A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers

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ABSTRACT

Biomarkers have become an essential component of Alzheimer disease (AD) research and because of the pervasiveness of AD pathology in the elderly, the same biomarkers are used in cognitive aging research. A number of current issues suggest that an unbiased descriptive classification scheme for these biomarkers would be useful. We propose the “A/T/N” system in which 7 major AD biomarkers are divided into 3 binary categories based on the nature of the pathophysiology that each measures. “A” refers to the value of a β-amyloid biomarker (amyloid PET or CSF Ap42); “T,” the value of a tau biomarker (CSF phospho tau, or tau PET); and “N,” biomarkers of neurodegeneration or neuronal injury ([18F]-fluorodeoxyglucose-PET, structural MRI, or CSF total tau). Each biomarker category is rated as positive or negative. An individual score might appear as A++/T-/N−, or A+/T−/N−, etc. The A/T/N system includes the new modality tau PET. It is agnostic to the temporal ordering of mechanisms underlying AD pathogenesis. It includes all individuals in any population regardless of the mix of biomarker findings and therefore is suited to population studies of cognitive aging. It does not specify disease labels and thus is not a diagnostic classification system. It is a descriptive system for categorizing multidomain biomarker findings at the individual person level in a format that is easy to understand and use. Given the present lack of consensus among AD specialists on terminology across the clinically normal to dementia spectrum, a biomarker classification scheme will have broadest acceptance if it is independent from any one clinically defined diagnostic scheme. Neurology® 2016;87:539-547

GLOSSARY

Ap = β-amyloid; AD = Alzheimer disease; FDG = [18F]-fluorodeoxyglucose; IWG = International Working Group; MCI = mild cognitive impairment; NIA-AA = National Institute on Aging-Alzheimer’s Association; p-tau = phosphorylated tau; SNAP = suspected non-Alzheimer pathophysiology; t-tau = total tau.

By providing measures of relevant pathophysiology in living persons, biomarkers have become increasingly important to understanding the biology of Alzheimer disease (AD). Biomarkers are also used in all modern research diagnostic criteria across the AD clinical spectrum,1,4-6 in therapeutic trials, and by regulatory agencies.7 Because AD pathology is so frequent in the elderly, AD biomarkers are also commonly used in cognitive aging research. However, several current issues suggest that a different approach to biomarkers used in AD research might be useful.

First, available evidence points to recently developed tau PET tracers as useful measures of neurofibrillary tangles in AD, while utility in non-AD tauopathies has not yet been clarified.8,9 Elevated tau PET tracer signal, particularly in neocortical regions, is highly associated with the...
presence of positive amyloid PET scans as would be expected in a ligand that binds to the tau deposits in AD.\textsuperscript{10,11} Tau PET ligand binding correlates well with clinical impairment in individuals who lie along the AD clinical spectrum.\textsuperscript{10,11} When easily characterized off-target and nonspecific binding is accounted for, the topographic patterns of ligand uptake match quite well what is expected from Braak staging of neurofibrillary tangles.\textsuperscript{12} However, because of its recent introduction, tau PET is not yet integrated into any current AD diagnostic schemes.

Second, many details of AD pathogenesis remain uncertain.\textsuperscript{13,14} One of the most contentious issues, and one of the oldest, is which proteinopathy “causes” the disease in the elderly. Some propose that AD pathogenesis follows a specific cause and effect order of events, where \( \beta \)-amyloidosis potentiates the spread of tauopathy, tauopathy is associated with neurodegeneration, which is the immediate cause of clinical symptoms.\textsuperscript{15} Others argue for different, less \( \beta \)-amyloid (A\( \beta \)) centric pathways to clinically symptomatic AD.\textsuperscript{13,14,16} Interdependent pathways have also been proposed.\textsuperscript{17} A biomarker classification system will have the broadest use if it makes no assumptions about temporal ordering of biomarkers or their putative causal relationships.

Third, current biomarker classification systems are linked to disease or syndromic labels and are based on consensus diagnostic criteria rather than certainty of disease pathogenesis. The 2 major such diagnostic schema are those of the International Working Group (IWG),\textsuperscript{1,18} which first proposed the use of a common biomarker algorithm for all clinical stages of the disease, and the National Institute on Aging–Alzheimer’s Association (NIA-AA).\textsuperscript{3,6} Although there are areas of agreement, important disagreements exist concerning staging, nomenclature, and interpretations of biomarker findings. We recognize that associating biomarkers with clinical findings is important. However, given the confusion that has arisen over the use of competing definitions of clinical impairment in the AD spectrum,\textsuperscript{19} a biomarker classification scheme will have broadest acceptance if it is independent from any one clinically operationalized diagnostic scheme. The biomarker classification scheme we propose is applicable across all clinical diagnostic states, and is thus independent of cognitive status.

Fourth, the prevalence of AD, non-AD, and mixed brain pathologies increases with age in both individuals who are clinically impaired and those nonimpaired.\textsuperscript{20} To be an effective tool in cognitive aging research, a biomarker classification system must include all possible biomarker profiles and all individuals in the population. For example, classification schemes that require A\( \beta \) positivity do not classify individuals who are A\( \beta \) negative but positive on tau or neurodegenerative biomarkers, yet the latter biomarker profile is common.\textsuperscript{21}

The objective of this report is to propose an unbiased descriptive classification scheme for biomarkers commonly used in AD research that addresses each of these 4 issues.

\textbf{AD BIOMARKERS} We propose that the major biomarkers used in AD research can be divided into 3 binary categories based on the nature of the underlying pathophysiology each measures. Biomarkers of fibrillar A\( \beta \) deposition are high ligand retention on amyloid PET\textsuperscript{22} or low CSF A\( \beta \).\textsuperscript{12,23–25} Biomarkers of tau pathology (neurofibrillary tangles) are elevated CSF phosphorylated tau (p-tau) and tau PET.\textsuperscript{24,26} Biomarkers of AD-like neurodegeneration or neuronal injury are CSF total tau (t-tau), \([\text{\textsuperscript{18}}\text{F}]\)-fluorodeoxyglucose (FDG)-PET hypometabolism, and atrophy on structural MRI in regions characteristic of AD.\textsuperscript{27}

CSF biomarkers report a single absolute value reflecting degree of abnormality but that does not indicate topographic extent of pathology. In contrast, imaging biomarkers contain information about both the severity and topographic extent of the abnormality. Typical AD (i.e., amnestic multidomain dementia) is associated with a characteristic topographic pattern of FDG-PET hypometabolism that appears earliest and most severely in the medial parietal and lateral temporal-parietal isocortex (figure 1A).\textsuperscript{28} Typical AD likewise is associated with a pattern of atrophy on MRI that appears earliest and most severely in the medial temporal allocontex and the basal-lateral temporal isocortex (figure 1C).\textsuperscript{31} A\( \beta \) deposition on PET does not seem to follow a sequential topographic progression through the isocortex (figure 1E). Available evidence indicates that in the typical AD spectrum, tau PET captures the topography of tau spread as described at autopsy by Braak\textsuperscript{12}—medial temporal to basal and lateral temporal, then to other isocortical areas (figure 2).
While each of the 7 commonly used core biomarkers is associated with AD, they are not equally specific. Biomarkers of β-amyloidosis are specific for AD pathology. However, amyloid PET tracers do bind to Aβ deposits in vessel walls, and increased tracer binding can be found following acute traumatic brain injury. CSF Aβ42 is decreased (i.e., abnormal) in some non-AD conditions such as HIV encephalitis and multiple system atrophy. Typical AD shows an increase in both t-tau and p-tau and a tight correlation between these biomarkers. Neither CSF t-tau nor p-tau shows any change in primary tauopathies such as frontotemporal dementia, progressive supranuclear palsy, or corticobasal degeneration. However, findings on CSF t-tau and p-tau diverge in conditions with acute brain damage. There is a marked temporary increase in t-tau with normal p-tau levels in traumatic brain injury and stroke that correlates with the severity of neuronal damage. It is the same for Creutzfeldt-Jakob disease, which shows a large increase in t-tau (reflecting rapid neurodegeneration) but normal p-tau since there are no neurofibrillary tangles in this condition. The CSF level of p-tau correlates with severity of tau pathology postmortem, and high p-tau has not been found in disorders other than AD. Taken together, these data indicate that CSF t-tau reflects the intensity of neuronal degeneration in AD at a specific point, while p-tau seems more specific for the burden of AD-type tau pathology accumulated over time. Tau PET is being actively investigated, but initial data indicate that tau PET ligands have high binding affinity for paired helical filament tau in AD but have much weaker affinity in non-AD tauopathies, especially those with straight filament tangles.

Atrophy and hypometabolism involving AD-like regions occur in a variety of disorders and are the least specific for AD. Atrophy in the anterior/medial/basal temporal lobes occurs in a wide variety of pathologic conditions including AD but also cerebrovascular disease, epilepsy, anoxia, hippocampal sclerosis, TDP-43-opathy, primary age-related tauopathy, chronic traumatic encephalopathy, argyrophilic grain disease, and non-AD primary tauopathies such as progressive supranuclear palsy and Pick disease. Temporoparietal hypometabolism can be found in non-AD conditions, such as corticobasal degeneration, primary progressive aphasia, and cerebrovascular disease. This nonspecificity is the explanation for the frequent and consistently observed finding of abnormal FDG-PET and structural MRI (and CSF t-tau) in non-AD conditions—a state that has been labeled suspected non-Alzheimer pathophysiology (SNAP).

Interpreting biomarker data is confounded by the common coexistence of AD pathology, and therefore positive AD biomarkers, with other age-related pathologies. Multidomain amnestic dementia and mild cognitive impairment (MCI) are most commonly associated with multiple pathology, especially with advancing age.

THE A/T/N CLASSIFICATION SYSTEM In the proposed A/T/N classification system, the 7 major
AD biomarkers are divided into 3 binary classes. “A” refers to the value of an Aβ biomarker (amyloid PET or CSF Aβ42); “T,” the value of a tau pathology biomarker (CSF p-tau or tau PET); and “N,” a quantitative or topographic biomarker of neurodegeneration or neuronal injury (CSF t-tau, FDG-PET, or structural MRI).

The A/T/N classification system is related to the biomarker classification proposed in recent consensus diagnostic criteria. In both IWG and NIA-AA diagnostic criteria, A refers to Aβ (PET or CSF Aβ). Segregation of MRI and FDG-PET from CSF tau biomarkers was proposed by the IWG (2014), while in the NIA-AA criteria, MRI, FDG-PET, and CSF tau proteins were grouped together as biomarkers of neurodegeneration or neuronal injury. The rationale for grouping CSF tau, FDG-PET, and MRI atrophy into a single category in the NIA-AA criteria had strong support from numerous observations that the 3 behaved in a similar manner relative to clinical symptoms. More abnormal values in all 3 of these biomarkers are strongly associated with worse cognitive symptoms throughout the clinical spectrum, which is not the case for amyloid biomarkers. The topography of hypometabolism and atrophy maps well onto the expression of clinical symptoms, which is not the case for amyloid PET.

We recognize that having both T and N categories adds complexity in comparison to simply grouping tau PET, FDG-PET, MRI atrophy, CSF t-tau, and p-tau into a single catch-all N category. However, the simpler approach would fail to take advantage of information that is available. Some (perhaps quite a bit) of the neuronal injury/neurodegeneration present in elderly individuals is related to non-AD etiologies. Separating biomarkers of neurofibrillary tangles (tau PET and CSF p-tau) from markers of neuronal injury/neurodegeneration might differentiate neuronal injury/neurodegeneration that is attributable to AD from non-AD causes.

In the A/T/N system, each biomarker is rated as positive or negative. An individual score might appear as A+/T+/N−, or A+/T−/N−, etc. In the event that a biomarker class was unavailable, it would be denoted “u.” Conflicting results within a category would be labeled “c.” For example, if an individual had conflicting results from amyloid PET and CSF Aβ, he or she might be labeled Ac. While we regard atrophy, hypometabolism, and total tau each as exemplars of neuronal injury/neurodegeneration, we do not believe these 3 measures should be equated. Analyses show that neurodegeneration biomarkers are only modestly correlated with one another. Therefore, if possible, within a given research study, the N category should be described by only one N marker, not either/or mixtures of the 3. Individuals can be fully classified by CSF alone, imaging alone, or combinations.

**POSITIVE/NEGATIVE OR NORMAL/ABNORMAL BIOMARKER CUTPOINTS** Although every biomarker exists on a continuous scale, normal vs abnormal cutpoints exist in most disease categories to make diagnostic categorization of individuals practical and inform clinical decision-making. We recognize that cutpoints can be arbitrary, and many individuals will have biomarker values close to cutpoints. This is true for any disease and is not unique to biomarkers used in AD research. The presence of positive/negative cutpoints is not inherently problematic provided that values close to cutpoints are interpreted and used properly.

Amyloid biomarkers have been bimodally distributed in some research samples where participants are highly selected, while neurodegenerative biomarkers typically are not. This has led to the suggestion that cutpoints are not valid for neurodegenerative biomarkers. However, most physiologic measures...
are continuously, not bimodally, distributed—blood pressure, for example.\textsuperscript{50} This has not prevented medicine from identifying a cutpoint and designating those above hypertensive and those below normotensive. It seems illogical to treat AD differently from other diseases.

We emphasize that binary, +/− categorization does not imply that individuals who fall below the cutpoint for a particular biomarker have no pathology in the brain. For example, an individual designated as A may well have amyloid plaques in the brain, but not at a sufficient level to cross the in vivo detection threshold of amyloid PET. Current biomarker readouts are not sensitive to low but perhaps biologically important levels of early pathology.\textsuperscript{51,52} The +/− designation is a convenient shorthand to facilitate communication, ease of use, and understanding.

Several different approaches to selecting normal/abnormal cutpoints in the continuous range of biomarker values exist. These include selecting values that best separate clinically normal individuals from those with dementia, values that have predictive power for future clinical decline,\textsuperscript{53} or using autopsyed individuals with antemortem biomarker studies to guide selection of cutpoints.\textsuperscript{51,52} In laboratory medicine, the 95th percentile based on a healthy control population is commonly used.\textsuperscript{54} A popular approach has been to select cutpoints based on the (most normal) 10th percentile of values seen in typical AD dementia.\textsuperscript{21,55} Validating specific cutpoints will be an ongoing exercise for research groups working in each separate modality.

Experience labeling tau PET scans positive vs negative is limited at this point. Tauopathy confined to the medial temporal lobes with minimal or no neocortical β-amyloidosis is very common at autopsy and whether this should be regarded as AD or simply an aging phenomenon is controversial.\textsuperscript{12,13,54} One possible approach to categorizing tau PET is to label scans that have tracer uptake exceeding an analytically determined threshold in AD-like isocortical areas as “AD positive” (figure 2). Where tau is located and its topographic progression over time will be important. But for purposes of labeling a scan abnormal, we provisionally propose that a scan with tracer uptake confined to the medial temporal lobes would not be considered positive\textsuperscript{44} but a scan with uptake in AD-like isocortical areas would.\textsuperscript{10}

**ALTERNATIVES TO POSITIVE/NEGATIVE SCORING OF BIOMARKERS** Advantages of binary, +/− categorization of each biomarker class include economy, conceptual clarity, and ease of use. Thus, we recommend binary, +/− categorization. Alternatives exist however and are briefly discussed for completeness. One alternative is to score the severity of each biomarker on a continuous or semicontinuous scale. An example of this, termed the centiloid scale,\textsuperscript{56} has been proposed for amyloid PET. The process requires empirically establishing reference values for the abnormal part of the distribution using individuals with AD dementia and the normal part of the distribution using young, clinically normal individuals. Biomarker values are then scaled linearly from 0 (normal) to 100 (abnormal). The centiloid scale is related to but not identical to percentiles because centiloid values below 0 (i.e., below the mean for the normal group) and above 100 (i.e., above the mean for the abnormal group) are possible. An example of how this might appear is A80/T50/N20, where this individual ranks at the 80th centiloid for amyloid, 50th for tau, and 20th for neurodegeneration. This approach would require a 0 to 100 scale that was standardized across all biomarkers.

A second alternative to binary, +/− biomarker scoring is topographic staging. This approach would only be applicable to imaging and might best apply to tau PET. Topographic tau PET staging would mirror pathologic Braak neurofibrillary tangle stage whereby individuals would be assigned to 1 of 3 stages based on anatomical locations of tracer uptake—i.e., stage 0, limbic stage, isocortical stage. Since cortical atrophy on MRI closely mirrors Braak stage and tau density in imaging–autopsy correlation studies,\textsuperscript{57} and the topographic spread of atrophy within individuals over time also mirrors progressive Braak stages, this Braak-like topographic staging approach might be valid for MRI as well.

Generalizability of AD biomarker categorization is dependent on standardization and reproducibility of the measures.\textsuperscript{58}

**ATYPICAL AD, CEREBROVASCULAR DISEASE, AND EXPANSION OF THE CORE A/T/N SYSTEM** The descriptions of FDG-PET, tau PET, and MRI topography outlined above reflect patterns of typical multidomain amnestic AD (figures 1 and 2). Because MRI, FDG, and tau PET topographic patterns map onto clinical phenotype, a different set of imaging signatures is needed to describe atypical variants of AD. Although not detailed in the present report, the A/T/N system is equally applicable to atypical AD variants by modifying the topographic search pattern. For example, pattern recognition algorithms could easily be modified to recognize atrophy, hypometabolism, and tau PET deposition in the frontal, dominant temporal lobe, or posterior cortical regions for atypical AD.

Our primary focus is the core A/T/N system, which addresses biomarkers of AD; however, biomarkers of other proteinopathies could be added if/when they become available. The category of synaptic dysfunction (S) may be a useful future addition and this might include FDG-PET, task-free functional
However, not defined. This combination was not addressed in NIA-AA preclinical AD criteria on the assumption that established Stage 1 Asymptomatic at risk of AD (if Aβ established by amyloid PET).

Stage 1 Asymptomatic at risk of AD (if Aβ established by amyloid PET).

Not defined. Described as MCI-SNAP (suspected non-Alzheimer pathophysiology) in several publications.

Asymptomatic at risk of AD (if Aβ established by amyloid PET).

Stage 2/3 Asymptomatic at risk of AD.

Not defined. Not defined. Described as SNAP (suspected non-Alzheimer pathophysiology) in several publications.

Typical AD

Individuals who meet clinical criteria for MCI

| A/T/N score | NIA-AA classification | 2014 IWG classification |
|-------------|------------------------|-------------------------|
| A−/T−/N−   | MCI, unlikely due to AD | Not defined              |
| A+/T−/N−   | MCI, core clinical criteria| Typical AD (if Aβ established by amyloid PET) |
| A+/T+/N−   | MCI, core clinical criteria| Typical AD              |
| A+/T+/N+   | MCI due to AD, high likelihood | Typical AD              |
| A−/T+/N−−  | Not defined | Not defined              |
| A−/T+/N+−  | Not defined | Not defined              |
| A−/T+/N+−− | Not defined | Not defined              |

Table 2

Table 1

Clinically normal individuals

| A/T/N classification | NIA-AA classification preclinical AD | 2014 IWG classification |
|----------------------|-------------------------------------|-------------------------|
| A−/T−/N−             | Not defined                          | Not defined              |
| A+/T−/N−             | Stage 1 Asymptomatic at risk of AD (if Aβ established by amyloid PET) |
| A+/T+/N−             | Stage 2/3 Asymptomatic at risk of AD |
| A+/T+/N+             | Stage 2/3 Asymptomatic at risk of AD |
| A−/T+/N−−            | Not defined                          | Not defined              |
| A−/T+/N+−            | Not defined                          | Not defined              |
| A−/T+/N+−−           | Not defined                          | Not defined              |

Abbreviations: AD = Alzheimer disease; FDG = F-fluorodeoxyglucose; IWG = International Working Group; NIA-AA = National Institute on Aging-Alzheimer’s Association.

MRIs, EEGs, EMEGs (magnetoencephalography), as well as synapse-specific proteins in CSF. However, if neurodegeneration is defined as progressive loss and shrinkage of neurons and processes with a corresponding impairment in neuronal function, then synaptic dysfunction is subsumed within the category of neurodegeneration.

The core A/T/N system could also be supplemented by adding a cerebrovascular disease category. A limitation is the absence of an agreed pathologic summary scoring system for cerebrovascular disease on which to base an imaging counterpart. Nonetheless, systems in which the MRI findings of ischemic cerebrovascular disease are combined to form a vascular (V) summary score have been described. The A/T/N system would then be extended to A/T/N/V by compressing the vascular index into V+ or V−.

APPLICATION OF THE A/T/N SYSTEM IN COGNITIVE AGING AND DEMENTIA RESEARCH: A/T/N/C

The A/T/N system provides a common framework by which investigators can describe and communicate multidomain biomarker profiles at the individual person level. Application in cognitive aging and dementia research, however, will require the inclusion of clinical information about each individual. Clinical status (C) could be denoted in several possible ways resulting in A/T/N/C notation. Setting aside detailed syndromic descriptions, cognitive function can be thought of categorically or as a continuum. The cognitive/functional continuum could be divided into normal for age (n), mildly impaired (m), or demented (d), resulting in designations of A/T/N/Cn, A/T/N/Cm, or A/T/N/Cd. The cognitive continuum could also be expressed as a continuous variable on a 0 (normal) to 100 (abnormal) scale; individuals are assigned values along this 0 to 100 scale.

HOW DOES THE A/T/N SYSTEM RELATE TO EXISTING AD CLINICAL CLASSIFICATION SYSTEMS?

The IWG and NIA-AA criteria both integrate 5 biomarkers into the diagnostic classification process: CSF Aβ42 and tau proteins, amyloid PET, FDG-PET, and MRI. In the most recent version of the IWG criteria, CSF Aβ, tau, and amyloid PET are regarded as pathophysiologic biomarkers of AD while FDG-PET and MRI are considered topographic downstream biomarkers. Biomarker support for AD pathophysiology consists of a positive amyloid PET scan or both depressed Aβ42 and elevated t-tau or p-tau in CSF. In the NIA-AA criteria (2011), separate guidelines were outlined for 3 clinical phases—preclinical, MCI, and AD dementia. The NIA-AA preclinical AD criteria were predicated on the concept that AD biomarkers follow a specific temporal ordering where β-amylloidosis occurs before tau-related neurodegeneration, which in turn is the proximate correlate of clinical symptoms. By contrast, NIA-AA criteria for MCI and AD dementia attribute equal diagnostic weight to all AD biomarkers included in the criteria.

Tables 1 to 3 outline how the A/T/N system maps onto these 2 existing diagnostic classification systems. Conceptual differences both between and within these sets of diagnostic criteria are evident. For example, a clinically asymptomatic individual with a positive CSF Aβ42 and negative CSF tau profile is labeled preclinical AD stage 1 by the NIA-AA criteria but is classified as not being in the AD pathway by IWG. A clinically asymptomatic individual with positive CSF Aβ42 and tau is labeled preclinical AD stage 2 by the NIA-AA criteria and as “asymptomatic at risk for AD” by IWG. Disagreement in how these different diagnostic criteria treat biomarkers creates uncertainty for
profiles will emerge as the A/T/N system is applied empirically.

**AUTHOR CONTRIBUTIONS**

Dr. J. study concept and design and critical revision of the manuscript for important intellectual content. Dr. B. critical revision of the manuscript for important intellectual content. Dr. B. critical revision of the manuscript for important intellectual content. Dr. C. critical revision of the manuscript for important intellectual content. Dr. D. critical revision of the manuscript for important intellectual content. Dr. E. critical revision of the manuscript for important intellectual content. Dr. F. critical revision of the manuscript for important intellectual content. Dr. G. critical revision of the manuscript for important intellectual content. Dr. H. critical revision of the manuscript for important intellectual content. Dr. I. critical revision of the manuscript for important intellectual content. Dr. J. critical revision of the manuscript for important intellectual content. Dr. K. critical revision of the manuscript for important intellectual content. Dr. L. critical revision of the manuscript for important intellectual content. Dr. M. critical revision of the manuscript for important intellectual content. Dr. N. critical revision of the manuscript for important intellectual content.

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