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Special Topic Section: Responses to the NIA-AA Research Framework

"Alzheimer's disease" is neither "Alzheimer's clinical syndrome" nor "dementia"

In this issue of *Alzheimer's & Dementia*, Sweeney et al. [1] propose to extend the recently published NIA-AA Research Framework [2] by incorporating measures of vascular dysfunction as putative AD biomarkers. Although we strongly agree with the importance of a wide range of vascular factors in the development of cognitive decline, the authors misunderstand a central issue addressed in the framework: the fundamental definition of Alzheimer's disease (AD) and its distinction from the terms "Alzheimer's clinical syndrome" and dementia. We propose these terms to distinguish between the pathological features of the disease and its clinical consequences. Although there is extensive evidence that vascular factors contribute to the Alzheimer's clinical syndrome and dementia, the evidence that they contribute to AD pathological changes is limited.

For decades, AD has been defined as a clinical dementia syndrome confirmed at autopsy by the neuropathological observation of neuritic plaques and neurofibrillary tangles, which are now known to be composed of β-amyloid and paired helical filament tau. This has most recently been codified in the 2012 NIA-Alzheimer's Association guidelines for the neuropathologic evaluation of AD that define an approach to characterizing the plaque and tangle hallmark lesions [3]. These guidelines note the likely importance of other pathological findings to the clinical presentation and specifically suggest the measurement of a number of them including vascular brain injury, Lewy body disease, and TDP-43 inclusions. However, none of these pathologies is, or have ever been, required for the neuropathological diagnosis of AD, which for decades has been and remains entirely based on the density and distribution of neuritic plaques and neurofibrillary tangles. The neuropathologic guidelines accomplished two important goals: (1) they provided a clear measure for neuropathologists to define AD neuropathologic change and (2) they divorced the pathological diagnosis of AD from the clinical diagnosis. This latter point is crucial because the clinical features associated with the pathologic changes are highly variable, including multiple cognitive and behavioral syndromes along with the complete absence of symptoms.

The NIA-AA research framework built on these neuropathologic advances now that we can detect amyloid and pathologic tau *in vivo*. The NIA-AA research framework specifically defined AD as a biological entity and not a clinical-pathological entity for the same reasons that the neuropathological guidelines made this important distinction. Thus, an individual with amyloid and pathologic tau accumulation in this framework has AD, whereas an individual without these features does not have AD. We understand that the implementation of the framework raises legitimate concerns about situations in which biomarkers to detect AD pathology are not measured for scientific or logistical reasons. In part for this reason, we included the term "Alzheimer's clinical syndrome" for cases in which biomarkers could not be obtained, and individuals fit the typical clinical picture associated with AD. However, individuals who have been evaluated and who show a definite lack of Aβ plaques and pathologic tau cannot be said to have AD. Depending on clinical presentation, they can be diagnosed as having MCI or dementia, but the etiology of the dementia syndrome must be assigned to some other cause based on different underlying pathologic change(s) that may or may not be measurable at this time. The field has never questioned this approach—we just had to wait for the autopsy. Today we need not wait. The NIA-AA research framework approach does not require that Aβ plaques and pathologic tau necessarily cause the disease but simply reflects the accepted neuropathologic definition of AD.

The core argument of Sweeney et al. [1] denies the distinction between AD and the terms "Alzheimer's clinical syndrome" or dementia. At the outset, the authors state that they "use the term AD (not strictly defined as amyloid+ and tau + biomarkers) but rather more broadly inclusive of AD as a multifactorial and heterogeneous disease." This is a radical statement that simply does not represent the long-standing definition of AD in the field. We are unaware of any commonly accepted criteria related to AD that would continue to use the term after an autopsy that failed to find neuritic plaques and neurofibrillary tangles.

After suggesting that AD does not require plaques and tangles, Sweeney et al. then proceed to cite evidence that "vascular disease very commonly accompanies AD and may also be in [the] causal pathway." This is true when describing the Alzheimer's clinical syndrome. However, a

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close look at the literature shows little evidence that vascular disease or dysfunction causes the hallmark pathologic changes of AD.

For example, a number of neuropathological studies are reviewed in the study by Sweeney et al. with the contention that they demonstrate associations between AD and vascular disease. These studies, however, actually demonstrate that the Alzheimer's clinical syndrome is often associated with cerebrovascular pathology [4,5]. In these studies, there is no evidence of any association between vascular disease and plaques and tangles. The individuals in these studies often suffered from a combination of AD and vascular diseases, but there was no evidence that greater vascular injury was associated with greater AD pathologic change. Thus, these cited studies do not show an association between cerebrovascular disease and AD, but rather between cerebrovascular disease and a clinical outcome that is fundamentally syndromic in nature. Other data support the interpretation that vascular risk factors exert their effects on cognition through pathways independent of plaque and tangle pathology [6].

Similarly, the authors cite imaging studies that have demonstrated reductions in cerebral blood flow, alterations in the blood-brain barrier (BBB), and the presence of vascular injury such as brain microbleeds in the brains of individuals diagnosed with "AD." There are two crucial problems with the arguments raised. The first is again that these associations are not with any measure of AD pathologic changes. For example, cited studies showed an association between microbleeds and age or cognition [7,8], with age and multiple different dementias (including the Alzheimer's clinical syndrome, vascular dementia, alcoholic dementia, and unspecified dementia) [9], and between microbleeds and structural connectivity in patients with the Alzheimer's clinical syndrome [10]. One study showed diminished cerebral blood flow in large and medium vessels in individuals at risk for AD [11]; however, this was a group of asymptomatic individuals with a high proportion of individuals with a family history of AD, but the only AD-related variable, apolipoprotein E (*APOE*) genotype, was unrelated to perfusion measures. In other words, these studies do not demonstrate an association between vascular factors and what we have termed AD, but rather between vascular factors and either an Alzheimer's clinical syndrome, or dementia, or other features even more remotely associated with dementia. Similarly, although evidence of BBB alterations in aging and cognitive impairment is an important potential link between blood-brain transport and AD pathologic changes [12,13], this link remains unestablished. The second problem is that for modalities for which associations are better established, there is no evidence of causality. For example, perfusion reductions in the Alzheimer's clinical syndrome are widely reported, but these can also be interpreted as reflecting a phenomenon secondary to reduced tissue demand. Thus, the cited evidence is neither specific to AD pathologic changes nor is it linked to causal mechanisms underlying AD pathologic changes.

A key step in their argument involves a radical reinterpretation of FDG-PET data by proposing that reduced tracer uptake does not reflect hypometabolism but rather vascular dysfunction at the BBB. This is a radical notion if for no other reason than by this account virtually all brain disorders would reflect BBB dysfunction because virtually every neurological brain disorder and many psychiatric illnesses are associated with reductions in FDG-PET signal. There are more fundamental reasons to doubt this interpretation though. First, although it is true that FDG does not track the entire metabolic pathway of glucose metabolism, there is no requirement that a PET tracer behave identically to its tracked substrate; for example, neuroreceptor ligands do not have to trigger signal transduction, and dopamine tracers do not have to be metabolized to dopamine. FDG is, as the authors state, a substrate for hexokinase. Hexokinase is regulated by metabolic need, specifically by intracellular glucose-6-phosphate concentrations. As metabolism increases, glucose-6-phosphate concentrations decline, increasing hexokinase activity. This is perfectly captured by greater tissue trapping of FDG through its phosphorylation. FDG certainly does not capture every step in the metabolic production of ATP by either glycolysis or oxidative phosphorylation. However, its trapping based on hexokinase activity reflects metabolism. From a pharmacokinetic perspective, the Sweeney et al. interpretation is also incorrect. It is true that some dynamic PET studies have demonstrated evidence for reduced BBB transport of FDG. This is seen as a reduction in the fitted model parameter K_1, which itself reflects the product of perfusion and extraction. Both perfusion and extraction decline in response to reduced metabolic demand. Thus, the cited PET studies do not necessarily reflect a primary abnormality at the BBB. More to the point, a number of these cited dynamic studies have also shown reductions in the model parameter k_3, which reflects phosphorylation by hexokinase [14–16], consistent with a primary defect in metabolism. Finally, recent data obtained with magnetic resonance spectroscopy actually show that glucose is increased in the brain of individuals with the Alzheimer's clinical syndrome, indicating that vascular factors do not limit transport and likely reflect reduced tissue glucose consumption [17].

Sweeney et al. advocate using gadolinium (Gd)-based diffusion contrast imaging as a BBB integrity measure in AD research. First, we point out that (unlike amyloid or pathologic tau PET tracers for example) Gd accumulation in tissue implies no specific molecular affinity. Gd accumulates in any area of the brain where the BBB is disrupted and in any disease where this occurs (multiple sclerosis, tumor, etc.), and therefore this phenomenon bears no disease specificity. Accumulated Gd accelerates the natural relaxation rate of nearby water protons. More importantly, though, we urge caution on the part of AD researchers who might consider employing this approach. Gd contrast compounds may not be innocuous. In addition to the rare possibility of nephrogenic systemic fibrosis in patients with renal

insufficiency, Gd appears to be retained in certain brain regions (e.g., cerebellar dentate) in people with intact BBBs. This is more likely with less-stable Gd chelates (macrocyclic are more-stable than linear compounds), and the clinical significance if any is unclear at this point. However, owing to the uncertainty of long-term safety, the FDA now requires notification of potential risks to all outpatients receiving Gd injections. FDA medication guides that include guidelines for various MR contrast agents can be found here: https://www.fda.gov/Drugs/DrugSafety/ucm085729.htm. Investigators considering adding Gd-based diffusion contrast imaging to their research protocol should be aware of this requirement.

We are well aware of the importance of vascular factors in the development of dementia, including the Alzheimer's clinical syndrome. Sweeney et al. stated: "[we] suggest that adding vascular biomarkers to the proposed AT(N) biomarker system will help to better characterize and understand contributions of vascular dysfunction to cognitive impairment in patients suffering from AD." However, in the NIA research framework, we proposed the "V" biomarker category as a logical expansion of the AT(N) biomarker system. In fact, this is explicitly emphasized by prominently placing this concept in one of the text boxes. We reproduce part of Text Box 3 in the NIA-AA research framework for the reader's reference. A "V" biomarker category is not suggested as an AD biomarker but rather as an addition to the future suite of biomarkers that will be used to fully characterize the heterogeneous group of neuropathologic entities relevant to studies of brain aging and cognitive impairment. To date, no consensus notion of a neuropathologic, neuroimaging, or other *in vivo* definition of "V" exists. Thus, the addition of "V" to AT(N) is listed as a future development. Along similar lines, the authors' recommendation for the addition of vascular imaging measurements ignores much of current practice. The proposed measures of FLAIR, DTI, T2*-weighted sequences, and so on, already are included in many research programs in the AD field, such as ADNI, DIAN, the A4 study, and many epidemiological studies and Alzheimer Center protocols.

We do not know what causes AD, and we have no effective treatments. Although Aβ plaques and pathologic tau are the hallmark pathologic changes, we have limited understanding of how they come about. In this setting, it is important to examine all possible mechanisms. There are interesting suggestions from PET studies that cerebrovascular risk factors such as hypertension and hyperlipidemia may play a role in increasing brain Aβ [18–20] or pathologic tau [21]. However, there are also multiple studies that have used amyloid imaging to look for associations between vascular factors and AD pathologic changes and failed to find them [22–24]. In addition, many other factors have been proposed to directly affect Aβ, including metabolic tissue characteristics, neural activity, plasticity, inflammation, genetics, and physical activity. In fact, figure 1 in the study by Sweeney et al. provides an extensive listing of factors that may drive the pathologic changes of AD. None of these, however, including vascular factors, have reached the level of evidence where they are accepted as causal mechanisms of AD. In contrast, we included measures of neurodegeneration in the research framework because there is strong evidence that protein aggregates, especially tau, are related to brain degeneration, which in turn is related to cognition, placing it squarely in the causal pathway [25–29]. Furthermore, although we agree that targeting vascular disease through public health or medical interventions offers the potential to reduce the burden of dementia, all existing evidence suggests that it may do so independent of any effects on plaque and tangle accumulation in the brain. Although vascular factors are important in the development of dementia, there are so many different ways to characterize them—including risk factor measurement, large and small vessel infarction, functional BBB alterations, CSF- and blood-based biomarkers, measures of CAA, microbleeds, and changes in white matter—that adoption of a simple dichotomous term as "V" in the framework is impossible at this point. For these reasons, we strongly support further investigations of the mechanisms through which vascular dysfunction may lead to dementia, as well as interventions to reduce vascular brain injury and thereby the risk of dementia. We also agree that measurement of these factors is important in fully characterizing research participants in terms of their risk for dementia. However, this is quite different than considering vascular dysfunction to represent

Text Box 3 (reprinted from NIA-AA research framework)

1. Flexibility of the AT(N) system
2. The AT(N) system is designed to incorporate new biomarkers within existing AT(N) groups. For example, neurofilament light chain (cerebrospinal fluid or plasma) or neurogranin will likely be added to the (N) group.
3. The AT(N) system is also designed to incorporate new biomarkers in categories beyond AT(N). The notation ATX(N) might be useful when conceptualizing the incorporation of new biomarker groups, where X represents an array of biomarkers that may become available in the future. For example, when a measure that incorporates and appropriately weights the many sources of information about cerebrovascular disease has been developed and standardized, AT(N) will be expanded to ATV(N). When biomarkers for both V and synuclein have been developed, AT(N) will be expanded to ATVS(N), and so on, for biomarkers of inflammation (I), TDP-43, etc.

a core feature of AD, and for this reason, we do not favor its incorporation as such into the current framework.

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