiB), a derivative of thioflavin T with an attached carbon 11 atom, shown to bind parenchymal Aβ in senile plaques.21 Data from our group and others firmly established that PiB detects vascular as well as senile plaque amyloid. Our group has reported the first postmortem pathological examination of a human brain that showed severe CAA in the absence of significant parenchymal amyloid from a patient with positive PiB scan obtained 3 months before death.22 Global PiB retention in nondemented CAA subjects was significantly increased when compared to healthy control subjects (HC) of similar age and education, a finding that was confirmed in 2 well-designed studies.22,23 Interestingly, occipital PiB retention relative to global cortical PiB retention was significantly greater in CAA than in AD patients (occipital/global: 0.99±0.07 versus 0.86±0.05; P=0.003), suggesting a potential specificity of this pattern in view of the known posterior predominance of CAA (Figure 1).22 Ly et al reproduced these results and also showed strong correlation between PiB retention on PET and abundant CAA without parenchymal plaques in a frontal biopsy.23 The ability of PiB to detect CAA was further demonstrated by PiB-PET of a familial form of CAA with no parenchymal fibrillar plaque pathology. A 42-year-old man with Iowa-type hereditary CAA diagnosed by genetic testing, without ICH or dementia, underwent research MRIs and PiB-PET. The results have reported the first postmortem pathological examination of a familial form of CAA with no parenchymal fibrillar plaque pathology.24 This patient died 3 years later because of a massive CAA-related lobar ICH. PiB was also used to label brain sections from a related patient with Iowa-type CAA, and this histopathologic

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<th>Molecular Imaging Techniques</th>
<th>Potential Uses/Data Obtained</th>
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<tr>
<td>Amyloid positron emission tomography (PET) imaging</td>
<td>Quantification of vascular amyloid load to study its causes and consequences&lt;br&gt;Aide in diagnosis of cerebral amyloid angiopathy (CAA) in the appropriate context&lt;br&gt;Identification of amyloid negative vascular cognitive impairment due to small vessel diseases (SVD) mainly driven by systemic vascular risk factors (hypertension, diabetes mellitus, etc)</td>
<td>Current tracers are not specific for vascular amyloid or parenchymal Alzheimer’s Disease (AD) pathology, they label both types</td>
<td>Developing PET tracers that specifically label vascular amyloid</td>
</tr>
<tr>
<td>Tau PET imaging</td>
<td>Measuring brain tau load, the main constituent of neurofibrillary tangles&lt;br&gt;Might help identify patients with more “pure” forms of vascular cognitive impairment (amyloid and tau negative)&lt;br&gt;Might help delineate AD and vascular contributions to dementias</td>
<td>No validated/approved tau tracer that can help in the diagnosis of AD</td>
<td>Development and validation of tau tracers that can be used clinically for the diagnosis of AD</td>
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<tr>
<td>Magnetic resonance spectroscopy (MRS)</td>
<td>Might provide measures of neuronal integrity and other molecular changes at and around sites of SVD-related lesions&lt;br&gt;2D and 3D MRS techniques can provide more global information on molecular alterations in VCI</td>
<td>MRS voxel is relatively large making it difficult to study small lesions&lt;br&gt;Difficult to use for cortical regions/lesions</td>
<td>Further development of 3D multivoxel MRS might allow more widespread use in research</td>
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<td>Molecular/Metabolic magnetic resonance imaging (MRI)</td>
<td>Efforts underway to develop MRI probes and techniques that can help detect relevant molecules in VCI research (amyloid, fibrin, etc)</td>
<td>No molecular/metabolic MRI probe used in clinical VCI research yet</td>
<td>Development of safe probes specific for the target molecules</td>
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Table. **Summary of the Molecular Neuroimaging Techniques in Vascular Cognitive Impairment (VCI) Research**

[1] Aide in diagnosis of cerebral amyloid angiopathy (CAA) in the appropriate context.
[2] Occipital PiB retention relative to global cortical PiB retention was significantly greater in CAA than in AD patients (occipital/global: 0.99±0.07 versus 0.86±0.05; P=0.003), suggesting a potential specificity of this pattern in view of the known posterior predominance of CAA (Figure 1).
[3] The ability of PiB to detect CAA was further demonstrated by PiB-PET of a familial form of CAA with no parenchymal fibrillar plaque pathology. A 42-year-old man with Iowa-type hereditary CAA diagnosed by genetic testing, without ICH or dementia, underwent research MRIs and PiB-PET. The results have reported the first postmortem pathological examination of a familial form of CAA with no parenchymal fibrillar plaque pathology.24
essay demonstrated exclusively vascular labeling, without evidence of plaque-associated PiB. These studies show that vascular amyloid deposition can be specifically imaged using PiB PET and also highlight the intriguing possibility that CAA can be noninvasively detected years before it triggers ICH or other SVD-related injury.

Vascular Amyloid and Hemorrhagic Brain Lesions in CAA

Based on the aforementioned studies, we have next undertaken the task to identify the spatial relationship between PiB retention and lobar CMB, the radiological hallmark of CAA. A spatial relationship between vascular amyloid and lobar bleeds in CAA has been suggested by a cross-sectional radiological analysis using PiB-PET imaging. In a longitudinal study, PiB retention expressed as distribution volume ratio (DVR) at baseline was greater at sites of future bleeding than at simulated sites randomly placed by a probability density map (mean DVR=1.34, 95% confidence interval 1.23–1.46 versus mean DVR=1.14, 95% confidence interval 1.07–1.22; P<0.001, after adjustment for multiple covariates). We additionally found that overall burden of CAA in a superior frontal/parasagittal region of interest was an independent predictor for number of future hemorrhages, a further indication of the link between vascular amyloid burden and risk of bleeding. The ability to use PiB retention on PET as a direct in vivo marker of vascular amyloid load thus allows better understanding of the relationship between the inciting pathology and possible associated lesions. One such newly proposed lesion is superficial cortical siderosis, shown by our group and others to be commonly found in CAA patients and to be a possible predictor of future hemorrhagic risk. We have performed a preliminary analysis comparing amyloid load in CAA patients with and without superficial cortical siderosis. Thirty patients who had superficial cortical siderosis were found to have significantly higher amyloid load when compared with 21 CAA patients without superficial cortical siderosis (mean PiB retention 1.41±0.19 versus 1.26±0.17; P<0.01), and this association was independent of age, sex, and presence of hypertension. The next important step in supporting causality between vascular amyloid and superficial siderosis will be to demonstrate a strong spatial relationship. This effort is complicated by the difficulty in identifying the exact site of bleeding in cortical superficial siderosis, as opposed to lobar microbleeds.

Vascular Amyloid Load and White Matter Disease in CAA

One problem about using PiB-PET in mechanistic research of potential CAA-related ischemic lesions, such as WMH, is that PiB is not specific to vascular amyloid and that senile plaques and CAA commonly coexist. In this context, the associations between PiB and WMH can be driven by senile plaques or even primarily by the WMH itself. This problem makes it mandatory to test associations between vascular amyloid load and WMH in multiple appropriate cohorts to confirm that any correlation is really specific to CAA. We have hypothesized that global PiB retention and volume of WMH on fluid-attenuated inversion recovery MRI would be independently associated in patients with CAA but not in HC or patients with AD. We have tested this hypothesis in a group of 42 CAA, 43 AD patients, and 50 HC. Global PiB retention and WMH showed strong correlation in the CAA group but not in HC or AD group. These associations did not change in the multivariate models controlling for potential confounders. Lobar microbleed count, another marker of CAA severity, also remained as an independent predictor of WMH volume. These findings support the idea that vascular amyloid burden directly contributes to chronic cerebral ischemia in the CAA population, independent of the effects of aging and AD pathology. The lack of correlation between PiB and WMH in AD and healthy elderly in this study and others also show that PiB retention values are not driven by the severity of WMH or any other related ischemic mechanism.

Centrum semiovale EPVS on MRI, thought to represent impaired interstitial fluid drainage, have been associated with...
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CAA in recent studies. In a pilot study involving 10 CAA and 20 healthy subjects of different ages, Charidimou et al have found a nearly linear increase in PiB as centrum semiovale EPVS score (range 0–4) increased but just a trend when only probable CAA patients and older healthy subjects were analyzed. If future work shows strong correlations between PiB and centrum semiovale EPVS in a larger CAA cohort, impaired interstitial fluid drainage hypothesis would be further supported.

Molecular Changes Associated With Cerebral Microlesions
Magnetic resonance spectroscopy (MRS) is an imaging method that allows the interrogation of the molecular structure of a region of interest through the use of an electromagnetic field to elucidate the relative presence, absence, and ratio of certain metabolites. The metabolites identified on MRS represent relatively established pathophysiological markers, such as N-acetyl-aspartate (molecule present in healthy neurons), choline compounds, myo-inositol, and creatine. A recent community-based study in healthy elderly without dementia showed a significant association between choline/creatine ratio and lower scores on domain-specific cognitive tests independent of Aβ load. Patients with higher choline/creatine ratios had a higher risk of developing dementia in another large community-based cohort, and both reports proposed that these associations may reflect the consequences of ischemic vascular disease. As choline/creatine results have been inconsistent in AD cohorts (high, equal, or low when compared with HC), the correlations mentioned above might be explained by the ischemic effects of SVD rather than parenchymal amyloid pathology. Including specific SVD-related markers in this line of research can further clarify these associations.

The number of lobar microbleeds is an established marker of disease severity in CAA, whereas microinfarcts are more recently identified markers. One important question in SVD research is whether these microlesions disrupt neuronal integrity in situ and the type and extent of local tissue reaction if present. One way of approaching this question is to detect in situ metabolite concentrations using MRS. We performed MRS in 23 patients with probable CAA to compare molecular data from the sites of 46 lobar microbleeds to nonlesioned mirror image areas in the contralateral hemisphere. In a preliminary analysis, comparison of the N-acetyl-aspartate peaks revealed a significant decrease in N-acetyl-aspartate/creatine ratio at sites of microbleeds using paired tests (1.48±0.33 at microbleed voxels versus 1.63±0.33 at the symmetrical contralateral hemisphere voxel; \(P<0.01\)). These preliminary results suggest decreased neuronal integrity around sites of lobar microbleeds, even within the relatively large MRS voxels used. Larger samples will be needed to perform mixed effects models to control for effects of potential covariates, such as age and risk factors. Applying this approach to microinfarcts detected on ultrahigh field fluid-attenuated inversion recovery MRI will also provide information on the presence and type of in situ damage caused by these microlesions.

Severity of CAA, Structural Connectivity, and Cognition
Another mechanism for the multiple small spatially distributed CAA-related lesions to affect cognition might be through disruption of brain connectivity. A recent study that used graph theory–based connectivity measures from diffusion weighted MRI, PiB-PET, and a detailed cognitive test battery shed light into this presumed mechanism. Global efficiency of the brain network, a measure of structural connectivity, was reduced in nondemented patients with CAA when compared
with HC. Network disturbances were most pronounced in posterior brain regions. Lower global network efficiency was related to higher cortical amyloid load, MRI markers of SVD, including increased WMH, and finally to worse performance on tests of processing speed, executive functioning, gait velocity, but not memory. These associations were all significant after adjustment for relevant confounders. This study, made possible by in vivo molecular neuroimaging, established clear links between the molecular causative pathology (vascular amyloid load), the resultant microstructural brain damage (disruption of brain networks), and finally the associated cognitive worsening. Longitudinal studies that use a similar framework will help clarify the progression of the inciting molecular pathology and how that affect structural brain damage and consequent cognitive changes that culminate in VCI.

Molecular Neuroimaging in Other SVD Cohorts

The majority of PET-based studies discussed in earlier sections have used amyloid imaging to estimate vascular amyloid load in CAA patients and correlate this measure to other imaging and clinical markers of disease severity. An emerging use of amyloid imaging focuses on explaining specific contributions of other common SVDs, such as perforating arteriolosclerosis on VCI in non-CAA patients who have severe clinical and imaging manifestations of SVD. This is an important line of research because mechanisms by which arteriolosclerosis result in VCI are understudied despite the higher prevalence of arteriolosclerosis. Park et al have looked at the interactions between amyloid burden, MRI markers of SVD, and cognition in a cohort of 136 patients with subcortical vascular cognitive impairment.6 These older patients with severe vascular risk (hypertension present in >75%), clinical features (all had a focal neurological symptom or sign), and MRI manifestations of severe SVD (mean WMH in mL =38.6±17.1) constitute a unique cohort to evaluate the effects of classical stroke risk factors on VCI. Although the number of lacunes was associated with performance on tests of both memory and executive function, WMH volume and PiB retention correlated only with memory function.6 No direct correlation between SVD markers and PiB retention was found, suggesting that the predominant type of SVD is probably perforating arteriolosclerosis in this cohort of patients who had strokes and severe stroke risk factors. A study of hippocampal and cortical thickness of patients with amyloid-negative PET scans derived from this cohort has given further insights into cortical atrophy that might be attributable to arteriolosclerotic SVD rather than Alzheimer’s pathology.7 The authors have diagnosed pure subcortical vascular mild cognitive impairment (MCI) and pure subcortical vascular dementia based on PiB(-) PET scan, defined as a PiB retention ratio <1.5. Subjects with pure subcortical vascular MCI had lower mean cortical thickness and hippocampal volume than HCs, and both these measures were significantly decreased in patients with pure subcortical vascular dementia when compared with those with pure subcortical vascular MCI.8 Despite the fact that the classification into amyloid-negative category may not totally rule out amyloid-related effects on cerebral cortex, this study suggests a dose-dependent relationship between pure forms of moderate-to-severe SVD and cortical atrophy in patients without AD. The same group of investigators has also presented topographical changes in cortical thickness in PiB(−) and PiB(+) amnestic MCI patients compared with HC. Although PiB(+) MCI demonstrated a cortical thinning pattern reminiscent of AD, PiB(−) MCI exhibited cortical atrophy in different cortical regions, suggesting contributions from different pathologies, including SVD.9 Overall, these studies that used molecular amyloid imaging approaches showed intriguing findings, suggesting that arteriolosclerotic subcortical SVD contributes to VCI, possibly through direct effects on cortical atrophy.

Cerebral amyloid imaging is also increasingly used in asymptomatic older populations to explore its associations with MRI markers of SVD. The prevalence of lobar microbleeds among PiB(+) elderly subjects was similar, regardless of clinical classification as AD, MCI, or HC, despite significantly higher global PiB burden in AD. HCs with lobar CMBs had significantly higher mean cortical PiB binding than HCs without lobar CMBs.9 Only within the HC group, there was an association between amyloid load and number of lobar CMBs, the latter a relatively specific marker of CAA severity even in individuals without ICH.10,41 This interesting work by Yates et al suggests that asymptomatic lobar CMBs might be related to CAA in older HCs but also highlights one of the fundamental problems of using PiB-PET for SVD research in elderly cohorts without overt CAA. Parenchymal senile plaques are a major source of confounding in this setting, and this problem increases with age. Another similarly well-designed recent study showed a strong correlation between incidental CMBs in cortical locations and widespread reductions in resting-state cerebral blood flow of nondemented individuals with a mean age of 86.8.42 The most plausible explanation is indeed CAA causing both cortical CMBs and also vascular dysfunction, the latter resulting in decreased perfusion. Not surprisingly, however, CMBI(+) participants did not have a higher amyloid load than CMBI(−) participants, probably because of confounding by fibrillary parenchymal plaques commonly found in this old cohort. Correlations between amyloid imaging data and SVD markers from cohorts without a clearcut diagnosis of CAA by Boston criteria will need to be carefully interpreted until molecular imaging probes that can specifically label vascular amyloid are developed. For now, finding of lobar CMBs in older patients who present with nonspecific neurological symptoms without a neurodegenerative condition and possibly multiple lobar CMBs in older individuals without ICH might indicate the presence of significant CAA pathology if the potential confounders are ruled out. At that time, there still is no molecular imaging method sensitive and specific enough to prove or exclude the diagnosis of CAA in these situations.

Challenges and Future Directions

Following quickly behind developments in AD research have been important advances in our understanding of molecular mechanisms of SVD-related VCI. Despite the relatively limited number of techniques available, molecular neuroimaging has significantly contributed to the growing body of knowledge in this field. Currently, the biggest challenge is the lack of
 imaging probes that can specifically label molecules involved in physiopathological pathways of different SVDs. PiB binds to both parenchymal and vascular Aβ deposits, and its usefulness in SVD research might be somehow limited outside of patient cohorts with a clear diagnosis of CAA. Even for such asymptomatic elderly and non-CAA SVD settings, including specific MRI markers, such as lobar CMs, and considering patterns of uptake (occipital predominance) will help PiB-PET to continue to be a strong research tool. Nontrivial efforts to produce imaging tracers that can label vascular amyloid with high specificity are underway. Scyllo-inositol labeled with fluorine-18 [18F] gave promising results in specifically binding CAA in vitro but it did not penetrate blood–brain barrier in small animal models.43 Resorufin (a phenoxazine derivative) and multidentate 18F-polypegylated styrylpyridines showed preferential binding of cerebrovascular Aβ deposits over neuritic plaques in vitro but they have not been shown to cross blood–brain barrier in vivo.44,45 More recently, 99mTc(CO)3-labeled benzothiazole derivatives were studied as potential single-photon emission computed tomography imaging probes for cerebrovascular Aβ deposition. Among β-as potential single-photon emission computed tomography barriers in small animal models.43 Resorufin (a phenoxazine derivative) and multidentate 18F-polypegylated styrylpyridines showed preferential binding of cerebrovascular Aβ deposits over neuritic plaques in vitro but they have not been shown to cross blood–brain barrier in vivo.44,45 More recently, 99mTc(CO)3-labeled benzothiazole derivatives were studied as potential single-photon emission computed tomography imaging probes for cerebrovascular Aβ deposition. Among them, 99mTc[24 showed higher affinity for Aβ[1-42] aggregates, the more abundant component of vascular amyloid, and it also had favorable initial uptake and fast blood washout in normal mice.46 Further preclinical radiological–pathological studies are needed before this tracer is ready for testing in humans. PET tracers are now available for selective tau imaging,47 and they might help further clarify particular contributions of AD and vascular pathologies in dementia. Because of its short half-life that makes its distribution impossible, PiB has never been studied as a potential diagnostic marker. Several fluorinated PET tracers, including [18F] AV-45 (florbetapir/AMYVID), [18F] GE067(flutemetamol/VIZAMYL), and [18F] BAY-94 to 9172 (florbetaben/NEURACEQ) were developed to overcome this problem, and they have been approved as clinical radiopharmaceuticals for the diagnosis of AD by the US Food and Drug Administration.48 If ongoing research shows that any of these clinically available compounds show good vascular amyloid binding, they might be helpful for diagnosis of CAA and research in VCI.

It is hoped that advances in MRS that allow 3-dimensional multivoxel acquisitions with improved resolution will make this existing technique more readily available for VCI research. The use of bioengineered protein-based MRI contrast agents can provide highly specific functionality for targeting and sensing molecules of biological interest, even allowing to dynamically map chemical processes in the brain. Validation of relevant molecular neuroimaging probes will undoubtedly expedite the development and testing of targeted therapies in VCI, the ultimate goal in dementia research.

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