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Amyloid accumulation and cognitive decline in clinically normal older individuals: implications for aging and early Alzheimer's disease

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Abstract

The aberrant accumulation of the amyloid protein is a critical and early event in the Alzheimer's disease (AD) cascade. Given the early involvement of this pathological process, it is not surprising that many clinically normal (CN) older individuals demonstrate evidence of abnormal A β at post-mortem examination and in vivo using either CSF or PET imaging. Converging evidence across multiple research groups suggests that the presence of abnormal A β among CN individuals is associated with elevated risk of future clinical impairment and cognitive decline. Amyloid positivity in conjunction with biomarkers of neuronal injury offers further insight into which CN are most at risk for short-term decline. Although in its infancy, Tau PET has demonstrated early increases among A β ⁺ that will likely be an important indicator of risk among CN. Overall, the detection of early A β among CN individuals has provided an important opportunity to understand the contributions of this pathology to age related cognitive decline and to explore early intervention with disease modifying strategies.

Background: Alzheimer's disease and Amyloid

Alzheimer's disease (AD) is a devastating neurodegenerative disorder that typically begins with episodic memory impairment and eventually impairs the ability to function independently. Over 5.5 million Americans are currently living with AD dementia, with approximately 10% of individuals over age 65 and 40% of individuals over age 85 impacted. There are no disease-modifying treatments that directly target the underlying disease. Current treatment options offer only mild relief of symptoms.

AD dementia is characterized pathologically by the presence of two hallmark protein aggregations—beta-amyloid into plaques and phosphorylated tau into neurofibrillary tangles [1, 2]. Whereas the aberrant accumulation of the amyloid protein is considered an early initiating event in the AD cascade [3], the spread of Tau within the medial temporal lobe and into neocortex is thought to occur downstream to abnormal accumulation of amyloid and is

more proximal to clinical symptoms of dementia [4–6]. However, the exact sequence of events involving these two hallmark pathological features of the disease, as well as the mechanisms by which these pathological aggregations influence neuronal integrity and clinical symptoms is unknown, and is currently under investigation in biomarker studies that aim to visualize and track these pathologies throughout the course of AD [7].

Although multiple biomarkers exist to capture different aspects that occur throughout the AD continuum, the focus of this review will be primarily on the measurement of beta-amyloid via positron emission tomography (PET) imaging, and how this technology has been applied to clinically normal cohorts to identify individuals with evidence of early AD pathology. ^{11}C -PIB ('Pittsburgh Compound-B') was one of the first radiotracers to enable the visualization of A β plaques [8], with imaging-postmortem studies showing high correspondence between in vivo signal and moderate to frequent amyloid plaque pathology at autopsy [9, 10]. The success of ^{11}C -PIB in the research setting accelerated the development of ^{18}F Amyloid PET compounds that have greater feasibility given the shorter half of ^{18}F isotopes (110 minutes for ^{18}F compared to 20 minutes for ^{11}C). The longer half-life enables ^{18}F compounds to be delivered over a long distance from distribution centers rather than depending on an on-site cyclotron; thus the overall utility of Amyloid PET in research and in clinical settings has dramatically increased over recent years. Between 2012 and 2014 there were three ^{18}F compounds approved by the FDA to assess A β deposition in patients with clinical symptoms—florbetapir/Amyvid [11], flutemetamol/Vizamyl [12], and florbetaben/Neuroceq [13]. Thus, in addition to the large role of Amyloid PET imaging in specialized research settings, it has become increasingly common across medical and research settings across the globe. Given the lack of disease modifying treatments for AD dementia, the utility of Amyloid PET in the clinical setting is a topic of debate and large-scale studies are currently underway to understand the impact of Amyloid PET in the clinical setting according to "appropriate use criteria" [14], specifically, in impaired patients that are suspected to have AD dementia but have atypical non-amnesic clinical presentations, as well as in mild cognitive impairment patients, a population that is heterogeneous with various contributing etiologies. This multi-site study of over 18,000 Medicare beneficiaries, the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS), will provide important insights into how Amyloid PET scans influence patient management and medical outcomes [15].

Prevalence of A β in clinically normal older individuals

Although A β plaques are a central feature of AD dementia, they are also commonly observed in the brains of clinically normal (CN) older individuals that do not show signs of objective cognitive impairment as detected with neuropsychological assessment. This observation has consistently been observed in postmortem studies [6, 16], CSF studies [17, 18], and Amyloid PET imaging studies [19]. The prevalence of CNs with evidence of elevated A β (A β +) increases with older age as well as the APOE4 genotype [20, 21], with little evidence of abnormal A β accumulation before age 60. Interestingly, the regional distribution of Amyloid plaques throughout the brain tends to be widely distributed with involvement across multiple association cortices [22]. This global distribution pattern is common among A β + CN, suggesting that specific focal regions do not seem to be

susceptible to amyloid accumulation among older individuals (at least using the current Amyloid PET ligands). However, some work has suggested that large areas encapsulating highly connected heteromodal cortical regions seem to be most impacted by A β deposition [23, 24].

The presence of abnormal A β accumulation within CN individuals is consistent with models of AD suggesting that A β is an early initiating event that eventually leads to “downstream” brain changes and clinical impairment [3, 7]. Consistent with this framework, A β + CN individuals are at greater risk of gray matter atrophy in the medial temporal lobe as well as lateral association cortex when assessed longitudinally [25], which may reflect downstream changes A β -related toxicity. Interestingly, longitudinal studies examining the rate of A β accumulation over time among CN has shown very slow rates, suggesting that this process may occur for decades before neurodegeneration is clearly evident and clinical symptoms of dementia are present. Specifically, Villemagne and colleagues have estimated that it may take 20 years to transition between A β levels typically found in A β + CNs compared with A β levels found in AD dementia, highlighting the prolonged period over which A β accumulation may occur within CN individuals before clinical symptoms of dementia are present [26]. Given this prolonged stage of abnormal A β accumulation that occurs during among CN individuals, much research has focused on identifying subtle changes that occur in brain structure and function during this stage. These studies have suggested that A β + CN show subtle decreases in gray matter measures [27, 28], resting state connectivity [29–31], as well as task related activation during memory processing [32, 33], highlighting that early effects of this pathology on brain structure and function can be detected concurrently with abnormal levels of A β , before clinical symptoms of dementia.

Cognitive decline in “normal” aging

Lifespan studies report age-related decrements in performance across multiple cognitive domains, including memory, working memory/executive functions, and processing speed in CN cohorts [34–36]. As an illustration, normative data suggest that recall of 8 words on the 15-word Rey Auditory Verbal Learning List (RAVLT) is normal performance for a 70-year-old woman whereas recall of 8 words would reflect borderline impaired performance in a 30-year-old woman. The largest age-related cognitive effects are observed in the domains of episodic memory and processing speed [37]. However, age-related decline at the group level is generally small with some estimates of annual decline ranging from between 2–4% of one standard deviation in individuals aged 50+ [36]. Although subtle multi-domain cognitive decline is generally associated with age, some aspects of cognition remain relatively stable including speech and language processing [38] and procedural memory [39]; in addition, there is evidence that vocabulary knowledge [37, 40] and other aspects of semantic memory [41] not only remain stable but may improve throughout the lifespan.

Methodological challenges to quantifying “normal” aging exist. Cross-sectional studies may suffer from covariance between age and sampling bias with 30-year-old and 70-year-old subjects reflecting fundamentally different cohorts with unique reasons for participating in research. Longitudinal studies must account for practice effects and selective attrition. For example, Josefsson et al. 2012 showed that age-related declines in memory over a 15-year

longitudinal period were under-estimated prior to statistically accounting for attrition; participants who dropped out of the study were more likely to exhibit decline in their memory performance prior to study discontinuation [42].

Despite these methodological hurdles, multiple cross-sectional studies of cognitive aging show linear relationships between age and cognitive decline starting as early as in the late 20's. Park et al has reported decrements in cognitive performance that were present linearly across the lifespan, suggesting that subtle cognitive decline occurs well before the ages in which risk of dementia is highest [43]. Other studies also suggest linear decline but with the addition of an inflection point around age 60-65 with a subsequently greater magnitude of age-related cognitive decrements [37].

The presence of this inflection point highlights both the theoretical and methodological challenge of differentiating benign versus pathological cognitive aging. More specifically, multiple risk factors for dementia (such as hypertension, diabetes) are both associated with age and, furthermore, may confer independent risk of normative cognitive decline. In addition, there is significant overlap between the most prevalent cognitive complaints in typical aging such as difficulty with proper name recall and weaknesses in memory retrieval which mirror the earliest cognitive signs associated with AD [44]. Given that age is the primary risk factor for AD dementia, the ability to measure AD pathology in vivo provides a unique opportunity to understand the contributions of early pathology to decline observed in aging, as well as potential interactions between "normal" and "pathological" aging.

Elevated risk of clinical progression among A β + CN

Studies that have examined older CN individuals in conjunction with A β status have consistently revealed that A β + CNs have greater risk of progression on functional measures, such as on the clinical dementia rating scale [45] and progression to mild cognitive impairment and dementia [46]. Examining a mean follow up of 3.70 years (ranging between 1 and 7.5 years of follow up across participants), Roe et al reported a hazards ratio of 3.68 describing risk of progression in A β + versus A β - CN individuals classified according to PIB PET (with similar hazards ratios when CN were classified according to CSF Amyloid levels rather than PIB PET) [45]. Likewise, a separate study from AIBL of CN individuals reported odds-ratios of 4.8 when examining the proportion of A β + CN that progressed to a clinical diagnosis of MCI or AD dementia after 3 years of follow up compared to A β - CN [46].

Although these aforementioned studies highlight that the A β + CN group is at greater risk of clinical progression, it is important to note that the overall rates of progression are low for studies with short follow up durations (<4 years of follow up). Specifically, the aforementioned AIBL study by Rowe et al reported 26% of A β + CN progressed to MCI/dementia compared to 7% in the A β - group after 3 years. Recent work from Donohue and colleagues from the ADNI suggests although significant albeit low rates of progression on the Clinical Dementia Rating (CDR) scale are greater in A β + CN compared to A β - CN 3 to 4 years after baseline, much larger rates of CDR progression are apparent after 6 years of

follow up in the A β + group [47], highlighting the slow time course in which clinically meaningful changes occur in CN cohorts.

Greater longitudinal cognitive decline in A β +

Observational studies investigating longitudinal decline using neuropsychological measures have converged to show that the A β + CN group shows worse cognitive performance over time compared to A β - CN. Although some groups have identified specific decline in episodic memory among A β + CN [48, 49], others have reported decline across multiple cognitive domains, such as executive function, semantic memory, and processing speed (see meta-analysis by Baker and colleagues [50]). Interestingly, we have found early changes in semantic fluency among A β + CN that remains significant after controlling for non-semantic aspects of verbal fluency (i.e. phonemic fluency) [51]. Petersen and colleagues have published the largest study to date that examined prospective cognitive decline among CN classified at baseline as A β + or A β - using PIB PET across 564 CN followed on average for 2.7 years [52]. This study also identified multi-domain cognitive decline, with significant differences between A β + and A β - groups of -0.09 z-score units per year for a composite measure of executive function (Trail Making Test Part B and Digit Symbol Substitution) and -0.07 z-score units per year for a composite measure of memory (delayed recall measures from the Wechsler Memory Scale-Revised Logical Memory II delayed recall, Wechsler Memory Scale-Revised Visual Reproductions II, and the Auditory Verbal Learning Test).

Data driven approaches examining patterns of retrospective decline preceding dementia diagnosis have similarly suggested that measurement of decline across multiple cognitive domains is optimal for capturing the gradual decline that occurs prior to dementia onset [53, 54]. Given that decline may not be restricted to episodic memory changes during the preclinical stage, cognitive composites scores spanning multiple domains have been utilized to explore A β related decline in observational cohorts [49, 52, 55, 56] as well as integrated into cognitive endpoints in clinical trials targeting at risk CN [57]. In addition to showing significant cognitive decline, A β + CNs also show decline in measures of global cognitive function that are established proxies for clinically relevant change, such as in the MMSE [58] and ADAS-cog [59, 60]. Thus, at the group level there is consistent evidence that A β + CN show worse cognitive performance over time in memory and also non-memory domains compared to A β - CN, as well as decline in global cognitive measures that are likely more proximal to clinically meaningful change.

Implications of multi-domain cognitive decline

The presence of multi-domain cognitive decline among A β + CN may reflect sequential involvement across different cognitive domains, such that impairments in episodic memory precede decline in executive function, and that these declines occur among CN prior to clinical impairment [61]. This is consistent with the notion that in typical presentations of AD, the most early and prominent cognitive feature is episodic memory loss which coincides with tau proliferation in the medial temporal lobe [62]. Another possibility is that there is heterogeneity in the patterns of cognitive decline among A β + individuals, such that some A β + CN show memory decline whereas others show decline in non-memory domains

such as executive function or language. The notion of heterogeneity in clinical presentations of AD dementia has long been established, with clinically “atypical” presentations involving disproportionate deficits in executive function (behavioral/dysexecutive-variant AD), language (Logopenic progressive aphasia), and visuospatial processing (Posterior Cortical Atrophy). While these variants are infrequent, there is evidence for amnesic versus non-amnesic subtypes within relatively typical AD dementia [63, 64]. Importantly, these non-amnesic subtypes may be associated with distinct patterns of atrophy and neurofibrillary tangle burden [65–67], as well as a younger age and the absence of the APOE4 risk allele. Interestingly, although patterns of atrophy and Tau accumulation tend to correspond well with the clinical phenotype, Amyloid is globally distributed in these different subtypes. Thus, there may be “vulnerable” brain networks for a given individual that influences the clinical presentation of AD that are not driven by the regional impact of A β plaques.

The role of disease heterogeneity in cognitive trajectories during the preclinical stage of AD has largely been understudied, and may explain the presence of subtle declines in cognition that are not restricted to episodic memory among A β + CN. As is the case when interpreting heterogeneous clinical symptoms among dementia patients, heterogeneity in cognitive decline among A β + CN may reflect individual differences in response to late life Amyloid rather than the regional distribution of Amyloid itself, given that patterns of Amyloid uptake tend to be widely distributed throughout cortex even among CN. For instance, differences in development, lifestyle factors, genetics, and/or co-morbidities such as cerebrovascular disease, synucleinopathies, and transactive response DNA binding protein 43 kDa (TDP-43) may be important indicators that explain individual differences in patterns of decline among older A β + CN.

Greatest cognitive decline in A β + CN with evidence of neurodegeneration

Although the A β + CN group consistently shows worse cognition over time when followed longitudinally, these changes are small in magnitude and above the magnitude of decline needed to be diagnosed with mild cognitive impairment (typically <0.10 z-score units per year difference across A β groups [52, 68]). Thus, biomarkers that may capture underlying neurodegenerative processes may improve the identification of A β + CN most at risk for short term decline, with the idea that A β + CN that additionally have evidence of neurodegeneration may indicate a later preclinical stage than A β + CN without evidence of neurodegeneration [69]. Along these lines, in 2011 the National Institute on Aging–Alzheimer’s Association work group proposed a staging criteria for preclinical AD that incorporated markers of A β with markers of neurodegeneration (ND) to facilitate research focused on understanding the asymptomatic stage of AD and the identification of CN individuals most at risk for future decline. This initial NIA-AA framework classified individuals into A β + and A β – groups based on either CSF or PET markers. This framework also incorporated markers of ND, which at that time included CSF Tau/pTau, hippocampus volume measured with structural MRI, and hypometabolism in regions impaired in AD dementia. Unlike CSF and PET measures of Amyloid which are highly correlated [18], markers of ND vary in their associations which makes this dimension of the NIA-AA 2011 research framework less straightforward to implement and interpret than classification along the A β dimension [70]. Thus, selection of ND marker will likely influence which

participants are classified as ND+. Implementation of this criteria results in four groups: preclinical stage 0 is defined as $A\beta^-/ND^-$, stage 1 is defined as $A\beta^+/ND^-$, and stage 2 is defined as $A\beta^+/ND^+$. The fourth group, $A\beta^-/ND^+$ CN individuals were initially not described in the NIA-AA 2011 research guidelines and subsequently labeled as “suspected non-AD pathophysiology” (SNAP) [71], with the implication that non-AD etiologies contribute to an AD-like pattern of ND in this group. Stage 3 was also proposed within the NIA-AA framework to encapsulate $A\beta^+/ND^+$ individuals that show subtle memory decline or cognitive complaints. However, given the complexities of defining this group, many studies have elected to keep all $A\beta^+/ND^+$ CN together in the Stage 2 group rather than further dividing $A\beta^+/ND^+$ CN into Stage 2 and Stage 3.

Despite concerns regarding discrepancies across ND markers, studies examining the proportion of CN classified across the proposed stages have been remarkably consistent [71–76]. In general, preclinical stage 0 CN comprise anywhere from 40 to 60%, stage 1 is about 10–20%, stage 2 is 5–15%, and SNAP is around 25%. A major contributing factor to these proportions is cohort age, with younger cohorts showing more biomarker negative individuals (Stage 0) than $A\beta^+$ individuals (Stages 1 and 2). Using this biomarker staging framework, investigators have examined longitudinal clinical progression to either MCI or AD dementia across preclinical stages defined at baseline, as well as change in cognition over time. Among the studies investigating clinical progression, most studies to date suggest elevated risk of clinical progression in Stage 2 CN compared to other groups, with unclear risk in the Stage 1 and SNAP groups [76, 77]. An important consideration for studies examining clinical change in CN is the small number of progressors across the four biomarker defined groups. For instance, in the study by Knopman and colleagues, 127 CN were classified as Stage 0, 44 as Stage 1, 46 as Stage 2/Stage 3, and 69 as SNAP. However, after one year of follow up, only 6 Stage 0, 5 stage 1, 11 stage 2/3, and 7 SNAP progressed to either MCI or AD dementia [76, 77]. Future studies with longer follow up will be needed to clarify risk of clinically meaningful progression among different biomarker staging frameworks.

Given the slow progression rates within CN, a number of studies have investigated cognitive decline as a function of baseline preclinical staging using the NIA-AA framework. These studies consistently show the greatest decline among Stage 2 individuals compared to all other groups [72–74]. However, the presence of cognitive decline among Stage 1 and SNAP is inconsistent. For instance, Soldan and colleagues examined longitudinal change in a global cognitive composite using data from the BIOCARD study. At baseline CN were an average of 57 years old and followed for 11 years. Classification into preclinical stages was based on baseline CSF measures for both $A\beta$ and Tau. This study found that a slope difference of -0.05 z-score units per year between Stage 2 and Stage 0, and no differences between the other three groups (Stage 0, Stage 1, SNAP) [74]. In a study by Burnham and colleagues using data from the AIBL, CN were an average of 73 years of age at baseline and followed for 6 years. Classification was performed using Amyloid PET and hippocampus volume for ND. In this study there was a slope difference of -0.25 z-score units per year for memory between Stage 2 and Stage 0, and also a slope difference of -0.08 z-score for global cognitive decline between Stage 1 and Stage 0 (with no difference between Stage 0 and SNAP) [72]. Finally, our work in the Harvard Aging Brain Study examined CN with an

average age of 74 at baseline and followed for 4 years. Classification was performed using PIB PET and both hippocampus volume in conjunction with patterns of hypometabolism for ND [78]. Consistent with the other studies, we reported significant decline in global cognition between Stage 2 and Stage 0 (−0.22 z-score units per year difference). However, we also found a group difference between SNAP and Stage 0 (−0.07 z-score units per year) and no difference between Stage 1 and Stage 0. In a follow-up paper, we did not find any difference in the pattern of decline across biomarker stages when examining different cognitive domains rather than global cognition (memory versus executive function) [73]. Direct comparison across these studies is difficult given that a number of parameters vary that may influence cognitive trajectories—specifically, age at baseline, follow up duration, and ND classification. Nevertheless, across all these studies preclinical Stage 2 was consistently shown to have the greatest cognitive decline. Cognitive decline among Stage 1 and SNAP remains unclear and may be more susceptible to cohort and analytical differences across studies.

Initial studies with Tau PET in CN

In addition to A β plaques, intracellular aggregations of the Tau protein into neurofibrillary tangles (NFTs) are the other hallmark pathological feature of AD. Interestingly, the regional involvement and time course of NFTs throughout the lifespan follows a different pattern compared to A β plaques [79]. Specifically, NFTs begin in the transentorhinal cortex (Braak I/II); spread to other portions of entorhinal cortex as well as the CA1 subregion of the hippocampus and adjacent inferior temporal cortex (Braak III); and then finally are deposited in additional hippocampal subregions and cortical regions (Braak IV and higher) [80, 81].

When considering the postmortem literature, there are three consistent observations regarding the overall involvement of NFTs and A β plaques with respect to age and clinical status: (1) NFTs in early Braak regions are common in middle age and ubiquitous in older age (50% of 50 year olds and 90% of 70 years old have NFTs in entorhinal cortex), whereas abnormal A β (in a globally distributed pattern) is present later in the lifespan compared to entorhinal cortex Tau (10% of 60 year olds and 30% of 75 year olds) [79, 82]; (2) exacerbation of NFTs in entorhinal cortex and beyond entorhinal cortex into neocortex is coupled with accumulation of A β [4, 5]; and (3) widespread neocortical NFTs (Braak V) are associated with clinical dementia and are very uncommon among CN individuals [6]. Thus, it is expected that among older CN individuals, NFTs will be common albeit restricted to the entorhinal cortex, whereas variations within the MTL and involvement of regions beyond entorhinal cortex (i.e., hippocampus and inferior temporal cortex) are expected among older CN individuals that additionally have abnormal A β (although widespread neocortical involvement of Tau beyond inferior temporal cortex is not expected among CN).

Recent advancements in Tau PET imaging now enable the visualization of neurofibrillary tangles [83, 84], enabling multimodal imaging studies that investigate both hallmark pathologies of AD (A β and Tau) during the preclinical stage of AD. Initial work applying Tau PET using the ligand F18-AV1451 in CN have shown that A β + CN have greater levels of Tau compared to A β − CN, especially in medial temporal lobe and inferior temporal

cortex [85, 86]. These patterns are consistent with pivotal postmortem work by Price and Morris that showed elevated medial temporal lobe Tau in CN with moderate and frequent plaque counts compared to CN with little evidence of A β plaque pathology [5]. Interestingly, Tau PET among CN has shown only moderate associations with markers of ND used to classify CN into preclinical stages using the 2011 NIA-AA framework. For instance, elevated Tau in the medial temporal lobe and inferior temporal lobe has been shown to relate moderately to hippocampal volume measures only among A β + CN and not A β - CN [73]. Furthermore, even associations between Tau PET and CSF Tau are not highly correlated when samples are restricted to CN [87, 88]. Specifically, a lack of significant correlation between regional Tau measured with AV1451 and CSF total Tau or phosphorylated Tau has been reported across two independent cohorts of CN [87, 88]. Contrary to these studies, Chhatwal and colleagues found significant associations between Tau from CSF and PET from some regions among CN. Specifically, CSF phosphorylated Tau shared 31% of variance with entorhinal cortex Tau and 53% of the variance with inferior temporal Tau [89]. Given that CSF and PET measures of Tau capture distinct forms of this pathological process (Tau protein in the CSF versus intracellular neuronal inclusions), it is not surprising that these measures are not highly concordant and may show different levels of sensitivity among CN. Importantly, studies that combine CSF and PET within CN will be able to directly determine whether these measures of Tau provide sequential information relevant to early AD, and/or provide unique information regarding future risk of cognitive decline and clinical impairment.

An initial study by Scholl and colleagues applying AV1451 to CN found that elevated Tau in the medial temporal lobe was associated with worse memory both at the time of the Tau scan as well as retrospectively [90]. Future work in larger samples will be necessary to examine the independent and synergistic effects between A β and Tau on cognition, as well as the ability to predict prospective cognitive decline following the Tau scan. Given the potentially complementary information gained by Tau PET and Tau from CSF within CN [88], it will be informative to understand whether these Tau measurements independently contribute to cognitive decline among A β + CN.

Synergistic effects between A β and genetic risk factors

A priori genetic factors, such as genotypes from Apolipoprotein E (APOE) and brain-derived neurotrophic factor (BDNF), have also been shown to interact with A β status to accelerate longitudinal cognitive decline among CN individuals. We have shown that A β + CN individuals that are also APOE4+ show greater short term decline in global cognition as well as memory over a median follow up period of 1.5 years than other groups (APOE4-/A β -, APOE4+/A β -, and APOE4-/A β +) [91]. Although the APOE4 genotype is known to influence AD risk through pathways related to abnormal A β accumulation [16, 92], this genotype also effects neuronal integrity through A β -independent mechanisms. For instance, APOE4 genotype has been shown to impact the response to neuronal injury, with the apoE4 protein being less effective than apoE3/2 proteins in responding to neuronal injury [93]. It is therefore possible that in addition to promoting A β accumulation, the APOE4 genotype also confers greater levels of neuronal toxicity in response to A β accumulation, ultimately making this A β +/APOE4+ group the most susceptible to short term cognitive decline than

A β + that are APOE4-. However, given the earlier age of A β accumulation among APOE4+ carriers [16], it is also possible that APOE4+ CN individuals have harbored abnormal levels of A β for a longer duration than their A β + /APOE4- counterparts and are therefore at a more advanced preclinical stage of the disease.

Similar to the increased risk of cognitive decline identified in APOE4+ /A β + CNs, in a study of 165 CNs followed over 3 years, Lim et al. demonstrated that A β + CNs that also have the val66met BDNF polymorphism show greater rates of cognitive decline [94]. Although this polymorphism is not associated with greater levels of A β accumulation, it results in decreased production of the BDNF protein and impairment of neuronal and synaptic growth [95]. Thus, the combination of abnormal A β in conjunction with the val66met BDNF polymorphism may influence an individual's ability to tolerate underlying levels of A β and more susceptible to A β related toxicity. Interestingly, in a follow up study by the same authors, independent effects were identified for both APOE and BDNF genotypes, such that A β + CN that additionally have both genetic risk factors show the most rapid memory decline [96]. The additive effect across these two genetic loci implies that there are synergistic effects between genetic risk and A β among CN, suggesting that consideration of genetic risk factors may provide important information regarding immediate cognitive decline among biomarker positive CN.

Sensitivity and specificity of cognitive testing in CN

Most neuropsychological measures were designed for the detection of impairment within clinical populations. These measures may thus be insufficient in their level of difficulty and degree of specificity among CN adults to reliably detect 1) subtle relationships between cognition and AD biomarkers and 2) AD biomarker-related cognitive decline, particularly at shorter follow-up intervals and at the earliest stage of preclinical AD. For example, the Face Name Associative Memory Exam (FNAME) originated from the cognitive neuroscience literature and involves learning and remembering names associated with faces. The task is not only challenging but may also have greater ecological validity as older adults commonly report difficulty with proper name recall. Worse FNAME performance has been associated with greater amyloid burden in CN adults [97]. The Memory Binding Test (MBT; [98]) has similarly been shown to be correlated with amyloidosis in CN adults [99]. This measure, along the lines of the Free and Cued Selective Reminding Test (FCSRT) enhances learning and recall through use of a semantic association paradigm. Decrements in recall on these measures, particularly those that persist despite semantic cueing, are prototypical in MCI due to AD [100]. We recently found that although decrements in cued recall on the FCSRT were rare among CN adults, A β + individuals were 3.55 times more likely to show cued recall decline and that decline was associated with greater risk of clinical progression on the clinical dementia rating scale [101].

Other cognitive measures with promise include the Short-Term Memory Binding Test (STMB) which requires a participant to identify whether there has been a change in either the shape alone or shape and colors of polygons across trials. Feature binding in short-term memory has been associated with perirhinal activation [102] and thus hypothesized to potentially tap into early transentorhinal tau deposition. Decrements in this task were

observed in asymptomatic presenilin-1 mutation carriers compared with non-carrier controls [103]. Borrowing from both animal and cognitive neuroscience literature is the Behavioral Pattern Separation Task (BPS-O). Older adults are more susceptible to the interference of previously learned information when differentiating similar but new information. Deficits in pattern separation have been associated with increased hippocampal CA3 and dentate gyrus fMRI activity [104], and worse BPS-O performance is associated with worse memory performance in otherwise normal older adults [105].

Novel platforms for Cognitive Testing

There is currently significant interest in the use of digital technology to measure early cognitive changes in preclinical AD. While well-validated paper and pencil measures are current gold standards in clinical trials, digital technology may confer significant advantages including 1) increased ease of administration (self-administered versus rater administered platforms; remote administration; frequent serial measurements) 2) more precise and reliable scoring particularly for timed measures and 3) potential for more extensive mineable data to examine individual variations in performance. There are numerous well-validated computerized batteries (see [106] for a review) with differing advantages (e.g., non-proprietary, web and/or tablet based application).

Many of these platforms do not simply digitize traditional tests but instead incorporate novel paradigms. For example, in the Cogstate Brief Battery, playing cards are used to measure reaction time, working memory, and incidental learning. Recently published data from 335 CN from an observational study showed longitudinal decline in Cogstate card Identification (a measure of choice reaction time) and One Card Learning (a visual memory measure using a pattern separation paradigm) among A β + compared with A β - [48], highlighting the ability of these computerized tests to detect early A β related cognitive decline among CN.

Beyond tablet and web-based interfaces for cognitive testing, commercially available digital pens can capture extensive information about how a task is performed including information about pen strokes, pen velocity, and pen time off the page to capture “thinking” time. Digital Cognition Technologies (DCT) harnesses the well-known clock drawing task, but through machine learning techniques using thousands of administrations and thousands of variables per administration, they have developed software that identifies features of performance that offer precise measurement of thinking processes, such as mental speed, time to decision-making, and organizational details. These features have the potential to move beyond simple measures of accuracy and detect subtle cognitive changes reflected in the performance of the task that may be meaningful in early AD [107]. In addition, there are smartphone based functional instruments that may detect the emergence of difficulty with everyday skills including using an ATM to perform banking tasks, managing prescription refills over the phone/computer, or navigating a telephone menu [108, 109] and thus may particularly useful for tracking clinical progression.

Finally, advances in technology have resulted in myriad sensors, trackers and monitors that collect information in real-time and offer the opportunity for passive monitoring. For example, a recent study in individuals with CN adults and those diagnosed with MCI

showed that the MCI group exhibited a significant decline in their overall computer use and an increase in their day-to-day use variability in comparison with the CN adults [110]. Continuous collection of smartphone and internet use information allows for acquisition of an unprecedented amount of data. Analysis of this data using machine learning and other data driven techniques has the very exciting potential of identifying indirect and very subtle changes in behavior and provides a novel frontier for maximizing the predictive utility and precision of cognitive measurement at the level of the individual.

Summary

Amyloid PET imaging has provided a unique opportunity to understand early AD changes among clinically normal individuals. Work across multiple laboratories highlights that cognitive decline is detectable among CN with abnormal levels of Amyloid, and that this group is at elevated risk for clinically meaningful change at follow up. Our ability to predict which A β + CN are most at risk will increase as additional biomarkers and risk factors are integrated, such as Tau PET, sensitive markers of neuronal integrity, as well as genetic and lifestyle variables. Importantly, the ability to measure the pathophysiology of AD before symptoms are present, and the converging research that has shown that CN with early evidence of AD are at risk for future cognitive decline, has provided an unprecedented opportunity to explore early intervention with disease modifying strategies [111]. The results of these prevention trials will undoubtedly have a large influence on the conceptualization of AD and “normal” aging.

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