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REVIEW ARTICLE

The link between cardiovascular risk, Alzheimer's disease, and mild cognitive impairment: support from recent functional neuroimaging studies

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Objective: To review functional neuroimaging studies about the relationship between cardiovascular risk factors (CVRFs), Alzheimer's disease (AD), and mild cognitive impairment (MCI).
Methods: We performed a comprehensive literature search to identify articles in the neuroimaging field addressing CVRF in AD and MCI. We included studies that used positron emission tomography (PET), single photon emission computerized tomography (SPECT), or functional magnetic resonance imaging (fMRI).
Results: CVRFs have been considered risk factors for cognitive decline, MCI, and AD. Patterns of AD-like changes in brain function have been found in association with several CVRFs (both regarding individual risk factors and also composite CVRF measures). In vivo assessment of AD-related pathology with amyloid imaging techniques provided further evidence linking CVRFs and AD, but there is still limited information resulting from this new technology.
Conclusion: There is a large body of evidence from functional neuroimaging studies supporting the hypothesis that CVRFs may play a causal role in the pathophysiology of AD. A major limitation of most studies is their cross-sectional design; future longitudinal studies using multiple imaging modalities are expected to better document changes in CVRF-related brain function patterns and provide a clearer picture of the complex relationship between aging, CVRFs, and AD.

Keywords: PET; SPECT; fMRI; Alzheimer's disease; cardiovascular risk factors

Introduction

The term functional neuroimaging refers to a group of radiological, nuclear, and molecular imaging techniques used to evaluate brain function. These methods have been increasingly applied to investigate brain activity abnormalities associated with neuropsychiatric disorders in vivo. Alzheimer's disease (AD) – the commonest cause of dementia – has been extensively studied using neurofunctional techniques and these findings have provided important insights about its pathophysiology.[1]

In this review, we will highlight the following functional neuroimaging modalities: positron emission tomography (PET) and single photon emission computerized tomography (SPECT). The latter has been used to document regional cerebral blood flow (rCBF) abnormalities with perfusion tracers such as technetium-labeled hexamethylpropylene amine oxime (^{99m}Tc-HMPAO, exametazime) and the former has been applied to demonstrate regional brain glucose metabolism using 18F-fluoro-[2]-deoxyglucose (FDG-PET). We also review recent results from functional magnetic resonance imaging (fMRI) that measures changes in neural activity by relying on the blood oxygenation level-dependent (BOLD) signal.[2]

In AD, consistent patterns of localized functional brain abnormalities associated with cognitive decline have been described using both PET and SPECT. Such brain changes are most significantly located in the precuneus and posterior cingulate gyrus,[3-6] with some additional involvement of the hippocampus, amygdala, parahippocampal gyrus, and the posterior parietal and temporal neocortices.[7-9] Such AD-related functional changes can aid in the diagnosis of AD.[10] Accordingly, the U.S. National Institute on Aging and Alzheimer's Association diagnostic criteria for AD recommend the incorporation of FDG-PET as an imaging biomarker to help diagnose the condition.[11,12] Moreover, longitudinal changes in FDG-PET might reflect disease progression and can be used as secondary surrogate markers of outcome in trials evaluating novel treatment strategies.[13]

Individuals with objective cognitive decline not severe enough to fulfill the criteria for dementia receive the diagnosis of mild cognitive impairment (MCI) and have a high risk of developing dementia.[14] FDG-PET studies

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have identified regional deficits of glucose metabolism in the hippocampus as well as in the posterior cingulate gyrus of patients with MCI.[15] Functional neuroimaging studies – using fMRI, FDG-PET, and SPECT – have been used to predict conversion from MCI to AD.[16-18] Because MCI is etiologically heterogeneous,[19] FDG-PET has been investigated as a tool to estimate which MCI patients have high likelihood of converting to AD.[20] Finally, functional neuroimaging findings that correlate with cognitive changes in MCI have been described by a number of studies. One example is that increases in hippocampal activation during memory encoding and retrieval have been documented in MCI patients (compared with healthy controls), possibly suggesting an early compensatory strategy that disappears as the disease progresses to clinical dementia.[21-23]

Cardiovascular risk factors (CVRFs), such as hypertension, diabetes, dyslipidemia, obesity, and smoking, are highly prevalent in the population and have a significant impact on cognitive performance.[24-26] Such conditions are now recognized as risk factors not only for vascular dementia (VaD) but also for AD.[27-30] The present article aims to critically review functional neuroimaging studies that have investigated the impact of CVRFs on brain functioning in individuals with AD and MCI, and to discuss how such findings have provided new insights about the pathophysiology of AD and MCI.

Methods

We carried out a comprehensive search using the MEDLINE database (http://www.ncbi.nlm.nih.gov/pubmed/) for neurofunctional studies investigating the impact of CVRFs on brain function. To identify relevant articles, we used the following keywords: 1) for functional neuroimaging: PET, "positron emission tomography," SPECT, "single photon emission computerized tomography," "functional magnetic," "functional resonance," FMRI, "blood oxygenation level-dependent response," "blood oxygenation level dependent response"; 2) for CVRF: "diabetes mellitus," hypertension, obesity, overweight, smoking, tobacco, dyslipidemia, hypercholesterolemia, cholesterol, apolipoprotein, "physical fitness," sedentar*, cardiovascular (sedentar* was used as a wildcard in the search strategy to retrieve keywords related to sedentary lifestyle, such as "sedentariness," "sedentarism," and "sedentary"); and 3) for AD and MCI: "Alzheimer's disease," Alzheimer, Alzheimer's, "mild cognitive impairment," MCI.

The search strategy was not limited to a particular period of time or set of languages, and it retrieved a total of 1295 articles.

We included those studies that were considered important to summarize the current knowledge about the relationship between brain function, CVRFs, AD, and MCI. The references from the included articles were also examined and relevant cited studies were included. We selected recent articles that provided relevant information for a critic and broad overview of the current knowledge in this field.

Results

We organized the information resulting from this review into subsections. We first present findings regarding the relationship between CVRFs, cognitive decline, and dementia in "CVRFs and cognitive decline." Next, we focus on brain metabolism and perfusion ("CVRFs and reduced cerebral blood flow and glucose metabolism: PET and SPECT findings") and then on results from resting-state fMRI studies ("the potential of resting-state fMRI studies"). After that, because of the great potential of amyloid imaging to provide information about AD and risk factors, we dedicate a section to studies using amyloid markers ("unraveling the relationship between AD and CVRFs with PET amyloid imaging"). The importance of composite measures is highlighted in "the effects of combined CVRFs" and, finally, we provide a summary of hypothetical mechanisms that contribute to the association between CVRFs, AD, and MCI in "microstructural and molecular mechanisms underlying cardiovascular risk-related brain function deficits."

Cardiovascular risk factors and cognitive decline

The two leading causes of dementia are AD and VaD.[31-33] While the symptoms of VaD are traditionally thought to be a direct consequence of cerebral infarcts, senile plaques and neurofibrillary tangles associated with neuronal death are the neuropathological hallmarks of AD.[34] Postmortem investigations show that the AD neuropathology begins and is more severe in the hippocampal and entorhinal regions, spreading progressively to the temporal and parietal cortices and finally to frontal regions.[35]

A large body of epidemiological and clinical evidence in recent years has indicated that, rather than separate entities with distinct causes, VaD and AD share similar CVRFs.[36] Thus, several studies have suggested that, even in the absence of stroke, the incidence of AD is significantly influenced by the presence and severity of elevated blood pressure,[37-39] diabetes,[30,40] smoking,[41] and physical inactivity.[42] High cholesterol levels have been associated with increased risk of AD in a number of studies, but there are also negative reports, and these conflicting results are thought to be caused by different mediating effects of age, gender, and *APOE* genotype.[43]

Moreover, amyloid-β deposition – a pathological hallmark of AD which can now be measured in vivo with amyloid imaging techniques – has been associated with vascular risk factors such as physical inactivity, higher plasma concentrations of cortisol, and hypertension.[44-46] The diagnosis of MCI has also been associated with several CVRFs; these include hypertension,[47,48] diabetes,[49,50] and increased cholesterol levels.[51,52]

A recent large neuropathological study (5,715 cases) found that vascular pathology is more prevalent in patients with AD than in those with frontotemporal lobar degeneration, dementia with Lewy bodies, or Parkinson's disease dementia.[53] This study also provided further evidence supporting the notion that cerebrovascular

disease increases the risk of dementia in patients with AD pathology.

Clinical trials evaluating the effects of CVRF-controlling agents also reinforce the relationship between cognitive decline and CVRFs.[54-57] There is evidence that antihypertensive treatment in midlife can reduce the subsequent risk of cognitive decline and dementia in old age,[54,55] although negative results have also been reported (for a review, see Peters & Becket).[54] Furthermore, it is well established that CVRF-reducing lifestyle habits during early and mid-adulthood, including physical exercise and dieting, may reduce the risk of cognitive deficits and AD later in life.[56-58] Moreover, several studies have indicated that cognitive impairment may be present in individuals suffering from other cardiovascular conditions such as congestive heart failure (CHF),[59-61] atrial fibrillation (AF),[62,63] and coronary artery disease.[64-66] Such cognitive deficits may be reduced by stabilization of the cardiac condition.[67]

The blurring of boundaries between AD and VaD is also supported by different lines of structural neuroimaging research. For instance, white matter hyperintensities (WMH), which are thought to reflect microvascular injuries,[68-71] can be found in more than half of T2-weighted or fluid-attenuated inversion recovery (FLAIR) datasets of elderly individuals investigated with magnetic resonance imaging (MRI) [72,73]; the presence of such lesions is related to CVRFs, such as hypertension, diabetes, smoking, and hypercholesterolemia, as well as with signs of endothelial dysfunction.[68-71] WMH are seen in excess in samples of patients with either AD or VaD[74,75]; in elderly individuals with no overt signs of dementia, their presence may be related to a dysexecutive profile of cognitive deficits.[76,77] Besides, WMH burden at baseline has been associated with subsequent brain amyloid deposition in a longitudinal study.[78] More subtle WM changes, such as those identified on diffusion MRI, have been associated with cognitive dysfunction in AD[79] and brain amyloid load.[80] However, there has also been reports of WMH being associated with cognitive decline but not with brain amyloid deposition or longitudinal change in AD-specific biomarkers, such as CSF $A\beta_{42}$.[81,82] Other brain lesions of vascular origin, such as silent infarcts, have also been associated with the diagnosis of AD.[74,75] Finally, morphometric MRI studies have shown that CVRFs are associated with gray matter volume reductions in the medial temporal cortex as well as in other brain regions implicated in the pathophysiology of AD, such as the precuneus and posterior cingulate gyrus.[83-86] Two recent systematic reviews have provided further evidence linking the cardiovascular system and AD: one review found that high blood pressure is associated with hippocampal volume reduction,[87] and the other described a correlation between medial temporal lobe volume and cardiorespiratory fitness.[88]

Based on the above epidemiological, clinical, and structural neuroimaging findings, it has been proposed recently that AD and VaD actually represent two extremes of a dementia spectrum ranging from patients with pure VaD to patients with pure AD, with a majority of patients having contributions from both neuropathological pathways.[53,74,89,90] Figure 1 (adapted from Viswanathan et al.[90]) illustrates the concept of a spectrum ranging from pure AD to pure VaD. Such lines of evidence have also provided support to a more ambitious "vascular hypothesis" for AD, which proposes that the neuropathological changes that characterize AD would originate primarily from microvascular abnormalities.[91]

Cardiovascular risk factors and reduced cerebral blood flow and glucose metabolism: PET and SPECT findings

Comparing healthy controls and elderly patients with CHF, our group found significant rCBF reductions in patients, which were circumscribed to brain regions commonly affected in the early stages of AD – namely, the precuneus and posterior cingulate gyrus. In addition, we found a significant direct association between lower cognitive test scores and rCBF reductions in the posterior cingulate gyrus.[92] This was, to the best of our knowledge, the first demonstration that a non-severe cardiac condition could lead to circumscribed brain functioning abnormalities similar to those considered typical of mild AD, even in individuals with no features of dementia or MCI. Similarly, subsequent rCBF investigations reported findings of AD-like hypoperfusion changes localized to regions such as the hippocampus and precuneus in association with other CVRFs, such as hypertension.[93]

More recently, a SPECT study of 18 overweight and obese participants showed extensive decreased prefrontal rCBF associated with obesity.[94] This study highlights the association of prefrontal cortex abnormalities to obesity, but it is difficult to establish if these findings are the cause of overeating, reflect a vulnerability of this brain region to the metabolic and cardiovascular changes induced by obesity, or both. Moreover, the age range of the sample was very wide (20-82 years), and it is possible

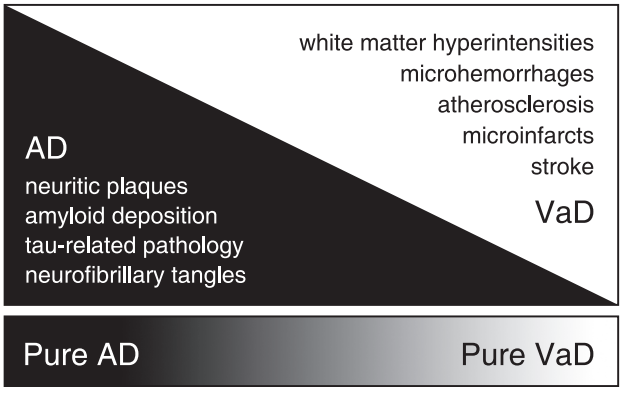

Figure 1 Model of the neuropathological spectrum encompassing AD and VaD. The color gradient represents the variable composite mixture of AD- and vascular-related pathology in clinical samples. Most patients present a combination of both neuropathological profiles, and a few rest on the extremes of the spectrum. AD = Alzheimer's disease; VaD = vascular dementia.

that the effects of increased weight are dynamic and change throughout the lifespan.

Recently, there have also been large studies in this field using FDG-PET. Reiman et al.[95] searched for significant associations between serum cholesterol levels and cerebral metabolic rates of glucose metabolism (CMRgl) in 117 cognitively normal middle-aged and elderly individuals (age 47-68 years). Higher serum total cholesterol levels were associated with lower CMRgl bilaterally in the precuneus, lateral parietal neocortex (encompassing the superior parietal lobule and angular and supramarginal gyri), lateral temporal neocortex (involving the superior temporal gyrus), and lateral prefrontal cortex (including the superior frontal gyrus), in a pattern that showed a substantial degree of overlap with the pattern of regional brain functional changes commonly seen in subjects with mild AD.[95]

Investigating a subgroup of the same cohort, Langbaum et al.[96] detected lower frontotemporal glucose metabolism in proportion to elevated blood pressure indices.[96] In additional studies with relatively modest samples, findings of CMRgl as assessed with FDG-PET have been described in association with CVRFs such as insulin resistance[97] and obesity[98] as well as with WMH volume, which has been considered a marker of cerebrovascular burden.[81,99] Taken together, these studies show a significant association between those risk factors and reduced CMRgl, variably implicating the precuneus, posterior cingulate gyrus, lateral parietal neocortex, and lateral temporal neocortex,[96,97] as well as the lateral prefrontal cortex.[96,98]

Both type 1 and type 2 diabetes mellitus have also been associated with neurofunctional deficits.[97,100] It has been reported that the regional pattern of brain hypometabolism in cognitively normal patients with diabetes resembles, to some extent, the regional pattern of AD-related neurofunctional abnormalities, because both involve the posterior cingulate cortex, precuneus, and the inferior lateral parietal lobe.[97] Moreover, higher fasting serum glucose levels in adults with no history of diabetes have also been correlated with lower CMRgl in the precuneus and posterior cingulate cortex, among other brain regions.[101]

In conclusion, FDG-PET and brain perfusion SPECT studies assessing non-demented individuals with a high CVRF burden have provided support to the ''vascular hypothesis'' of AD by showing patterns of brain functional abnormalities similar to those observed in AD.

A note of caution: it is still very challenging to unravel the relationships between AD and CVRF because they share several neuropathological features, such as brain atrophy and perfusion and metabolism deficits, which could hinder interpretation of neuroimaging findings obtained with current technologies.[102] Moreover, CVRFs may dynamically change neurofunctional findings in patients with AD. An interesting study showed that diabetic patients with AD had increased rCBF in the left inferior temporal gyrus on baseline SPECT when compared to non-diabetic patients with AD. In other words, functional changes related to AD may differ depending on the presence of diabetes.[103]

To date, the majority of published studies have been cross-sectional, with limited information about the temporal dynamics of functional brain changes. A longitudinal study of patients with AD showed that participants with more severe CVRFs at baseline presented greater cognitive decline and more widespread rCBF reductions.[104] Therefore, CVRFs can contribute to an accelerated progression of clinical and neurofunctional changes in patients with AD.

The APOE epsilon 4 (APOE ε4) allele is not only an important risk factor for AD and cardiovascular diseases,[27,105] but is also associated with functional brain changes[106-108] that can correlate with behavioral performance.[109]

Glucose hypometabolism has been associated with the presence of the APOE ε4 allele in non-demented older adults.[110-112] In the FDG-PET study by Reiman et al.,[95] the sample of cognitively normal middle-aged and elderly individuals was subdivided into APOE ε4 homozygous (n=24), heterozygous (n=38), and non-carriers (n=55). In some cortical regions, the relationship between hypometabolism and CVRFs had greater salience in ε4 allele carriers than in non-carriers. The authors postulated that higher cholesterol levels, particularly in association with the ε4 allele, would increase the risk of AD by accelerating some of the brain changes associated with normal aging.[95]

In our own FDG-PET study,[113] we aimed to investigate whether the associations between reduced CMRgl and elevated CVRF scores would be present regardless of *APOE* genotype. After controlling for the presence of the ε4 allele, the CVRF-related regional brain hypofunctional patterns retained statistical significance in the precuneus and posterior cingulate gyrus, suggesting that findings similar to those reported in AD subjects can be seen in association with the severity of CVRFs independently of *APOE* status. On the other hand, findings involving the lateral temporoparietal neocortices lost their significance when the analysis was repeated after controlling for the effects of the ε4 allele,[113] indicating that metabolism in those latter regions may be influenced by *APOE*, as suggested by previous PET studies of non-elderly subjects.[95,114,115]

Although ε4-related hypometabolism has been associated with the neuropathological processes of AD,[112,116] such findings may not be necessarily pathological or specifically linked to AD.[117] For instance, APOE ε4 is also a risk factor for vascular disease.[118] Moreover, a study that used both FDG-PET and amyloid imaging to assess cognitively normal older adults showed that cerebral hypometabolism associated with ε4 is not mediated by amyloid deposition.[119] Finally, posterior cingulate cortex hypometabolism has also been associated with vascular risk factors.[113] Thus, a vascular component – in addition to other AD-related processes – should be considered as part of the causal hypothesis of cerebral hypometabolism in ε4 carriers.

As many other genes, the effect of *APOE* in the brain is likely to be mediated by environment and lifestyle

factors.[120] In a study of middle-aged women, ε4 carriers with higher cardiovascular fitness exhibited increased metabolism in the inferior temporal cortex and decreased metabolism in the middle and superior frontal gyri and right inferior parietal lobule when compared with low-fitness participants.[121] Interestingly, such differences were not found among non-carriers of the ε4 allele, suggesting that physical activity may have a greater impact on the population at risk for AD/vascular disease. This is in accordance with a study that reported higher cerebral amyloid burden in sedentary ε4 carriers, while there were no significant differences between physically active and inactive subjects within the group of ε4 non-carriers.[122]

The potential of resting-state fMRI studies

PET and SPECT techniques rely on the use of radiopharmaceuticals administered via the intravenous route. Another option is fMRI, which consists of multiple acquisitions of brain images measuring changes in the ratio of deoxygenated to oxygenated hemoglobin (the BOLD effect); these changes reflect regional neural activity.[2]

During fMRI acquisitions, the subject may be asked to perform cognitive tasks or, alternatively, to lie still while not engaging in any specific task in order to study the brain during an unconstrained state (resting-state fMRI [rs-fMRI]). Interregional correlations of BOLD signal time courses can provide estimates of functional connectivity, and it has been shown that functionally related brain regions (e.g., the bilateral primary motor cortices) exhibit high resting functional connectivity.[123,124] Functionally discrete networks, such as the primary sensorimotor network, the frontoparietal attention network and the default mode network (DMN), can be identified on fMRI.[125] The DMN comprises the posterior cingulate cortex, the ventromedial prefrontal cortex, and the inferior parietal lobule, has been implicated in episodic memory retrieval,[125-127] and is one among a number of resting-state networks that have been characterized using fMRI (for a review, see van den Heuvel & Pol[125]).

The DMN is of special interest because: 1) age-related decreases in DMN functional connectivity have been the most consistent finding in rs-fMRI studies of the elderly population (for a review, see Ferreira & Busatto[128]); 2) patients with AD and MCI exhibit increased age-related changes in the DMN[129-131]; 3) hypoperfusion and hypometabolism (assessed by SPECT and PET) in the precuneus and posterior cingulate cortex – a major DMN hub – are frequently found in AD[132,133]; 4) functional connectivity within the DMN has been shown to correlate with behavioral performance in healthy older adults[128] and in patients with AD[129,130]; and 5) baseline functional connectivity within the DMN has been associated with conversion from MCI to AD.[134]

A study of middle-aged subjects with type 2 diabetes focused on the functional connectivity of the posterior cingulate cortex found decreased connectivity in the bilateral middle temporal gyrus, the left medial and right inferior frontal gyri, and the left thalamus in the diabetes group as compared with controls. Moreover, insulin resistance correlated negatively with the connectivity between the posterior cingulate cortex and the right inferior frontal gyrus and the right precuneus.[135] It is interesting to note the existing overlap between these results and the regions presenting negative correlations between resting CMRgl and insulin resistance as found by another group[97]; one possibility is that insulin resistance impairs neural metabolism, thus leading to less efficient interregional network integration and to a number of pathophysiological processes related to AD.[136,137]

Hippocampal connectivity has been studied in older adults with type 2 diabetes using rs-fMRI. These patients exhibited decreased connectivity between the hippocampus and major hubs of the DMN (posterior cingulate cortex, medial prefrontal cortex and inferior parietal lobule).[138] The decreased hippocampal connectivity with the medial prefrontal cortex has also been recently reported in women with higher fasting insulin levels (a marker of insulin resistance).[139] It is relevant to note that the impact of diabetes in resting brain networks has not only been found in the DMN but also in language and attention networks, especially in patients with microvascular complications.[140]

A rs-fMRI study demonstrated that connectivity of the precuneus and the anterior cingulate cortex with the whole DMN were, respectively, positively and negatively correlated with body mass index, and connectivity of the left insula to a temporal lobe network showed negative correlation.[141] Perhaps some of these findings are related to the modulation of eating behavior, while others may reflect brain changes secondary to the metabolic abnormalities associated with obesity. The multiple possibilities of interpretation highlight how challenging it is to understand results from cross-sectional studies of conditions (such as obesity) that can both determine and/or modify neural function patterns.

It is important to note that studying the impact of cardiovascular health in the brain using the BOLD signal can be problematic because it relies on hemodynamic response, which can be altered by cardiovascular disease[142] and is modulated by cardiorespiratory fitness.[143,144] Therefore, although the study of resting brain networks using fMRI has provided interesting information, there are still considerable challenges to be overcome before it can be considered a clinically useful and reliable indicator of early brain abnormalities due to CVRFs.[145]

Unraveling the relationship between AD and cardiovascular risk factors with PET amyloid imaging

In recent years, it has become possible to use nuclear medicine and molecular imaging techniques to study in vivo patterns of Aβ deposition, one of the pathological hallmarks of AD.[132,146] Amyloid imaging consists of injection of a radiolabeled ligand targeting Aβ aggregates followed by PET acquisition of brain images that represent the amyloid burden.[146] The first tracer

developed for this purpose was carbon-11 labeled Pittsburgh Compound-B (PiB). Studies using this technology have shown that amyloid deposition: 1) occurs years before clinical dementia[147,148]; 2) is not linearly related to cortical atrophy and cognitive decline[147-149]; 3) is more intense in patients with MCI who convert to AD than in nonconverters[150,151]; and 4) plateaus when clinical dementia is established (while other neurodegenerative imaging biomarkers, such as brain atrophy, keep progressing).[148,149]

For the next few years, the amount of information provided by amyloid imaging studies is expected to increase sharply. For instance, this imaging modality is now being used in a sub-study of the Alzheimer's Disease Neuroimaging Initiative, a large longitudinal multicenter project in the U.S. involving cohorts of elderly controls and subjects with MCI or AD. In this project, subjects have been investigated with multiple neuroimaging modalities and then followed up longitudinally, thus allowing measurements of change in these biomarkers over time.[152] Furthermore, in 2012, the U.S. Food and Drug Administration approved florbetapir (^{18}F) – a PET radiopharmaceutical agent that binds to amyloid aggregates – for clinical use in adults being evaluated for AD diagnosis.[153]

Regarding CVRFs, preliminary amyloid imaging studies with PET have shown that engagement in physical exercise may be associated with decreased amyloid deposition in cognitively normal older adults[154] and that sedentary APOE ε4 allele carriers exhibit greater amyloid deposition than physically active carriers.[122] Moreover, a study of late middle-aged to older adult subjects showed that systolic blood pressure correlated positively with ^{11}C-PiB accumulation in the posterior cingulate gyrus and precuneus, as well as in the frontal and temporal neocortices.[96] On the other hand, a prospective cohort study of 53 older adults could not find significant differences in ^{11}C-PiB retention between subjects with and without impaired glucose homeostasis.[155] Each CVRF may present a particular association with AD pathophysiology.

A recent florbetapir-PET study found not only that hypertensive APOE ε4 carriers showed higher amyloid deposition than subjects with just one of these risk factors (hypertension or APOE ε4 genotype), but also that the subgroup of APOE ε4+ individuals with unmedicated hypertension exhibited higher levels of amyloid burden than those with medicated hypertension.[45] These findings provide evidence that treatment of CVRFs may change the impact of *APOE* on amyloid deposition. The more widespread use of amyloid imaging is expected to foster longitudinal studies that use this technology to measure the effect of interventions. For instance, amyloid imaging findings have already been described as a secondary outcome in an AD clinical trial of liraglutide, a medication currently used for the treatment of diabetes,[156] as well as in a clinical trial of physical activity seeking to delay the progression of WMH to MCI.[157]

Advances in amyloid imaging have also provided interesting opportunities to unravel the relationship between cerebrovascular disease (CVD) and AD. In a recent study, PiB-PET was performed a few days after stroke, and, in 20 out of 21 individuals, there was higher PiB retention in the ipsilateral peri-infarct brain region than in the contralateral side.[158] In one recent longitudinal study, baseline severity of white matter lesions correlated with increased PiB retention after a mean follow-up interval of 28 months.[78] The authors suggested that the association between WMH – a sign of CVD – and progression of amyloid load might be mediated by impaired amyloid clearance due to vascular damage.

Subtle white matter changes as a suggestion of decreased axonal integrity (assessed by diffusion-weighted MRI) in the internal capsule and parahippocampal region have been associated with amyloid deposition in older adults.[80] Interestingly, such associations were no longer significant after controlling for *APOE* genotype; one hypothesis is that APOE ε4 increases amyloid deposition not only in the brain parenchyma but also in the blood vessels, thus leading to amyloid angiopathy, which is in turn associated with WMH.[159]

Finally, cerebral microhemorrhages (which are associated with several vascular risk factors) have been positively associated with amyloid deposition in the parieto-occipital region in a study of healthy older adults and patients with MCI or dementia.[160]

Overall, findings from in vivo amyloid imaging reinforce the relationship between AD and CVRFs. Further longitudinal studies should address in greater depth the relationship between CVRFs and Aβ deposition in the brain, using PET for amyloid imaging.[122] Such studies will be of key importance to demonstrate that the patterns of CVRF-related hypofunctioning reviewed in the present article may indeed be seen as correlates of AD-related neuropathology.

The effects of combined CVRFs

CVRFs rarely occur in isolation in elderly populations[161,162]; therefore, the approach of investigating the impact of single risk factors on the brain may be limited. As multiple combinations of different CVRFs are present in the population, including information on multiple risk factors can provide a more accurate profile of each individual.[163] The Framingham Coronary Heart Disease Risk (FCHDR) index is a widely used composite measure that takes into account multiple risk factors (age, sex, blood pressure, smoking status, total cholesterol and high-density lipoprotein cholesterol levels, and presence of diabetes) to assess the 10-year risk of coronary heart disease.[163-165]

Kuczynski et al.[166] obtained measures of CMRgl and cardiovascular risk as assessed with the FCHDR in a sample of elderly subjects (n=58, age $>$ 55 years, both healthy and with dementia), focusing specifically on the frontal lobe. They observed a significant inverse association between FCHDR scores and CMRgl in the lateral (i.e., superior frontal gyrus and ventrolateral

prefrontal cortex) and medial (i.e., superior medial frontal, and superior orbital frontal gyri) prefrontal cortices.[166]

With the aim of extending the above findings to more cognitively preserved elderly subjects, our group recently acquired FDG-PET data from 59 cognitively intact older adults. The subgroup with high FCHDR scores exhibited reduced CMRgl in the precuneus, posterior cingulate gyrus, and lateral temporal and parietal neocortices when compared to those with low scores (Figure 2).[113] This pattern of results provides further evidence of the substantial degree of overlap in regard to the location of foci of cerebral hypofunction across imaging studies of AD and CVRFs. Most of these results retained their statistical significance after correction for gray matter atrophy (partial volume correction); thus, the findings represent true metabolic deficits, unrelated to the degree of atrophic changes.[113]

One other feature of our FDG-PET results is reminiscent of findings reported in functional imaging studies of incipient AD: the lack of hypometabolism in frontal regions (Figure 2).[113] This stands in contrast both to the recently reported findings of cardiovascular risk-related prefrontal hypofunctioning in elderly subjects classified using the FCHDR index[166] and to the results of other FDG-PET imaging studies that investigated the influence of single CVRFs on brain functioning.[95-98] One important difference between our PET study and the one by Kuczynski et al.[166] is that the authors of the latter study did not exclude subjects with lacunar infarcts. They

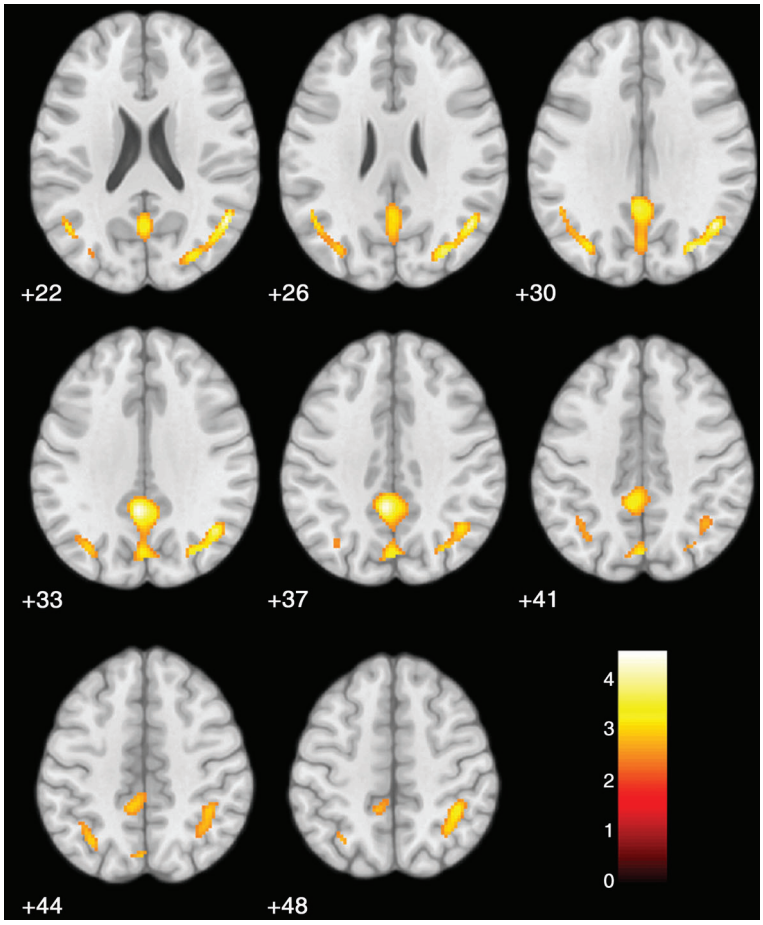

Figure 2 Reduced brain glucose metabolism in older adults with high cardiovascular risk. Areas of reduced cerebral glucose metabolism (as assessed with FDG-PET) in a group of cognitively intact older adults with high cardiovascular risk (according to FCHDR scores) compared to an age-matched group with low cardiovascular risk are highlighted in yellow, overlaid on axial slices of a reference MRI scan that approximates the Talairach & Tournoux stereotactic atlas[167] (for details, see Tamashiro-Duran et al.[113]). Data were analyzed using voxel-based, statistical parametric mapping methods and findings reached significance at a $p < 0.05$ threshold, corrected for multiple comparisons. Between-group differences were most prominent in the precuneus and posterior cingulate gyrus, in a pattern of location that resembles the findings of functional imaging studies of early stages of AD. Group differences in the proportion of carriers of the APOE ε4 allele alone cannot account for these findings, as the analysis was controlled for the presence of this gene polymorphism. The color bar represents T-values. The numbers associated with each frame represent standard coordinates in the x-axis. The left side of the image corresponds to the left side of the brain.

actually suggested that findings of frontal lobe hypometabolism in individuals with higher FCHDR scores could be determined by the greater incidence of lacunar infarcts in those subjects, leading to localized frontal metabolic changes.[166] This reasoning may explain the absence of frontal metabolic changes in our FDG-PET study, since we excluded subjects with vascular-related silent brain lesions as assessed by MRI, including lacunar infarcts. It is therefore plausible to argue that, in the absence of lacunar infarcts, the frontal lobe is not especially vulnerable to the damaging effects of CVRFs in cognitively intact individuals.

Beason-Held et al.[168] used FCHDR scores to investigate the relationship between baseline CVRFs and subsequent changes in resting rCBF (as assessed with PET) in cognitively preserved older adults (n=97) who underwent repeated annual imaging assessments over a period of up to 8 years. The authors found a significant relationship between higher baseline FCHDR scores and greater progression of rCBF deficits in the precuneus, as well as in frontal regions, the insula, and the brain stem. This was the first longitudinal PET study to provide evidence of progressive functional brain deficits in individuals with a high cardiovascular risk burden.[168]

The impact of summarizing vascular risk factors in one index has also been shown in a study of 43 elderly subjects with variable cognitive deficits; FCHDR index and amyloid deposition were positively correlated, but no individual component of the FCHDR (including diabetes, hypertension, and elevated lipids) was significantly associated with brain amyloid burden.[169]

Microstructural and molecular mechanisms underlying cardiovascular risk-related brain function deficits

The continued influence of CVRFs and cardiac disorders that lead to chronically reduced rCBF is thought to lead to numerous local neuropathological consequences,[170] including structural deformities of brain microvessels,[171,172] microembolic events, decreased oxygen and nutrient supply, metabolic deficits, toxic disturbances,[173-175] and endothelial dysfunction.[176] Such deficits at the microstructural level are all likely to contribute to the findings of regional brain hypofunction detectable using FDG-PET, rCBF SPECT, and rs-fMRI in clinical studies.

It is also important to consider the possibility of direct links between microvascular changes secondary to chronic cerebral blood flow reductions and triggering of the accumulation of Aβ-peptide that characterizes AD.[34] Recently, molecular models have implicated circulatory defects (i.e., alterations in vascular smooth muscle cells of meningeal arterioles due to CVRF) as critical factors that impair the removal of Aβ from the brain across the blood brain barrier.[171] Chronic inflammatory processes, closely linked to endothelial dysfunction, have also been increasingly implicated as relevant to the development of the Aβ-related molecular changes underlying the symptoms of AD.[177-181]

Specific CVRFs are associated with non-vascular microstructural and molecular changes, which may also contribute to the presence of cognitive deficits and related functional imaging deficits. In the case of smoking, for instance, nicotine self-administration has been shown to decrease neurogenesis and neuroplasticity and increase cell death in the hippocampus (dentate gyrus) of rats and mice.[182,183] Diabetes entails specific inflammatory changes involving protein kinase C activation, excess production of reactive oxygen species, protein glycosylation, and cellular activation of the receptor for advanced glycation endproducts.[184,185] Finally, recent research on glycogen synthase kinase-3 (GSK-3) provides one other interesting link between AD and diabetes. GSK-3 is a pivotal enzyme in glycogen synthesis and is thought to participate in the development of insulin resistance primarily by inhibiting glycogen synthase activity and, thus, decreasing the synthesis of glycogen.[186] GSK-3 has been implicated in the pathophysiology of AD because it promotes tau phosphorylation[187,188] and its activity is regulated by the Aβ peptide.[189]

There is evidence that impaired glucose metabolism plays an important role in the pathogenesis of AD (for a recent review, see Chen & Zhong[190]) and may represent a link between CVRFs/CVD and AD: persistently suboptimal glucose and/or oxygen supply may trigger a series of downstream events, such as oxidative stress, mitochondrial dysfunction, inflammation, GSK-3 activation, amyloid deposition, tau hyperphosphorylation, and neuronal death.[190,191]

In addition to the hypothesis that vascular impairments may lead or contribute to AD neuropathology, it is also plausible – and supplementary – to understand that AD and vascular burden can represent processes occurring simultaneously in the same individual that, when combined, lead to an increased risk of cognitive decline and dementia. In other words, brains suffering from this "double hit" may be more prone to declines in function, thus leading to clinical dementia.

Discussion

There is compelling evidence from neurofunctional studies to support that CVRFs are related to AD. Although some findings are conflicting and heterogeneous, a large body of the literature supports the understanding that CVRFs and CVD contribute to brain changes related to cognitive decline and increased risk of dementia in AD, and may also play a role in the pathophysiology of AD.

On the basis of these findings, we present in Figure 3 a hypothetical interaction between AD and CVD. If CVD contributes to the pathophysiological cascade of AD, then AD-related pathology is expected to start earlier and progress faster if CVD is present (black dash-dot line). Moreover, symptoms in people with comorbid AD and CVD would be expected to be more severe (black and gray dotted lines) than if only AD was present (solid black line). This model is, of course, an oversimplification of the complex interactions between AD and CVRF. Furthermore, CVD is itself a heterogeneous process; for instance, acute events such as strokes may occur (gray dotted line, stepwise progression) or not (black dotted

line), and the illustration only partially accounts for this heterogeneity. Nevertheless, two interesting aspects should be highlighted.

First, it would be very informative to test the accuracy of the model depicted by the dash-dot lines with longitudinal studies assessing amyloid deposition in middle-aged adults with normal cognition and different cardiovascular risk profiles. In other words, future research should provide more evidence to allow us to better answer the following questions: do baseline CVRFs increase subsequent amyloid deposition and/or tau-related pathology? Does treatment of CVRF modifies the longitudinal dynamics of AD-related neuropathology?

Second, because CVRFs and CVD contribute to cognitive decline (three lines to the right), adequate treatment of cardiovascular conditions and prevention of CVD should delay the onset of clinical dementia even in patients with co-occurring AD-related pathology. This aspect is particularly relevant for public health, as AD + CVD comorbidity is very common and the impact of delaying clinical onset by just a few years is substantial.[192]

The present article sought to summarize the current relevant knowledge in this field, and, although comprehensive, was not a systematic review. Instead, we provided a broad overview addressing a number of relevant topics, some of which can be further explored by future original studies or systematic reviews.

In conclusion, CVRFs are important determinants of brain health in older adults. Functional neuroimaging studies have provided multiple levels of evidence that CVRFs are associated with neuronal changes even in cognitively normal adults. Overall, these results point toward the hypothesis that CVRFs may be causally related to AD. Thus, greater knowledge about how these factors influence brain function over time may provide important insights for the development of strategies aimed at delaying or preventing pathologic brain changes, with relevant public health implications regarding the prevention of AD. Combining currently available resources for CVRF prevention/treatment and recent multimodal techniques for monitoring of AD-related pathology and changes in brain function can result in an unprecedented impact on how we understand the aging brain and promote successful aging.

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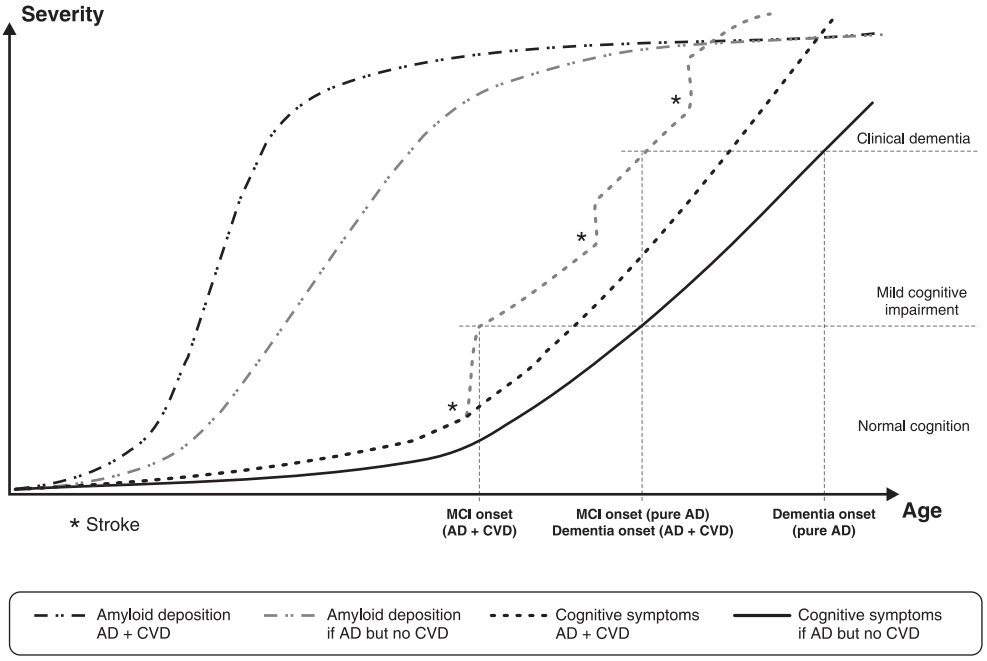

Figure 3 Hypothetical model of the dynamics of AD-related pathology and symptoms in people with and without comorbid CVD. The gray dash-dot line represents the dynamics of brain amyloid burden in AD (as described by Jack et al.[133]). The black dash-dot line illustrates the hypothetical acceleration of amyloid deposition if CVD is present. The three lines to the right represent the evolution of clinical symptoms: the solid line represents a case with AD but no CVD, the gray dotted line illustrates the progression of AD with CVD and multiple strokes (stepwise progression), and the black dotted line represents AD+CVD without strokes. The asterisk (*) indicates stroke events. Horizontal gray lines represent clinical thresholds for diagnosis of MCI and dementia, and the vertical dashed lines point to the age of MCI and dementia onset for pure AD and mixed AD+CVD with strokes. AD = Alzheimer's disease; CVD = cerebrovascular disease; MCI = mild cognitive impairment.

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Disclosure

The authors report no conflicts of interest.

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