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INVITED REVIEW

Antiquity, past, present, and future of *in vivo* diagnosis of Alzheimer's disease

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ABSTRACT

2026 will mark the 120th anniversary of the publication of the first case of Alzheimer's disease (AD). However, the first case was very atypical for today's standards: a lady with early-onset behavioral problems. This led to the classification of AD as pre-senile dementia, a very rare disease, and consequently, almost non-existent AD research in the first 3 quarters of the 20th century. This era can be named as the antiquity of AD. It ended with the realization that senile dementia is indeed AD. The last quarter of the previous century first witnessed the birth of behavioral neurology, which subsumed the entire cognitive disorders, including dementia, under its wings. This was followed by the publication of the first formal clinical diagnostic criteria set for AD (NINCDS-ADRDA). This was a major step in establishing a common language and more or less homogenous patient groups for AD research. However, it equated AD with its terminal dementia stage and allowed the use of laboratory methods only for exclusionary purposes. Ignoring the very long period of pre-dementia stages became a major flaw of that era, which we can call the past of AD. The very significant advances in all areas of AD research, including neuropsychology, neuroimaging, neuropathology, and genetics, during the last two decades of the past finally succeeded in getting rid of these flaws. This step was taken by International Work Group (IWG 2007) and marked the beginning of the present of AD. It was followed by the 3 sets of criteria of National Institute of Aging-Alzheimer's Association (NIA-AA 2011). In the present era, AD can now be diagnosed at any point during its progression with the aid of biomarkers, even during its preclinical stage. The IWG and NIA-AA criteria sets kept on being revised up to the present day. The NIA-AA 2024 was a biological-clinical integrated staging system (ISS), allowing for to follow the clinical and biological progression of AD along its ever-increasing stages. Not only this, but ISS also allowed the physician to differentiate the comorbidities. This may be considered as a door opened to the future of AD, signaling the end of its present. It can be claimed that the major flaw of the present was to conceive every neurodegenerative disease, including AD, as an effect caused by the singular protein deposits, and consequently targeting them for treatment purposes, despite repeated failures of this treatment strategy. It became increasingly clear that co-proteinopathies are not an exception but are the norm. Overcoming the flaw of the present will necessitate looking to the neurodegeneration through the co-proteinopathy lens in the already heralded future.

Keywords: Alzheimer's disease, biomarkers, co-proteinopathy, diagnostic criteria.

ANTIQUITY

Alois Alzheimer's first case, Auguste Deter, was born in 1851 and had developed memory, language problems, and delusional thinking in the late 1890s when she was still in her 40s. She was living in Frankfurt back then and was taken to Frankfurt Psychiatric Hospital (Irrenschloss) in 1901, where Alzheimer was a staff member, and she became his patient. Alzheimer moved to Munich the next year, but retained communication with his old colleagues about the patient. Deter died in 1906. Alzheimer received the brain and the medical records of his patient. He examined her brain tissue and reported his major findings, which were visualized using Max Bielschowsky's silver staining method, as characterized histologically by the presence of "neurofibrillary degeneration" of the neurons, especially of the cerebral

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cortex, and of senile plaques in the neuropil, associated with macroscopical generalized brain atrophy, in the same year at a congress of neuropsychiatrists in Tübingen (Alzheimer 1906). The report was titled "Über einen eigenartigen, schweren Erkrankungsprozess der Hirnrinde" (About a peculiar, severe disease process of the cerebral cortex). The next year, he wrote it as a case report,[1] thus starting the antiquity of Alzheimer's disease. His chief in Munich Lab, Emil Kraepelin, mentioned the clinical and neuropathological findings of Deter's case in the 1910 8th edition of his famous textbook, "Psychiatrie: ein Lehrbuch für Studi[e]rende und Aerzte" (Psychiatry: A Textbook for the Students and Doctors) and used the eponym Alzheimer to name this new clinical entity.[2] Yet, it was classified by Kraepelin under pre-senile dementias along with Pick's disease, not erroneously though, since Frau Deter was in her mid-forties when the disease had started. This classification became a misfortune for Alzheimer's disease (AD), since it was considered a rare disease, and senile dementia was equated with cerebral arteriosclerotic disease for decades in the 20th century. The only notable contribution came from Divry in 1927, who stated that the affinity of senile plaques to Congo-red suggested an amyloid nature (Divry 1927). There was no mention of AD in the first three editions of the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders (DSM I, II, and III) (APA 1952, APA 1968, APA 1980). DSM I and DSM II coined the term "chronic organic brain syndrome" for senile dementia, and DSM III changed it to "primary degenerative dementia" (PDD).

The dominant paradigm of antiquity of AD, which equated AD with a rare disorder, that is pre-senile dementia, changed at the end of the third quarter of the century. First, the British trio Tomlinson, Blessed, and Roth published two consecutive papers concluding that arteriosclerotic dementia was overdiagnosed in the senile population.[3,4] The decisive stroke came from American Robert Katzman, who proclaimed that "AD is the same thing as senile dementia", hence "it is the major killer in the elderly population".[5] This blow radically changed the prevailing perspective towards dementia and ushered in a new era, terminating the antiquity of AD, promising enriched funding opportunities for AD research.

PAST

The complete emergence of the new era can be claimed to coincide with the equation of AD with a major public health problem, senile dementia, thus liquidating the primary dogma of antiquity. However, it can be argued that there was also a strong institutional impetus for the new era that came with the 10-year-long birth process and the eventual establishment of a new neurological subspecialty: behavioral neurology.

The birth of behavioral neurology can be traced back to the publication of Norman Geschwind's 2-part, 117-page-long Brain monograph: Disconnexion syndromes in animals and man.[6,7] Marsel Mesulam attested this fact on the occasion of the 50th anniversary of its publication, rephrasing Orhan Pamuk from his novel New Life: "I read a book one day, and my whole life was changed".[8] Mesulam continues in his commemorative article: "For the past half century, this two-part monograph has remained the most influential work ever published in the discipline that came to be known as behavioral neurology". The year 1965 was also a milestone for a birth: The Aphasia Research Center at the Boston Veterans Administration (VA) Hospital (Boston City Hospital) was formally established in that year. The Aphasia Research Center can be considered as the forerunner of the first Behavioral Neurology Unit at the Beth Israel Hospital. Some of the most influential, first-generation leaders of behavioral neurology were trained at this center, names like Frank Benson, Marsel Mesulam, and Antonio Damasio. In 1972, Geschwind first introduced the term "behavioral neurology" at an American Academy of Neurology annual meeting (Barberis and Wright 2020). Among the founders of modern neuropsychology, Harold Goodglass, the co-author of Boston Diagnostic Aphasia Examination (BDAE), and Edith Kaplan, the co-author of BDAE and California Verbal Learning Test (CVLT), among others, were also at Boston VA Hospital, working with Geschwind. Modern neuropsychology was also a very influential impulse for the emerging new era. Frank Benson, commenting on this period, describes this as follows: "At the same time, the field of neuropsychology, previously a fledgling and somewhat struggling subspecialty, blossomed into a vast, robust, and exciting component of psychology".[9] In 1975, Harvard Medical School left Boston City Hospital and moved to Beth Israel Hospital, where the first Behavioral Neurology Unit (BNU) of the world was established (20 years later, the first BNU in

Türkiye was established at our department, and incorporated the first Neuropsychology Lab of the country, founded by Öget Öktem-Tanör in 1983). Sandra Weintraub, another prominent figure of modern clinical neuropsychology, finished her post-doctoral training in 1980 at Beth Israel Hospital-BNU and started working with Geschwind and Mesulam. According to the Cognitive Neuroscience Society's website, the term "cognitive neuroscience" was also articulated during the late 70s, in a taxi in New York by the founders of the discipline, Michael S. Gazzaniga and George A. Miller (https://www.cogneurosociety.org/background/). Geschwind passed away in 1982 and was succeeded by Mesulam. I had the privilege of working at the BNU under Dr. Mesulam's tutelage in 1989-90. Geschwind Team's major focus was originally on stroke aphasia, but after behavioral neurology emerged as a subspecialty, all the cognitive disorders, regardless of etiology (vascular, traumatic, neurodegenerative, etc.), were imported into its dominion. The first textbook of behavioral neurology appeared in 1985, written by Marsel Mesulam.[10] This was the very book that changed my life after reading it as a neurology resident. The second edition appeared in the year 2000.[11] The Turkish translation of the 2nd edition by our team was published in 2004 (Mesulam 2004). Mesulam also made a major contribution to the radical paradigm shift in the understanding of the brain-behavior relationship: the network approach to the cerebral organization of the mind. According to the prevailing localizationist view, the human mind was organized in dedicated cortical centers with little interaction with each other, subcortical structures being relay stations between the external world and those centers (thalamus, a sensory relay, and striatum, a motor relay). Thus, Broca's area was a grammar center, Wernicke's area was a comprehension center, and the right parietal lobe was a center for spatial attention. On the contrary, a large-scale distributed neural network was composed not only of interconnected cortical nodes but also possessed subcortical (thalamic and striatal) components, also interconnected with all its cortical nodes. There were relative specializations within the network. For example, in the language network, anterior frontal nodes were specialized in grammatical processing, therefore, their lesion resulted in agrammatic, non-fluent aphasias; posterior parietal nodes were specialized in semantic processing, therefore, their lesions resulted in fluent aphasias with comprehension deficits; peri-sylvien nodes were specialized in phonologic processing, therefore their lesions resulted in repetition deficits with fluent speech and intact comprehension. The aphasias after subcortical lesions, which were coined as "atypical" before, were no more atypical, because thalamic and striatal components of the language network were also playing roles in language processing. Mesulam had already depicted a right-lateralized large-scale neural network for directed attention, lesions of which resulted in left hemi-spatial neglect, with relative specializations reflected in different hemineglect syndromes: a motor-exploratory predominant hemineglect after right frontal lesions, a sensory predominant hemineglect after right parietal lesions, and a motivational predominant hemineglect after right cingulate lesions.[12] Severe hemineglect after right thalamic pulvinar nucleus lesions was no more "atypical". In his later paper dedicated to "large-scale neurocognitive networks", Mesulam described a limbic network for memory, in addition to left-lateralized language and right-lateralized directed attention networks.[13] Mesulam, referring to Rumelhart and McClelland, defined the information processing strategy of these networks as parallel distributed processing (PDP).[14]

Initial significant contributions of the new era started to come by the new decade, the 1980s. In 1984, the first formal clinical diagnostic criteria set of AD was published by a work group from NINCDS (now National Institute of Aging-NIA) and ADRDA (now Alzheimer's Association-AA).[15] The fulfillment of the criteria diagnosed "Probable AD" (PRAD), if the onset was insidious over the age of 65, the course was slowly progressive, the presentation was with an amnestic core among multiple cognitive deficits, which were severe enough to impair activities of daily living (ADLs), thus causing dementia. Any atypical feature like the style or age of onset, course, clinical presentation, or co-morbidity, which was deemed that was not severe enough to cause the dementia, was labeled as "Possible AD" (PosAD), increasing the sensitivity at the cost of decreased specificity. NINCDS-ADRDA criteria did not allow clinicians to diagnose "Definite AD", leaving it to neuropathologists. Ten years later, DSM-IV criteria of the American Psychiatric Association (APA) repeated almost the same criteria set (also DSM-IV-Text Revision in 2000), this time naming the disease as "Dementia of Alzheimer's Type" (DAT) (APA 1994, APA 2000). The major limitation of both sets of criteria can be said to be their equation of AD with its terminal stage, that is dementia, thus ignoring much longer pre-dementia stages. The other shared limitation

can be underlined as their use of laboratory work-up not in support of the diagnosis, but for exclusion of other possible causes of dementia, primarily cerebrovascular disease.

Regarding the pre-dementia stages, Kral used the term "senescent forgetfulness" as early as 1962, dividing it into two: a "benign" (BSF), age-associated form and a "malignant", progressive form.[16] In 1975, the first and still most commonly used cognitive screening instrument in the world, the "Mini-Mental State Examination" (MMSE) was introduced by Marshal Folstein.[17] In 1982, even before the NINCDS-ADRDA criteria, Reisberg et al.[18] introduced a staging system, the "Global Deterioration Scale" (GDS) that envisaged the AD process as a continuum, starting from normal cognition (CN) (Stage 1), passing through "very mild" and "mild cognitive decline (Stages 2 and 3 respectively), going beyond dementia threshold thereafter, along the "moderate", "moderately severe", "severe" and "very severe" stages (Stages 4 to 7 respectively). Nevertheless, the authors refrained using "AD dementia" for those late stages and preferred the DSM-III term "PDD" instead, preserving the term AD for the neuropathologically verified cases. In today's terminology GDS-Stage 2, which was roughly the equivalent of Kral's BSF, can be seen as the "subjective cognitive impairment" (SCI) and Stage 3 as the "mild cognitive impairment" (MCI). In the same year, the other still commonly used staging system, the Clinical Dementia Rating Scale (CDR), was also published.[19] CDR stages are 0, 0.5, 1, 2, and 3, where 0 is CN, and 1-3 are mild, moderate, and severe dementia, respectively. CDR 0.5 was first named "questionable dementia". Today, after the intervention of O'Bryant et al.,[20] depending on the sum of the scores of a total of 6 sub-ratings (sum of the boxes score), it corresponds to either MCI (CDR-SOB 0.5-2) or very mild dementia (CDR-SOB 2.5-4). In 1986, a workgroup from the National Institute of Mental Health (NIMH), which included 2 co-authors of the GDS (Crook and Ferris), proposed formal diagnostic criteria for BSF or Stage 2-GDS, changing its name to "Age-Associated Memory Impairment" (AAMI) (Crook 1986). The criteria required a memory test performance of 1 standard deviation (SD) below the normative means of young adults in an individual over 50 years of age with subjective memory complaints without dementia (a MMSE score >24). Although not a formal clinical diagnostic label, the popular jargon term "worried-well" was also an established label for individuals with BSF or AAMI. Finally, the new term "subjective cognitive decline" (SCD) or SCI replaced the previous terms in 2014, implying not just a "benign" age-association, as being the initial period of the cognitive decline continuum, a likely progression to objective decline as well, that is MCI.[21,22] Subjective decline corresponds to subjective memory complaints of an individual whose cognitive performance is within the established normative range of the given age group, whereas objective decline is the performance below the pre-defined SDs, lower than the normative range.

Although it was further developed and was established in its current version by the Mayo group, led by Petersen (also including Emre Kökmen), two of the GDS co-authors (Riesberg and Ferris) were among the first to introduce the term MCI in 1991.[23] The MCI-labeled patients without dementia performed poorer as compared to controls on multiple cognitive domains, and 72-80% of them showed progression in a 2-year follow-up. Petersen et al.[24] first used the label MCI in 1995. In the 1995 study, they followed up 220 MCI patients for 3-6 years and found an annual dementia conversion rate of 12% and at the end of 6 years 80%. The original Mayo Criteria for MCI were first published in 1999.[25] These were: 1. Memory complaint, preferably qualified by an informant, 2. Memory impairment for age, 3. Preserved general cognitive function, 4. Intact activities of daily living, 5. Not demented. As seen, the emphasis was on the memory, the "typical" presentation of prodromal AD, thus ignoring the atypical, non-memory presentations and prodromal stages of other dementing neurodegenerative diseases. This shortcoming was eliminated 5 years later in the 2004 revision.[26] In the revised criteria, Petersen divided the general MCI umbrella term into two subdivisions, namely amnestic (a: memory is the primarily impaired cognitive domain) and non-amnestic (na: a non-memory cognitive domain [language, visuo-spatial skills, executive functions, praxis or social cognition] is the primarily impaired cognitive domain) MCI, which were in turn further divided into two: single-domain MCI (aMCI and naMCI: memory or a non-memory cognitive domain is the isolated impairment) and multi-domain MCI (aMCI-md and naMCI-md: there were multiple cognitive impairments with a memory or non-memory core) forms.

The focus on pre-dementia stages also prompted the development of new cognitive screening instruments to replace MMSE, which was considered

not sensitive enough, particularly in these early stages. Mayo group preferred to use the Short Test for Mental Status (STMS), which was developed by Emre Kökmen.[27] STMS has been adapted to Turkish.[28] In Canada, the Montreal Cognitive Assessment (MoCA) was specifically designed to overcome the lack of sensitivity and specificity of the MMSE in detecting MCI stage.[29] Finally, the Cambridge group developed somewhat more comprehensive Addenbrook Cognitive Examination (ACE),[30] which had two subsequent revisions: ACE-R[31] and ACE-III.[32] The Turkish adaptation of ACE III was recently published.[33]

In the neuropathological sphere, the exciting developments in the early 1980s were the discovery of the identity of protein deposits within the senile plaques and NFTs. Three close publications made certain that senile plaques contained amyloid, as Divry suggested much earlier.[34-36] This was already hinted at by Kidd after Divry, in 1964, with an early electron microscopy study.[37,38] Kidd saw the amyloid content but was hesitant about whether they were present in all the plaques and their origin, whether they were coming from blood circulation or the result of a viral infection. After the 80s contributions, the name of the senile plaques was changed to the amyloid plaques (APs). Moreover, NFTs also revealed their disguises in 1985,[39] it was discovered that they were hosting hyperphosphorylated microtubule-associated protein tau (MAP-τ).

Thus, AD was established as a double proteionopathy, which turned out to be unique amongst other neurodegenerations, revealed afterwards as singular protein deposits. This doublet led to claims of the primacy of one over the other, resembling a religious fanaticism: Baptists claimed that β-amyloid is the trigger, tau is the follower; on the contrary, Tauists claimed that tau is the mover, β-amyloid is the bystander.

The first formal neuropathological criteria set was published in 1985 after a workshop, and this criteria set was later named after its author: Khachaturian criteria.[40] Khachaturian criteria focused on the number of APs per microscopic field, regardless of the AP type, neglecting the NFTs. The number of AP requirements increased with the increasing age (8+ APs in ages 50-65, 15+ APs in ages 75+). The second set of neuropathological criteria, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria, was published in 1991.[41] Number of neuritic plaques (diffuse plaques and NFTs were neglected) per microscopic field, which were rated as sparse, moderate, and frequent, in 3 age groups (<50, 51-75, and 75<), indicated 3 probabilities: A. Uncertain AD, B. Suggestion of AD, C. Indication of AD. Even a sparse number of neuritic plaques was enough for a C grade in the <50 age group, but in the 75< age group, this would mean an A grade, moderate numbers would mean a B grade, and only frequent numbers would mean a C grade. The C-level probability with a history of dementia corresponded to "definite AD", whereas a B-level with a positive history meant "probable AD", and an A-level with a positive history meant "possible AD a", and a B or C-level with a negative history meant "possible AD b".

Heiko and Eva Braak, using Gallyas silver staining method (Gallyas 1971), revealed the spread pattern of NFTs and showed that this pattern closely correlated with clinical severity, but there was no such pattern to AP spread, nor correlation with clinical severity.[42,43] These findings were a strong support for the Tauist claims. This NFT staging system was later named as B&B after the initials of the authors and followed Roman numerals, where I-II were transentorhinal (TEC) stages, corresponding clinically to the pre-clinical stage, III-IV were limbic stages and clinically MCI stage, and V-VI were isocortical stages and clinically dementia stage. B&B staging served as a catalyst for a new revision of neuropathologic criteria. In 1997, the National Institute of Aging and Reagan Institute (NIA-RI) criteria set was published.[44] The new guidelines combined the semi-quantitative assessment of both neuritic plaques (according to CERAD criteria) and NFTs (according to B&B staging). Briefly, in the post-mortem analysis of a patient with dementia sparse number of neuritic plaques plus B&B I&II meant that there was a low likelihood that dementia was due to AD. Although not explicitly stated, this was the first connotation of an unveiled co-morbidity as the likely cause of clinical dementia. A moderate number of neuritic plaques plus B&B III-IV meant that the likelihood was intermediate, and a frequent number of neuritic plaques plus B&B V-VI meant that the likelihood was high. From the mid-90s onwards, neuropathologic findings showing amyloid deposition in cognitively normal elderly and non-demented MCI patients started to accumulate, resulting in the emergence of terms like "pre-clinical AD", "AD-MCI", and "prodromal AD".[45-50]

Heiko Braak's team also succeeded in staging amyloid at the turn of the century using the

Campbell-Switzer silver (CSS) staining technique in 47 brains with AD-related pathological change.[51] Eva Braak had passed away before this report in 2000. Later named after its first author, the so-called Thal staging starts with 3 pre-clinical phases, where in phase 1 APs are already widespread in the neocortex, in phase 2 the allocortical/limbic areas are also involved, and in phase 3 subcortical structures such as thalamic, striatal, and basal forebrain nuclei are additionally involved, thus completing the invasion of the entire cerebrum, without any clinical counterpart. The clinical stages of Thal were phases 4 and 5, where in phase 4, brainstem nuclei start to be involved, and in phase 5, the brainstem is completely invaded along with the cerebellum. The pre-clinical completion of cerebral amyloid deposition was, this time, a support to the Baptist claims from the Braak team.

Under the influence of these developments in neuropathology, the neurobiological field emerged and matured rapidly. During the 1990s and early 2000s, we were able to learn how two normal proteins with important roles in the central nervous system (CNS) evolve in a pathologic direction, leaving their physiologic roles and becoming prone to aggregation and thus toxic to their adjacent tissue.

The amyloid precursor protein (APP) is a 770-amino acid, neuronal membrane-spanning protein with physiological roles in cell signalling, harbors the proximal part of the β-amyloid peptide (Aβ) in its transmembrane region, and distally it is in the extracellular region, close to the amino (N) terminal, between 671st and 711/713th positions (amino-acid numbering starts from the extracellular N-terminal and ends at the intracellular carboxy (C)-terminal. The transmembrane region of APP lies between positions 700-723. Distally, in the extracellular space, the physiological proteolytic cleavage of APP is carried out alternatively by two other membrane-spanning proteins, called secretases: either α-or β-secretase (or BACE1). α-secretase cleavage at position 687 also cleaves the distal one-third of the Aβ (hence non-amyloidogenic cleavage) and produces sAPPα and the α-C-terminal fragment (α-CTF83), while β-secretase cleavage at position 671 leaves Aβ intact (hence amyloidogenic cleavage) and produces sAPPα and α-C-terminal fragment (β-CTF99). C83 and C99 are further cleaved proximally in the transmembrane region, at positions 711 or 713, by γ-secretase, which produces the inert P3 peptide by non-amyloidogenic cleavage, and a 40 or 42 amino acid-long Aβ peptide, depending on whether the cleavage is at the 711th or 713th position, respectively.[52] While $A\beta_{42}$ and $A\beta_{40}$ are the two primary Aβ species, $A\beta_{42}$ is more prone to aggregation and hence more prevalent than $A\beta_{40}$ in APs. Secreted Aβ binds to glutamatergic AMPA and NMDA receptors, inhibiting excitatory glutamatergic transmission. Thus, the physiologic role of Aβ is seemingly dumping long-term potentiation (LTP) and promoting long-term depression (LTD) instead. Having fulfilled its function, the free Aβ monomer should be cleared. Two types of clearance mechanisms, that are lysosomal autophagy and ubiquitin protaosomal system (UPS) proteolysis, are aided by chaperon molecules that include apolipoprotein E (APOE), triggering receptor expressed on myeloid cells 2 (TREM2), and insulin-degrading enzyme (IDE), among others, polymorphisms of which are genetic risk factors for AD. If the clearance fails, then the initial plaque formation, the "diffuse plaque", which is considered harmless or at least less harmful, intervenes and imprisons, particularly the 4-kilodalton (kDa)-weighted $A\beta_{42}$ monomers as extracellular depositions. This is not a strong and safe protection system, and the fugitive Aβ tends to misfold and oligomerize. The oligomerization phase passes through a soluble oligomers phase. The first of these is the low molecular weight (8-20 kDa) oligomer (LMW-Aβ), and the second in the row is the 20-100 kDa Aβ-protofibril. They are followed by >100 kDa, insoluble fibrillary-Aβ. They are, in turn, imprisoned in the late plaque form called "compact plaque". This plaque contains fibrillary-Aβ oligomers and dystrophic neurites and triggers an inflammatory response, surrounded by activated microglia and inflammatory cytokines, hence the other name, "neuritic plaque".[53] This is an evolutionary perspective towards plaque formation, which starts with Aβ secretion and terminates with the formation of the neuritic plaque. There is also an alternative one, which conceives each plaque type as an independent formation.[54]

Microtubule-associated protein tau (MAP-τ), as the name implies, has its primary physiological role in neurons in stabilizing microtubule assembly. MAP-τ has 6 isoforms depending upon its N-terminal neighboring insertions (N0, N1, and N2 insertions) and C-terminal microtubule binding region (MTBR) number of binding repeats (3R and 4R). Microtubules can be considered as the transport system from the cell body to the axon terminal and

from the axon terminal back to the cell body. It also fulfills its other physiological roles via post-translational modifications. There are 8 known such modifications, 3 of which have clarified roles in AD pathogenesis (Lei et al. 2026). The best-known post-translational modification is phosphorylation. Tau protein is phosphorylated mainly by the glycogen synthase kinase-3 beta (GSK-3β) enzyme. The basic function of phosphorylated tau (p-T) is in modulational neuroplasticity. In humans, after the termination of developmental neuroplasticity during the early 20 years of age and completion of mature cerebral neural architecture, another form of neuroplasticity, that is modulational, continues in the allocortical-mesocortical, limbic, paralimbic cortices hosting the large-scale neural network for episodic memory. Modulational neuroplasticity is necessary for inducing the new synaptic connections that will enable the long-term storage of episodic memories. p-T temporarily leaves its association with microtubules when active in plastic function. Having fulfilled its function, it must be dephosphorylated with the enzyme protein phosphatase 2A (PP2A) and then must reattach to microtubules. Therefore, hyperactive GSK-3β or hypoactive PP2A would end up with a pathologically hyperphosphorylated tau (p-T), which is unable to reattach to microtubules, resulting in disrupted microtubule assembly and failed axonal transport. Like free Aβ monomer, p-T also tends to oligomerize, forming the β-pleated oligomers initially. Misfolding evolves into heavier molecular weight oligomers, as in the case of Aβ, and the second step is the formation of paired helical filaments (PHFs). Ultimately, ubiquitinated PHF becomes imprisoned in the intracellular NFTs. NFTs contain both the 3R and 4R tau isoforms. As stated earlier, NFT load correlates with neuronal loss and the severity of cognitive impairment in AD. Finally, NFT presence kills the neuron, and the released tangle is called the "ghost tangle", containing only the 3R tau. Acetylation and glycosylation are two other detrimental post-translational modifications of tau.[55,56]

In the sphere of genetics of AD, in 1991, John Hardy's team reported the first mutation in early-onset, familial AD (EOAD/FAD) in two families: APP is encoded by the APP gene in chromosome 21, and this gene was carrying a point mutation.[57] Down syndrome, which inevitably ends up with AD in survivors until the ages of 40s and 50s, was already found to be caused by the three copies of chromosome 21 (21 trisomy).[58] Supported by these two genetic facts, Hardy first claimed that the amyloid deposition was the central event in the etiology of AD,[59] and the following year proposed his famous hypothesis: the amyloid cascade hypothesis (ACH).[60] Later in the last decade of the 20th century, all the genetic findings supported Hardy's hypothesis, hence Baptism. In 1985, the most frequent cause of EOAD/FAD was found to be the mutations in the Presenilin 1 gene (PSEN1) encoded by chromosome 14.[61] Presenilin 1 protein was known to be the active catalytic site of the γ-secretase complex, and as noted earlier, it cleaves the APP within the transmembrane region, just neighboring its Aβ part proximally. The same year also witnessed the finding of the last cause of EOAD/FAD. It is now well-established that autosomal dominant mutations in 3 different genes are the causes of FAD. The last cause turned out to be presenilin 2 gene (PSEN2) mutations in chromosome 1, which was also the cause of FAD in Volga Germans.[62,63] Presenilin 2 protein is the alternative active catalytic site protein of the γ-secretase complex. It is 90% presenilin 1 and 10% presenilin 2. Over the years, more than 200 fully penetrant mutations were found in these 3 genes.[64] It turned out that all FAD mutations, which were autosomal dominantly inherited (hence AD-FAD), increased the production of toxic $A\beta_{42}$ species, and none of the tau gene (MAPT) mutations in chromosome 17 caused FAD, but they only caused familial fronto-temporal dementia (fFTD). Genetic reasons play a role not only in EOAD/FAD as the sole determinants, but also become risk factors for the late-onset sporadic AD (LOAD/SAD). The first genetic risk factor for AD was also found in the 1990s. Apolipoprotein E is a chaperon protein, encoded by the APOE gene on chromosome 19. molecule that plays a role in the clearance of Aβ monomers, thus preventing its misfolding and oligomerization. The polymorphism in APOE results in the encoding of 3 allelic isoforms: ε2, ε3, and ε4. The increased risk of LOAD/SAD in APOE-ε4 carriers has been found in that decade.[65] Thus, while all the mutations causing FAD were playing their roles by increasing toxic $A\beta_{42}$, the major genetic risk factor, APOE-ε4 allele, played its role by decreasing the clearance of $A\beta_{42}$ monomers. These were undeniable findings in support of ACH/Baptism. Furthermore, genome-wide association studies (GWAS) revealed almost two dozen additional risk genes in the new century, most of which were playing a similar role, decreasing the clearance of $A\beta_{42}$ monomers.[66]

In the neuroimaging sphere, there were breathtaking steps. Computerized tomography

(CT) was introduced in the early 70s in Britain.[67,68] Allan M. Cormack and Godfrey N. Hounsfield were later awarded the Nobel Prize for Physiology or Medicine in 1979 for their contribution to the advancement and implementation of the CT in clinical practice. CT enabled, for the first time, the visualization of the soft tissue, including the brain. Density of the normal and pathologic tissue can be quantified using a scale called the eponymous Hounsfield unit (HU), defining water as 0 HU and air as -1000 HU. Thus, the diagnosis of mass lesions, infarcts, hamorrhages, and white matter integrity became possible. Atrophied brain tissue due to neurodegeneration could be concluded indirectly, seeing widened sulci and/or enlarged ventricles. The association of "unusual", unexpected lesion localizations with usual clinical presentations (e.g., aphasia with subcortical lesions) began to undermine the dominant localizationist view in the brain-behavior relationship, paving the way for the net paradigm: the network approach. The introduction of magnetic resonance imaging (MRI) was not delayed. The first use of nuclear magnetic resonance for image formation was as early as 1973, at Stony-Brook University, USA (Lauterbur 1973). The first MRI body scan of a human being was performed in 1977, in Nottingham, Britain.[69] MRI techniques developed with vertiginous speed during the 1980s and 90s. In addition to incomparably higher resolution of the visualized pathologies as compared to CT, newer MRI techniques added numerous pluses to the neuroimaging data. Neurodegenerative atrophy became quantifiable by volumetric MRI. While volumetric MRI can be considered a time-consuming effort, visual rating scales (VRS) that enabled the clinician to easily grade the region of interest using a Likert scale, enabled the quantified MRI using VRS to become part of the cognitive examination. The first VRS was for the medial temporal atrophy (MTA) scale, also called "Scheltens Scale," was developed by Philip Scheltens for the evaluation of typical AD cases.[70] Association fibres connecting neural networks were visualized by diffusion tensor imaging (DTI). Task-related brain activity was visualized by increased brain oxygen level-dependent (BOLD) signal in functional MRI (fMRI). Brain perfusion was visualized using arterial spin labeling MRI (ASL-MRI). Paul Lauterbur of Stony Brook University and Sir Peter Mansfield of the University of Nottingham were awarded the 2003 Nobel Prize in Physiology or Medicine for their "discoveries concerning magnetic resonance imaging". Measuring local cerebral glucose utilization (cerebral metabolism) in humans, using [^{18}F]Fluorodeoxyglucose-positron emission tomography ([^{18}F]FDG-PET) was introduced in 1979, at the University of Pennsylvania, USA.[71] In patients with suspected neurodegeneration, local hypometabolism was established as indicative of underlying neuronal loss. Before the advent of fMRI, FDG-PET was also used for functional neuroimaging purposes. Like the BOLD signal in fMRI, task-related hypermetabolism was taken as reflecting the cerebral localization of the processing of that particular task. The first amyloid PET tracer, the Pittsburgh Compound-B, an 11C-labeled radiotracer, was developed at the University of Pittsburgh in 2003.[72] The first PIB-PET study was also done in the same year in Sweden by a joint team from Pittsburgh and 3 centers from Sweden, including Karolinska Institute.[73] Researchers examined 16 mild AD dementia patients and 9 healthy control subjects and scanned them with PIB-PET and FDG-PET. PIB retention in the fronto-parietal cortex and striatum was significantly higher in AD cases compared to controls. The oldest control patient (77 years old) had a similar PIB retention as the patients. The authors were not sure if this was an indication of "pre-clinical" AD in that individual or a "false-positivity". Two years later, the same group published the results of a 2-year follow-up and rescanning of the original 16 patients with PIB-PET and FDG-PET.[74] They found that in the follow-up, there was no difference in PIB retention, although cerebral metabolism was significantly decreased compared to baseline. Both in the paper and in the accompanying commentary, the authors interpreted their findings as the progressive amyloid deposition occurring during the pre-symptomatic phase, then reaching a plateau or "late equilibrium", once the symptoms started.[75]

In the biochemical sphere, cerebrospinal fluid (CSF) biomarkers appeared before the turn of the millennium. In 1992, CSF-Aβ_{42} was shown using enzyme-linked immunosorbent assay (ELISA) for the first time.[76] In a short while, ELISA-based measurements of monoclonal antibodies (mAbs) against CSF levels of total tau (t-T), phospho tau (p-T), and Aβ_{42} were started. The initial papers in 1995 reported elevated CSF levels of t-T and p-T[77] and reduced CSF levels of Aβ_{42}[78] in AD dementia patients. Again in 2006, the same researchers from the University of Pittsburgh collaborated with those from Washington University in a joint PIB-PET, CSF-Aβ_{42} study.[79] 18 cognitively normal (CDR 0) individuals and 6 patients with AD

dementia (CDR 0.5, 1, and 2) were included in the study. PIB retention was high, and CSF-Aβ_{42} levels were low in the patient group. Three of the CDR 0 group had similar PIB-PET and CSF-Aβ_{42} findings as the patient group, which was interpreted as indicative of "pre-clinical" AD.

Thus, all the parallel developments in these spheres prove that the final blow for the liquidation of the principal dogmas of the past of AD, that were the equation of AD, a slowly progressive neurodegeneration, with its final dementia stage, allowing the clinicians to diagnose only "probable" disease, leaving the definitive diagnosis to the neuropathologists, and using laboratory methods only for the exclusionary purposes, was already at hand. This final blow came from an International Work Group collaboration (the group would be named as IWG later), which convened in 2005, intending to revise the NINCDS-ADRDA criteria.

PRESENT

The first paper of the IWG in 2007 described their purpose as the inclusion of the prodromal stages and the integration of biomarkers into the diagnostic framework.[80] The revised criteria retained the term "probable AD", dropping "possible AD". The criteria for probable AD focused on A. Memory impairment as the core feature and stated that it must be: 1. Reported by the patient and/or informants, 2. Documented by memory testing as a delayed free recall deficit that does not improve by cueing and/or recognition testing, 3. Recall deficit may be isolated or a core feature of multiple cognitive deficits. At least one of the supportive features must be present. They were: B. MTL atrophy, either by VRS or volumetric MRI, C. Low Aβ_{42} and high t-T and p-T CSF levels, D. Temporo-parietal hypometabolism on FDG-PET, E. Family history of AD-FAD. Atypical history, clinical features, and presence of co-morbidities were the exclusion criteria. Criteria for definite AD were the presence of both clinical and histopathological evidence of AD or both clinical and genetic (AD-FAD mutations) evidence of AD. Pre-clinical AD and atypical presentations, although mentioned in the text, were not included in this set of criteria.

Although one of the fundamental dogmas of the past (clinical diagnosis of AD is only "probable") was retained, the new conception of the disease process as insidously evolving from the pre-clinical protein deposition by slowly (and relentlessly) progressing to the very late dementia stages, allowing to conceive the full spectrum of the disease and its diagnosis in any stage by the integrated biomarkers has opened up radical new perspectives on therapeutic and even preventative options for AD. So, every step mentioned above from the initial production of Aβ, to final production of the neuritic plaque became a therapeutic target (α-secretase agonism, β- and γ-secretase inhibition, soluble and insoluble Aβ oligomer and/or AP clearence), as well as every step from the initial tau oligomer promotion to final production of NFT (GSK3β inhibition, PP2A agonism, even acetylation and glycolization antagonists and deacetylation and deglycolyzation agonists, tau oligomer and/or NFT clearence). Some had already started; no sooner, all these targets were being tested in the clinical trials.

By the turn of the century, in vivo imaging of human neural networks became available. It all started with a visionary meta-analysis of the "resting state" data of the functional neuroimaging studies, which revealed stereotypical, brain-topography-specific decreases during goal-directed action, leading the researchers to state that "These decreases suggest the existence of an organized, baseline default mode of brain function…".[81] This would subsequently be named as the first "intrinsic connectivity network (ICN), the "default mode network (DMN)." Ten years later, in 2011, both cortical parcellation by seven ICNs, including the DMN, was completed,[82] and also their cerebellar components were revealed.[83] The following year, the same group, this time, showed the ICN organization of the striatum.[84] Thus, ICN correlates of large-scale neural networks were accomplished. A close association between AD and functional connectivity changes (decreases and likely compensatory increases) within DMN was shown. This association was present not only in patients with AD dementia,[85] but also in cognitively normal (CN) individuals with preclinical AD (i.e., having positive amyloid PET)[86] and even in APOE-ε4 carrier CN individuals with no amyloid evidence.[87] Subsequently, distinct neurodegenerative processes have been shown to display distinct ICN-specific predilections.[88]

The IWG continued to convene, and its second publication for the revision of terminology appeared in 2010.[89] This time, the term "probable AD" was dropped, allowing the ante-mortem definite diagnosis by the clinicians. "Prodromal AD" was reintroduced to replace MCI as the initial stage of

the AD spectrum, reserving the MCI term for those who fulfill MCI criteria without evidence of AD biomarkers. Atypical clinical presentations (motor variant with cortico-basal syndrome presentation was somehow neglected) were now included in the diagnostic framework with biomarker evidence. In asymptomatic individuals, "Presymptomatic AD" diagnosis was for those who carried one of the FAD mutations, and "Asymptomatic at-risk state for AD" diagnosis was for those who had biomarker evidence of AD, without genetic evidence. Biomarkers were reduced to amyloid (amyloid PET or CSF $A\beta_{42}$) and tau (p-T or t-T) markers, lumping p-T and t-T together, although it is well-known that t-T is not specific to AD, but can be elevated in conditions like prion diseases and traumatic brain injury. FDG-PET and structural MRI were now reserved for monitoring the disease process.

In the same year, Jack et al.[90] proposed their still valid model of biomarkers and disease stage interaction, according to which the curve for Aβ biomarkers starts to elevate from normality to increasingly abnormal levels during the cognitively normal (CN) stage, thus initiating that stage, but having reached the MCI threshold, starts to plateau. Tau biomarkers start to elevate in the middle of the CN stage and continue to elevate during MCI and dementia stages. Brain structure biomarkers follow tau, starting to elevate during the late CN stage. Memory markers elevation towards abnormality initiates the MCI stage. Finally, when markers of daily functioning start to elevate, this indicates the initiation of the dementia stage.[90]

Prompted by the disappointments of recently failed disease-modifying drugs, such as the β-secretase inhibitor semagacestat, an active Aβ immunization agent AN-1792, Sperling, Jack, and Aisen published a warning, underlying the vital importance of the pre-clinical cognitively normal stage for the prevention of AD, and they concluded asking "So why do we keep testing drugs aimed at the initial stages of the disease process in patients at the end-stage of the illness?".[91]

Finally, the next year, in 2011, the NINCDS-ADRDA team woke up after 27 years with their new name, NIA-AA. Three separate work groups were organized for pre-clinical AD, MCI due to AD, and dementia due to AD diagnoses, and presented their findings in three separate, consecutive papers, which were preceded by an introductory paper.[92] While the first set of diagnostic criteria was proposed for research purposes only, the other two were for use in clinical settings. Biomarker evidence of AD was taken as proof that the (pre-) clinical condition was due to AD. Biomarkers were classified under 2 headings: 1. Biomarkers for Aβ were CSF $A\beta_{42}$ levels and amyloid PET; 2. Biomarkers for neuronal injury (NI) were CSF tau levels, structural neuroimaging findings of hippocampal volume by volumetric MRI or visual rating, rate of cortical atrophy, cerebral metabolism findings with FDG-PET, and "less well-validated biomarkers": fMRI activation studies, resting BOLD functional connectivity, ASL-MRI, MR spectroscopy, and DTI. The work group for pre-clinical AD, led by Reisa Sperling, divided this phase of the disease into 3 stages. The cognitively normal individual was in Stage 1, if she/he was Aβ positive, NI negative, Stage 2, if Aβ positive, NI positive, Stage 3, if Aβ positive, NI positive, and had subtle cognitive decline.[93] The authors defined "subtle cognitive decline" as a subtle change from baseline level of cognition, poor performance on challenging cognitive tests, and not meeting the criteria for MCI. The work group for MCI due to AD diagnosis, led by Marylin Albert, also included Bruno Dubois and Howard H. Feldman of the IWG and Ronald C. Petersen.[94] MCI definition included all 4 subtypes. The positivity of both Aβ and NI biomarkers indicated a high likelihood that the MCI syndrome was due to AD. The work group for dementia due to AD was led by Guy McKhann, the first author of the 1984 NINCDS-ADRDA criteria.[95] The terms from 1984, "probable AD" (atypical presentations were also accepted) and "possible AD" (the presence of evidence of cerebrovascular disease or motor and/or non-motor symptoms of Lewy body disease) were retained. The positivity of both Aβ and NI biomarkers indicated a high probability that the dementia syndrome was due to AD.

However, an amyloid PET study in the same year proved that an ante-mortem definite diagnosis of AD is indeed possible. Participants were brain donors from a nursing home, who underwent amyloid PET imaging a mean of 99 days before death. Researchers, using Florbetapir, which is an ^{18}F-fluorine labeled amyloid PET tracer, thus overcoming the problems created by the very short half-life 11C-carbon labeled tracers, such as PiB, showed that Florbetapir-PET images and postmortem results rated as positive or negative for β-amyloid agreed in 96% of the 29 individuals in the primary analysis cohort.[96]

The same year witnessed another breakthrough that came again from Braak's lab.[97] This time, in addition to Gallyas silver staining and CSS, they

used AT8-immunostaining in 2332 brains covering ages 1 to 100. They found 332 cases who were Gallyas (-)/AT8 (+). These AT8 (+) intra-neuronal lesions containing nonfibrillary, soluble p-T were labeled as "pretangles". Depositions of the soluble pretangles are named as the "condensates", in contrast to the "aggregates" of the insoluble fibrillary tau.[98] Pretangles appeared as early as the 1st decade and reached their climax by the 4th. Five pretangle stages were identified: a, b, c, 1a, and 1b. They were largely confined to the brainstem, predominantly to the cortically projecting noradrenergic dorsal locus coeruleus (dLC). In stage a, pretangles were restricted to the proximal axons of dLC. In stage b, dLC somas and dendrites were also involved. Stage c is defined as pretangles appearing in the somas of other neuromodulatory cell groups, especially in serotonergic dorsal raphe (DR). AT8 reactive tau is hypothesized to spread from locus coeruleus neurons to the interconnected neuromodulatory nuclei. These cortically projecting neuromodulatory, non-thalamic neurons have very long axons to connect them with their cortical targets. The closest cortical target appears to be the transentorhinal cortex (TEC). Accordingly, in stage 1a, traversing the shortest distance, pretangles reach these axon terminals and synapse with TEC neurons. In stage 1b, pretangles are taken over by TEC neurons, and this is the first and the last time that a cortical region displays AT8 positivity. It seems that pretangles gradually become Gallyas (+) NFTs, triggering the B&B stage 1. Three major conclusions can be drawn from this study: 1. AD is not an age-related phenomenon, since pathologic tau activity starts as early as the first decade of life; 2. It is not the amyloid but tau, the prime mover of the disease cascade during its pre-clinical phase; 3. It is not a cortical focus that is the central target of the disease process, but a brainstem nucleus, the LC. This was not only a significant blow to the Baptist claims, but also a contribution to Mesulam's Tauist-inclined "neuroplasticity failure hypothesis" of AD as the prime mover of the disease.[99] Briefly stated, tau phosphorylation associated with the ongoing modulational neuroplasticity requirements confined primarily to the limbic system is an attractive hypothesis explaining the topographical origins of the clinical disease process: insidious onset, progressive episodic memory loss due to limbic degeneration. Braak's contribution can be speculated as an additional push in Stage 1b by the newly arrived AT8+ pretangles in TEC to the already irreversibly hyperphosphorylated tau, helping to transform them into the insoluble PHFs.

The next year NIA-AA work group of neuropathologists published a revision of the NIA-RI criteria of 1997.[100] The new set of criteria recognized the pre-clinical stage of AD, proposed an "ABC" score ranging from 0 to 3 for each letter, for AD neuropathologic change that incorporates histopathologic assessments of Thal staging of Aβ deposits (A), B&B staging of NFTs (B), and CERAD scoring of neuritic plaques (C). It also aimed to establish protocols for the neuropathologic assessment of common co-morbidities like Lewy body disease, vascular brain injury, hippocampal sclerosis, and TDP-43 inclusions, and recommend standard approaches for the workup of cases and their clinico-pathologic correlation. This paper was followed by another one, which presented a practical guide for the implementation of this new set of criteria.[101]

In 2014, the IWG-2 criteria appeared.[102] The terminological revisions of 2010 were now included in the IWG-2 criteria set. In addition to the previous criteria set for typical AD with an amnestic core, there were separate sets of diagnostic criteria for atypical AD, mixed AD, and pre-clinical phases of AD. Atypical AD was a non-amnestic presentation of one of the following: posterior variant, logopenic variant, frontal variant, or Down syndrome. Mixed AD corresponded to additional evidence of cerebrovascular disease or Lewy body disease. Pre-clinical states were either an asymptomatic at-risk state with the biomarker positivity or a presymptomatic stage for AD with genetic evidence of a FAD mutation. Moreover, diagnostic biomarkers were reduced to amyloid (amyloid PET or CSF $A\beta_{42}$) and tau (t-T or p-T) markers, thus lumping p-T and t-T together, although t-T is well-known to be non-specific for AD. Other neuroimaging methods, like FDG-PET and various MRI techniques, were now reserved for monitoring the disease course.

In 2016, the fourth publication of IWG appeared, this time focusing solely on pre-clinical AD.[103] It was essentially the repetition of concerns of the IWG about the biological diagnosis of AD, on the grounds that not every pre-clinical individual with positive biomarkers inevitably develops symptomatic AD in her/his lifetime, so there are both medical (the risky side-effects of prevention trials, like ARIA reaction in anti-amyloid monoclonal antibody treatments) and ethical (labeling an healthy person with a dementing disease) concerns about this diagnosis. The major novelty of 2016 was the extension of the diagnosis

of presymptomatic stage AD, which was reserved only for individuals with genetic evidence in IWG-2, to include pre-clinical individuals with biomarker evidence of both Aβ and tau. This meant, in contrast to IWG 2014, symptoms were no longer required to reach a diagnosis of AD. "Asymptomatic at risk for AD" state was confined to either abnormal Aβ biomarker and normal tau (A+T-) as "at risk for AD, asymptomatic A+" or one with A-T+ as "at risk for AD, asymptomatic T+". They described the first status as in accordance with the "amyloid first" initiation of the disease, and the second as "tau first". However, the latter is most probably due to primary age-related tauopathy (PART), a term that was already described in 2014 to replace the previous one "tangle only dementia", which is known to be a distinct neurodegeneration of particularly the old age, unrelated to AD.[104]

A number of tau-PET tracers had already appeared by the mid-2010s. One of them, [^{18}F] THK5317, was used in a study with 33 individuals (9 AD dementia, 11 PIB+ MCI, 2 PIB- MCI, 1 CBD, 1 PSP, a total of patients, and 9 healthy controls), along with PIB-PET and FDG-PET. The patients with MCI and AD dementia had significantly higher tau retention than healthy controls in areas exceeding limbic regions, and their discrimination from this control group (using the area under the curve) was >98 %. One patient with CBD and one with PSP showed no PIB but high [^{18}F]THK5317 retentions with a different regional distribution from that in both MCI and dementia AD patients. The authors concluded that the tau-specific PET tracer [^{18}F]THK5317 mirrors in vivo the expected neuropathological regional distribution of tau pathology.[105] [^{18}F]AV-1451 is another tau-specific PET-tracer. It was used in 96 participants with typical and atypical AD presentations, along with PIB-PET, FDG-PET, and volumetric MRI. The researchers from Mayo Clinic found that [^{18}F] AV-1451 (flortaucipir) uptake showed the strongest regional correlation with hypometabolism, and the correlation with cortical thickness was second in line.[106] Off-target binding of many tau tracers became their major shortcoming. Over time, flortaucipir became the most widely used tau tracer, not exhibiting this shortcoming. In autopsy comparisons, flortaucipir showed specific binding to PHF tangles and correlation with the B&B NFT stage.[107]

The revision of the 2011 diagnostic guidelines of NIA-AA came in 2018 to update and unify the 3-part 2011 guidelines.[108] The authors stated that the "unifying update is labeled a 'research framework' because its intended use is for observational and interventional research, not routine clinical care." The diagnosis was not based on the clinical phenomenology in this research framework, which shifted the definition of AD in living people from a clinical to a biological construct. Based on the high concordance of the uptake of both amyloid and tau tracers with the post-mortem neuropathological findings of amyloid and tau deposition, the research framework focused on the diagnosis of AD with biomarkers in living persons. The current description was the development of a new biomarker classification system, which was named AT(N), that was previously introduced by a joint NIA-AA and IWG consensus.[109] Biomarkers were grouped into those of Aβ deposition (A: CSF-$A\beta_{42}$ or amyloid PET), pathologic tau (T: CSF-p-T or tau PET), and neurodegeneration [(N): CSF t-T, FDG-PET, structural MRI]. The separation of p-T from neurodegeneration markers was a novelty, which was explained by the high probability of co-morbidities giving rise to T-(N)+ states, especially in the elderly. Three separate clinical diagnostic labels were now unified as a full disease spectrum ranging from clinical stages 1 to 6, where stage 1 was clinically unimpaired (CU), stage 2 was SCI, and stage 3 was MCI. Stages 4-6 were mild, moderate, and severe dementia, respectively. According to the 2018 research framework, an A-T-(N)-individual is devoid of AD biomarkers, but since she/he is (N)-, the clinical stage must be 1 (CU). A+ person is in the "Alzheimer's continuum" (ACon). Then, he/she either has "Alzheimer's disease (AD)", if also T+, or "Alzheimer's pathologic change (APC)", if T-. Although not explicitly stated, one can proceed from here that an A+T+(N)- individual can be said to have AD and presumed to be in stage 1 (CU) or stage 2 (SCI), and an A+T+(N)+ individual has AD with any stage between 1 and 6. While A+T-(N)- state is APC within ACon, A+T-(N)+ state is APC and "concomitant suspected non-AD pathologic change" (SNAP), since (N) positivity must be driven by a co-morbid proteinopathy in this case. Three A- states that are SNAPs. Again, although not explicitly stated, A-T+(N)-, A-T+(N)+ states can be due to primary tauopathies, and A-T-(N)+ state can be due to α-synucleopathy or TDP-43 proteinopathy. The NIA-AA group also noted the flexibility of the AT(N) system and stated that notation might be modified as ATX(N), where X stands for the newly established biomarkers, such as V for vascular, S for synucleopathy, and I for inflammation,

The 5th publication in the IWG series came in 2021, and rather than being a revision of their previous criteria, it was a criticism of the 2018 Research Framework and a polemic with NIA-AA.[110] Without mentioning and explicitly giving up their 2016 acknowledgement of both Aβ and tau positivity as the pre-symptomatic AD, they were criticising this biological diagnosis of AD in CU individuals and insisting once again that AD diagnosis must only be made with the presence of symptoms. Moreover, while the A-T+ state in CU had been taken as the indication of "at risk for AD, asymptomatic T+" in 2016, now again, without mentioning that previous statement and NIA-AA criticism of it in 2018, they equated it with PART, which was in line with NIA-AA's SNAP classification. "Uncommon" clinical presentations, such as semantic variant and non-fluent, agrammatical variant progressive aphasias and cortico-basal syndrome, were also included among the clinical spectrum. The high frequency of co-morbidities was mentioned, and it was noted that, especially in the case of an uncommon clinical presentation, the biomarker positivity would not indicate that the clinical presentation was due to AD.

The last revision of NIA-AA appeared in 2024: "Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup".[111] The main motivations for the revision were stated as the availability of blood-based biomarkers (BBMs), the availability of new tau assays showing different tau species corresponding to progressively more severe biological stages of AD, thus enabling the biological staging in parallel with tau PET. The availability of new biomarkers for co-pathologies, such as the α-synuclein seed amplification assay (SAA), new biomarkers for inflammation, and for neurodegeneration. The new criteria set is an integrated clinical-biological staging system (ISS). The ISS approach was very recently used for Parkinson's/Lewy body disease and Huntington's disease as well.[112,113] The new notation, AT1T2NISV, replaced the old AT(N) in this revision. New notation denoted 3 subdivisions of the biomarkers: 1. Core 1 (AT1), 2. Core 2 (T2), 3. Non-specific (NISV). Core 1 positivity is a prerequisite for AD diagnosis. A stands for amyloid biomarkers, which are CSF $A\beta_{42}$ and amyloid PET. T1 is initially pathologic tau biomarkers, which are CSF pT181, CSF or blood pT217, and pT231. Core 2 T2 biomarkers are tau-PET and different tau species (pT205, MTBR-pT243, and non-phosphorylated mid-region tau fragments), which become positive later in the disease course and reflect tau-PET progression. In "non-specific biomarkers" subdivision N stands for neurodegeneration, and it is no more in parentheses. Also, CSF total tau is no longer an N biomarker, as it was shown to highly correlate with pT181, which starts to elevate during the earliest phase of the disease. CSF and blood neurofilament light chain (NfL) replaced it as an N biomarker. I stands for inflammation. Glial fibrillary acidic protein (GFAP) is a marker of astrocytic reactivity and can be measured in plasma or CSF. Another I biomarker that has received attention is soluble TREM2, which reflects microglial reactivity and can be measured in CSF. S stands for synucleopathy. CSF, blood, and skin αSyn-SAA are sensitive and specific for ante mortem identification of cortical α-synuclein pathologic change as a primary pathology or as a co-pathology. Finally, V stands for vascular pathology, and conventional neuroimaging methods are proposed as V biomarkers. The new criteria set contains an alphabetical biological staging and a numeric clinical staging, both of which form a biological-clinical ISS. In biological staging, (A) is the initial stage, where the biomarkers are A+T1+T2- (amyloid PET+, tau PET-). (B) is the early stage, where they are A+T1+T2+ (pT205 and or tau PET positivity restricted to MTL, shown as T2MTL). (C) is the intermediate stage, which corresponds to MTBR-pT243 positivity and/or tau PET moderate neocortical uptake, shown as T2MOD. (D) is the advanced stage, which corresponds to non-phosphorylated mid-region tau fragments positivity and/or tau PET high neocortical uptake, shown as T2HIGH. Clinical stages are the same as in 2018 (1 to 6), with the addition of stage 0. Stage 0 is defined as genetically determined AD, which includes autosomal dominant AD (ADAD) or Down syndrome AD (DSAD) in an individual who is biomarker negative and clinically asymptomatic. In the ISS table, the parallel, linear progression of the stages as 1A, 2B, 3C, 4-6D can be interpreted as the entire clinical progression is driven solely by the AD pathologic progression, without any contribution from a co-pathology and without any intrinsic resistance to its destructive neuroplasticity. However, there may be deviations from this parallel progression. A 4-6A or 4-6B integrated stage should lead a clinician to conclude that "since this person is in the early pathological stages of AD, his/her dementia cannot be the consequence of AD, hence it must be driven by a co-pathology. On the contrary, 1-2C or 1-2D integrated stages would mean, since advanced pathological stages did not cause an appreciable cognitive decline, something

inherent in this person must be resisting, hence the reparational neuroplasticity power of the resilience of cognitive reserve. Clinical adaptation of this ISS carries a significant potential for modifying the traditional perspective of the clinician towards neurodegeneration, which is largely in line with linear, parallel progression, where a singular cause creates expected, homogenous effects, leading to already imposed, unchanging intervention, treatment choices. However, the modified perspective enabled by this ISS can prompt the clinician for an immediate intervention for prevention in cases such as 1-2C-D. On the other hand, in cases such as 4A, he/she may refrain from an AD-targeted treatment and deal with the discrimination and targeting of the co-pathologic contributor.

The response from IWG did not delay this time.[114] However, similar to their 2021 article, this was also a polemic with AAWG. They repeated their refusal to accept preclinical biomarker positivity as the AD diagnosis and insistence on calling this state "at risk for AD". There were no revisions, modifications to their previous set of criteria. Neither were there any discussions, comments on the AAW's proposed ISS.

To conclude the "Present", I think that the 2024 AAWG ISS can be considered as a decisive step, terminating the present and opening the door towards the future.

FUTURE

In my opinion, the probability of a future enabled by the adaptation of 2024 AWG ISS will be realized by "rethinking neurodegeneration through a co-proteinopathy lens", to repeat the title of a very recent article.[115] This lens amplifies the image of a unique "pathotome", instead of a homogeneous protein deposit signature. The word "pathotome" is a neologism used by Younes and Mormino in a scientific commentary published in Brain on Robinson et al.'s article.[116,117] Robinson et al. reported neuropathological findings of 1647 autopsy cases. They found a very high frequency of co-proteinopathies. For example, in cases with the clinical diagnosis of AD, only 13% had singular ADNPC. 27% had +1, 30% had +2, 15% had +3 additional co-pathologies. The presence of multiple additive pathologies associated with older age, increasing disease duration, APOE ε4 allele, and the presence of dementia across the clinical groups. Pathotome is probably a neologism inspired by the connectome. The human neural connectome is a unique neural architecture, the result of multiple neuroplastic modifications, starting with the developmental and continuing lifelong with modulational, destructive, and reparational neuroplasticities, reflecting the unique subjectivity of a singular human being. In their scientific commentary, Younes and Mormino likened the pathotome to a fingerprint. They reported the pathotomic findings of 3 cases of Robinson et al.,[117] drawing pathotomes as fingerprints. The first case was an 80-year-old woman with an AD dementia diagnosis. Her pathotome displayed 30% NFTs, 30% APs, 10% TDP-43, 10% α-synuclein, 10% amyloid angiopathy, and 10% cerebrovascular disease (CVD). The second case was an 80-year-old man with a vascular dementia diagnosis. His pathotome displayed 60% CVD, 20% α-synuclein, 10% APS, and 10% NFTs. The third patient was a 75-year-old man with a Lewy body dementia diagnosis. His pathotome displayed 40% α-synuclein, 23% APs, 13% TDP-43, 10% NFTs, 7% CVD, and 7% unidentified deposit.

Identification of a pathotome by looking through the lens of co-proteinopathy requires a radically different conception of neurodegeneration that will be enabled by a new paradigm shift in the future. The traditional reasoning of the present is the linear determination of the homogeneous effect by a singular cause: i.e., deposition of APs and NFTs cause a slowly progressive cognitive decline with an amnestic core in every AD patient. After the paradigm shift, the new reasoning of the future will consider structural determination by the multiple causes giving rise to unique pathotomes. To use the French philosopher Louis Althusser's concept, structural determination is radically different from the linear determination, hence it is "surdetermination" (overdetermination) (Althusser 1962).[118] So, the new reasoning should implicitly acknowledge that the effect of the overdetermination is not the homogenous outcome as in linear determination, a unique one. Pathotomes do not contain homotypic protein assemblies but heterotypic ones, which are composed of co-proteinopathies. Through synergistic action, heterotypic co-proteinopathy assemblies more easily counter and disrupt the defence mechanism of the reparational neuroplasticity, such as lysosomal autophagy and UPS proteolysis, aided by the chaperon system. Targeting singular proteins deposited in homolog assemblies misses clinical heterogeneity and must

be one of the major reasons for the treatment failures or unsatisfactory outcomes, in addition to the timing of the treatment. Considering the extreme expense of single protein targeted monoclonal antibodies, thinking of using a combination of them for a pathotomic treatment does not sound wise and feasible. Zhang et al.[115] mention heterotypic assembly interface-targeted agents, multitarget strategies that address convergent aggregation mechanisms or shared vulnerabilities in proteostasis, instead of single protein-targeted ones.[115] They note that promising candidates include histone deacetylase inhibition, which can reduce both tau and αSyn pathology. It is shown that a ketogenic diet can modulate the lysosome-autophagy system. Pharmacological inducers such as rapamycin and lithium can also modulate the lysosome-autophagy system.

To conclude, it seems that in the future, the clinician must acquire a co-proteinopathy lens and learn how to look through it, then interpret the seen pathotome with the available ISS, then choose the optimal treatment strategy for counteracting the deleterious effects of the heterolog protein assembly.

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