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The Relevance of Beta-Amyloid on Markers of Alzheimer's Disease in Clinically Normal Individuals and Factors That Influence These Associations

Elizabeth C. Mormino

Department of Neurology, Massachusetts General Hospital, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA

Abstract

Aberrant accumulation of beta-amyloid (A β) is thought to be an early event in a biological cascade that eventually leads to Alzheimer's disease (AD). Along these lines, many clinically normal (CN) older individuals have evidence of beta-amyloid (A β) accumulation, which may be indicative of preclinical AD. However, relationships between A β and "downstream" AD markers are often inconsistent across studies. These inconsistencies may be due to the presence of other age-related processes that also influence AD markers, as well as additional risk factors that interact with A β to influence downstream changes. For instance, it is possible that the effect of A β is modified by neurodegeneration, genetics, sex-differences and cognitive reserve. Thus, a multivariate approach to determining risk of AD within CN participants may be more appropriate than reliance on A β status alone. An understanding of how additional risk factors interact with A β to influence an individual's trajectory towards AD is essential for characterizing preclinical AD and has implications for prevention trials.

Keywords

Aging; Preclinical Alzheimer's disease; Beta-amyloid; Amyloid PET imaging; Resilience

Introduction

The Amyloid Hypothesis of Alzheimer's Disease and in Vivo Visualization of A β

Alzheimer's disease (AD) is a progressive neurodegenerative disorder found in ~10% of individuals over age 65 and ~40% of individuals over age 85 (Alz.org 2014; Hebert et al. 2013). AD typically begins with episodic memory impairment, and slowly affects other cognitive domains such as executive function as the disease progresses (Grober et al. 2008). The amyloid hypothesis of AD posits that aberrant accumulation of the A β peptide is an early initiating event that eventually leads to clinical impairment (Hardy and Selkoe 2002), and is supported by research spanning multiple fields (Walsh and Selkoe 2007). For instance, autosomal dominant genetic variants that cause early onset AD involve mutations

that directly influence the production of the A β peptide (Bentahir et al. 2006; Citron et al. 1992). Down syndrome individuals have an extra copy of chromosome 21 (the locus of the amyloid precursor protein gene, which codes for the larger protein that beta-amyloid is cleaved from), produce high amounts of A β and have increased risk of developing AD (Lott et al. 2006). Experimental work in mice has shown a relationship between A β and memory that is reversed after passive immunization with an A β antibody (Dodart et al. 2002). Soluble A β has been shown to reduce synaptic strength and number in rodent models (Shankar et al. 2007; Walsh et al. 2002), which is consistent with the observation that neurons from AD patients have 15-35 % fewer synapses than controls (Davies et al. 1987). Overall, there is strong evidence that beta-amyloid is a central feature of AD development.

In sporadic Alzheimer's disease, for unknown reasons the A β peptide undergoes aggregation after its cleavage from the amyloid precursor protein and deposits into extracellular A β plaques. Although A β plaques have traditionally been studied during postmortem analysis of brain tissue using stains such as thioflavin-T, congo red, and Bielschowsky, the ability to measure A β plaques in vivo with positron emission tomography (PET) has emerged in the last decade. ¹¹C-PIB ('Pittsburgh Compound-B') was one of the first radiotracers to enable this visualization (Klunk et al. 2004), and has become the most widely studied tracer to date. Further advancements have been made to create amyloid imaging agents radiolabeled with ¹⁸F rather than ¹¹C, given the longer half-life and thus greater feasibility to use ¹⁸F radiotracers in both research and clinical settings. Excitingly, two ¹⁸F compounds have been approved by the FDA to determine whether patients have evidence of brain A β deposition—florbetapir (Amyvid) (Wong et al. 2010) and flutemetamol (Vizamyl) (Vandenberghe et al. 2010). Although in vivo assessment of aberrant A β accumulation can also be accomplished using cerebrospinal fluid (CSF) markers of A β (Fagan et al. 2006), the majority of the literature reviewed herein focuses on data utilizing PET amyloid imaging.

Prevalence of A β in Clinically Normal Older Individuals

Although A β plaques are a salient feature of AD, they are also commonly observed in the brains of clinically normal (CN) older individuals (individuals that function independently and do not show signs of objective cognitive impairment as detected with neuropsychological assessment). This observation has consistently been observed in postmortem studies and has been replicated in amyloid imaging studies. The prevalence of CNs with evidence of elevated A β (A β +) increases with older age (~10 % of CNs in their 60's are A β + whereas ~40 % of CNs in their 80's are A β +, Fig. 1). It is noteworthy to emphasize that these proportions describe individuals that have evidence of elevated A β that are clinically normal, and do not include individuals of that age that are diagnosed with mild cognitive impairment or dementia. Although the age at which A β plaque deposition begins is unknown, examination across the studies depicted in Fig. 1 suggests A β positivity is minimal before age 60. Given that quantification of A β across post-mortem and amyloid imaging studies specifically measures A β plaque levels, it is possible that abnormal production and aggregation of A β may still occur before age 60.

The presence of A β accumulation within CNs 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 (Hardy and Selkoe 2002; Jack et al. 2013a). Downstream brain changes are thought to encapsulate alterations in synaptic and neuronal function and structure, and are a more direct substrate of cognitive impairment than initiating A β accumulation. In humans, imaging proxies for these downstream brain changes span multiple modalities, such as functional magnetic resonance imaging (MRI), structural MRI, and [18 F] fluorodeoxyglucose positron emission tomography (FDG-PET), and will be discussed in detail throughout this review. Consistent with this framework, work from Villemagne and colleagues suggest that it may take upward to 20 years to transition between A β levels typically found in A β + CNs compared with A β levels found in AD, highlighting the prolonged period over which A β accumulation may occur within CNs (Villemagne et al. 2013). To understand whether A β accumulation within CNs is indicative of a preclinical AD state, many investigators have examined the association between A β and downstream changes within CNs. These studies are summarized in the following sections.

Associations Between A β and Cross-Sectional AD Markers Within CNs

Functional Brain Markers

A β has been shown to promote synaptic loss (Shankar et al. 2007) and impair long-term potentiation (Walsh et al. 2002). Given these effects on synaptic function, it is possible that the earliest A β -related changes within CNs may be detected using measures of brain function, before the high levels of neuronal loss typical of AD patients have occurred. Two widely used imaging modalities that measure brain function have also been used to investigate the association between A β and brain function: (1) functional magnetic resonance imaging (fMRI, which measures brain activation during task and rest) and (2) [18 F] fluorodeoxyglucose positron emission tomography (FDG-PET, which measures glucose metabolism during rest).

The majority of work investigating the association between task-related fMRI and A β within CNs focuses on memory tasks, although non-memory domains have also been investigated (Hedden et al. 2011). The default mode network (DMN) in particular has received ample attention, given the high degree of overlap between this network and patterns of cortical amyloid deposition (Buckner et al. 2009). Comprised of medial prefrontal, posteromedial (precuneus, posterior cingulate and retrosplenial) and lateral parieto-temporal cortices, as well as the medial temporal lobe (Buckner et al. 2008), the DMN typically deactivates during memory encoding and activates during memory retrieval (Daselaar et al. 2004; Huijbers et al. 2013). Interestingly, A β + CNs show impaired DMN deactivation during memory encoding (Kennedy et al. 2012; Sperling et al. 2009; Vannini et al. 2012, 2013) and impaired activation during memory retrieval (Vannini et al. 2013). However, impaired deactivation within the DMN has also been observed during an attentional control task (Hedden et al. 2011), suggesting that the effect of A β on the DMN may not be specific to memory processing. A β has also been associated with increased activation in “task positive” regions known to activate during memory encoding (Mormino et al. 2011a; Sperling et al. 2009) (however see (Kennedy et al. 2012)), which echoes previous fMRI experiments showing increased activation in old versus young CNs (Cabeza et al. 2002; de Chastelaine et al. 2011; Park and Reuter-Lorenz 2009; Rosen et al. 2002). Although increased task-related

activity has been interpreted as a compensatory response in aging individuals (Cabeza et al. 2002), it is also possible they reflect reductions in neural efficiency (Li et al. 2006; Logan et al. 2002). We showed that increased task positive activation during memory encoding was related to memory performance within A β + CNs (Mormino et al. 2011a), suggesting that these heightened activations are beneficial to A β + CNs.

In addition to task-related patterns of activation, integrity of brain networks during rest has also been related to A β status using function connectivity analyses (FC). Functional connectivity (FC) analyses of resting state fMRI data captures brain regions showing correlated, low frequency (<0.1Hz) spontaneous activity, and have been used to define multiple networks with known anatomical connectivity and co-activation during task-related fMRI (Fox and Raichle 2007). Although the biological mechanism underlying these low frequency fluctuations remains unclear, it is possible that resting state networks reflect spontaneous cognitive processes and/or an intrinsic property of the brain's "baseline" state (Buckner and Vincent 2007; Raichle and Snyder 2007). Similar to task related fMRI experiments, analyses investigating the effect of A β on resting state connectivity within CNs have also focused on the DMN. Interestingly, some studies have reported decreased DMN FC (Hedden et al. 2009; Mormino et al. 2011b; Sheline et al. 2010b) while others have additionally reported increased DMN FC in A β + CNs (Mormino et al. 2011b; Sheline et al. 2010b). It is possible that DMN regions are differently affected by regional A β deposition, with the medial temporal lobe subsystem (Andrews-Hanna et al. 2010) showing early decreases and regions beyond the medial temporal subsystem showing early increases (Mormino et al. 2011b). A longitudinal functional connectivity study also found regional discrepancies in DMN FC within AD patients. In this study, Damoiseaux and colleagues reported reduced FC in the posterior component of the DMN (comprised predominantly of the posterior cingulate/precuneus and lateral parietal cortex) whereas increased FC was observed in the anterior DMN component (comprised predominantly of the medial prefrontal cortex). Interestingly, anterior DMN areas showing increased FC at baseline subsequently decreased at the follow up visit (Damoiseaux et al. 2012a). This pattern suggests that distinct DMN components may follow different patterns of FC changes throughout the progression of the disease.

A similar mixed pattern has emerged across studies investigating the relationship between A β status and glucose metabolism as measured with FDG-PET within CNs. Although one recent large study of 628 CNs age 70 and older showed that elevated A β was associated with hypometabolism in ADvulnerable regions (Knopman et al. 2014), smaller studies have found hypermetabolism within A β + CNs (Johnson et al. 2014; Oh et al. 2014).

Overall, A β + CNs tend to show altered patterns on measures of brain function. However, the direction and regional distribution of these changes are often inconsistent across studies. It is possible that some measures of brain function show initial increases in response to A β followed by subsequent decreases. It is also possible that increased brain activation and/or metabolism may predate A β deposition (Jagust and Mormino 2011), given that A β release has been shown to be activity dependent (Cirrito et al. 2005). Specifically, neuronal inefficiencies that occur independently of A β may actually promote the deposition of A β late in life. Thus, A β + CNs with elevated measures of brain function may be CNs that have

recently become A β +, whereas A β + CNs that have been A β + for a longer period may begin to show AD-like decreases in functional brain measures. Interesting, recent work by Jack and colleagues revealed increased DMN FC in A β - CNs that subsequently became A β + over a short follow up period (1.3 years), offering support for the idea that increased connectivity may predate A β deposition (Jack et al. 2013b). Further longitudinal studies will be essential to disentangle the temporal relationship between A β and activation patterns within CNs.

Structural Brain Markers

A link between A β and cross-sectional structural brain markers within CNs has been difficult to establish, with some studies reporting reduced gray matter in A β + CNs (Becker et al. 2011; Dickerson et al. 2009; Dore et al. 2013; Mormino et al. 2009; Rowe et al. 2010; Storandt et al. 2009; Tosun et al. 2011) while others have not (Chetelat et al. 2010; Schott et al. 2010; Whitwell et al. 2013; Wirth et al. 2013a). These inconsistencies suggest that cross-sectional effects between A β and gray matter structure are likely subtle and may vary depending on cohort and the examined gray matter measurement. Whitwell and colleagues demonstrated the influence of measurement by examining gray matter volumes defined with the AAL atlas and gray matter thickness defined using Freesurfer. This analysis failed to find a consistent pattern across techniques when contrasting A β + and A β - CNs. However, a consistent pattern across methods emerged when contrasting A β + clinically impaired subjects (mild cognitive impairment and AD patients) to A β - CNs (Whitwell et al. 2013). Thus, although associations within CNs may be subtle and influenced by methodological approaches, A β -related gray matter reductions may become more evident once clinical impairment has been reached.

Cognition

Given that change in cognition is thought to be the most downstream event in the cascade leading to AD, it is not surprising that strong and consistent associations between A β status and cross-sectional cognition are not identified within CN samples. Furthermore, participants must perform within the normal range on neuropsychological screening tests to be included in a CN sample. Thus, the restricted variance in cognitive measures within studies of CNs will limit the ability to detect associations between A β and cross-sectional cognitive measures. Nevertheless, many studies have investigated whether associations between A β and cross-sectional cognitive measures exist within CNs. Given that episodic memory impairment is an early feature of AD (Grober et al. 2008; Small et al. 2000), many researchers have focused on the relationship between A β status and memory processes within CNs. Although some studies report lower memory scores in CNs with higher levels of A β compared to lower levels of A β (Pike et al. 2011; Rentz et al. 2011), others have not identified an association between A β status and memory (Aizenstein et al. 2008; Rodrigue et al. 2012; Storandt et al. 2009). Furthermore, subtle associations across multiple cognitive domains were reported in a large study of 408 CNs (higher levels of A β were associated with lower scores in memory, executive function, language and visual spatial function, with subtle albeit significant Spearman rho values ranging from -0.12 to -0.14) (Kantarci et al. 2012). This analysis highlights that the association between A β and cross-sectional cognition is subtle and may span multiple cognitive domains.

Additional Factors Contribute to Variance in Cross-Sectional AD Markers Within CNs

Although some biomarker models suggest that functional and structural brain changes relevant to AD occurs downstream to initiating A β accumulation (Hardy and Selkoe 2002; Jack et al. 2013a), other studies suggest that pathways promoting A β and these brain changes initially occur independently among CNs (Jack et al. 2013b; Wirth et al. 2013a). Although these early brain changes likely encapsulate alterations in brain function and structure (as discussed in previous sections of this review), recent emphasis in the field has been placed on markers of “neurodegeneration” (ND) (which are typically assessed with structural MRI and FDG-PET, as well as CSF tau) (Jack et al. 2012). Models suggesting that ND occurs downstream to A β versus models suggesting these processes initially occur independently are not mutually exclusive—A β and ND may initially begin via separate pathways, but at some point this association may strengthen as ND related to A β becomes more pronounced. The potential independence of pathways promoting A β and ND has been highlighted by attempts to classify older CNs into preclinical AD stages as recently proposed by the National Institute on Aging and the Alzheimer’s Association workgroup (Sperling et al. 2011). This staging approach classifies CNs into groups based on joint A β and ND status: Stage 0 is defined as A β -/ND-, Stage 1 as A β + /ND-, and Stage 2 as A β +/ND+. An additional category of A β -/ND+ CNs was initially not included within this staging criteria and subsequently labeled as “Suspected Non-Alzheimer’s disease Pathology” (SNAP) by Jack and colleagues (Jack et al. 2012). To classify CNs as ND+, proxy measures of neurodegeneration that are greatly compromised in AD have been used (such as hippocampus volume, glucose metabolism in cortical regions known to be vulnerable to Alzheimer’s disease, and CSF tau). The proportions classified across preclinical stages are remarkably similar across cohorts (Jack et al. 2012; Mormino et al. 2014; Vos et al. 2013; Wirth et al. 2013c), with approximately 40-50 % classified as Stage 0 (A β -/ND-), 10-15 % as Stage 1 (A β + /ND-), and 15 % as Stage 2 (A β + /ND+). Interestingly, approximately 25 % of CNs are classified as SNAP (A β -/ND+), emphasizing that many A β - CNs have evidence of ND.

It is likely that ND in the absence of elevated A β is influenced by non-A β factors in aging (Fjell et al. 2013; Jagust 2013). Given that the majority of CNs above age 60 will have neurofibrillary tangle (NFT) pathology in the medial temporal lobe (Braak and Braak 1997; Nelson et al. 2012), it is likely a proportion of the variance captured by markers of ND reflects tangle pathology (Jagust et al. 2009; Whitwell et al. 2008). The prevalence of NFTs and A β across the lifespan is consistent with two independent pathways, such that NFTs begin early in adulthood and are common in mid-life (although restricted to the medial temporal lobe) whereas A β accumulation is very uncommon until after age 60 (Fig. 1). Thus, although both NFT and A β pathologies are central to AD development, these processes likely occur independently during the early stages of AD and may account for the weak association between A β and ND within CNs. Non-AD pathologies are also likely contributors to ND within CNs, such as infarcts (Bennett et al. 2006), Lewy bodies (Bennett et al. 2006), TDP-43 (Wilson et al. 2013b), and/or hippocampal sclerosis (Barker et al. 2002). Furthermore, a sizeable subset of amnesic mild cognitive impairment (MCI) subjects demonstrate non-AD pathologies affecting the medial temporal lobe (Jicha et al. 2006), and associations between neuroimaging ND markers and non-AD pathologies have been

established. For instance, markers of cerebrovascular disease have been correlated with reductions in gray matter volume and glucose metabolism (DeCarli et al. 1995), whereas cortical gray matter reductions are prominent in patients with autopsy confirmed frontotemporal lobar degeneration with TDP-43 inclusions (Whitwell et al. 2010). In addition to associations between hippocampus volume and non-AD pathologies (Jack et al. 2002), hippocampus volume has also been associated with markers of inflammation (Marsland et al. 2008), stress (Lupien et al. 1998), and the use of estrogen replacement therapy (Eberling et al. 2004), highlighting that the hippocampus in particular may be vulnerable to many distinct processes. Overall, these pervasive associations across multiple factors highlight that imaging markers of ND are not specific for AD processes.

It is also possible that “normal aging” processes in the absence of underlying pathologies, such as synaptic alterations (Morrison and Hof 1997) contribute to the signal captured in neuroimaging markers of ND. Along these lines, associations between chronological age and markers of gray matter (Raz et al. 2004; Sowell et al. 2003) as well as glucose metabolism (Knopman et al. 2014) have been established. Importantly, these relationships are oftentimes gradual and consistent throughout the lifespan, occurring before the age at which abnormal levels of A β accumulation are apparent. Recent work directly investigating characteristics of older A β - CNs with evidence of ND have found associations with white matter hyperintensities (Wirth et al. 2013c) as well as with sex (such that A β - men are more likely to show ND than A β - women) (Mormino et al. 2014), offering additional insights into non-A β factors that may promote ND. Overall, it is likely that imaging markers used to assess AD-like ND within CNs are not specific to A β , but rather are influenced by a multitude of non-A β processes as well as normal aging (Jack et al. 2014). Thus, the contributions of multiple processes to ND in aging would likely obscure the ability to isolate effects between A β and cross-sectional AD markers within CNs (Fig. 2).

Associations Between A β and Longitudinal Changes in AD Markers

Associations between A β and longitudinal change in imaging and cognitive markers tend to be more consistent than associations between A β and cross-sectional measures. Discrepancies between cross-sectional and longitudinal analyses may be due to the limited range of values selected at baseline inherent to CN samples. As discussed in the above section, it is also possible that effects related to A β are superimposed upon changes influenced by many other age-related processes, many of which may occur gradually over the lifespan. For these reasons, isolation of A β -related effects in aging may be more readily detectable with longitudinal designs.

Longitudinal Structural Brain Markers

Many studies have reported that A β + CNs undergo faster rates of atrophy as measured with different gray matter measures, such as voxel based morphometry (Chetelat et al. 2012), gray matter thickness (Dore et al. 2013), gray matter volumes (Storandt et al. 2009), as well as in the boundary shift integral (a method that assesses volume loss by determining the amount a structure's boundary has shifted across longitudinally collected structural MRI measurements) (Schott et al. 2010). However, the spatial pattern of these changes is not consistent across studies, especially with respect to whether A β accumulation within CNs is

specifically associated with atrophy of medial temporal lobe structures. For instance, some studies have reported longitudinal atrophy in the medial temporal lobe (Chetelat et al. 2012; Schott et al. 2010), whereas other work suggest that medial temporal lobe atrophy increases at a similar rate in CNs with and without evidence of A β positivity (Fjell et al. 2009, 2014). Given the prolonged period of A β accumulation within CNs (Villemagne et al. 2013), it is possible that different brain regions show varying degrees of vulnerability throughout the period at which A β accumulation occurs. For instance, frontoparietal atrophy has been indentified in A β - CNs showing early signs of A β accumulation whereas a more distributed pattern of atrophy was present in CNs that had already surpassed the threshold of A β positivity. Interestingly, atrophy in the hippocampus was not observed within A β + CNs, but was present in A β + AD patients (Mattsson et al. 2014). Studies that simultaneously investigate the time course of both A β and ND will be able to establish whether a sequential involvement of brain regions tracks with A β accumulation in CNs.

Longitudinal Cognition

Studies assessing the relationship between A β and either retrospective or subsequent cognitive and functional decline within CNs have converged to reveal greater risk of decline within A β + CNs. Some studies have found cognitive decline that is specific to memory (Lim et al. 2013a), whereas decline in non-memory domains have been indentified in other studies (Snitz et al. 2013; Wirth et al. 2013b). Specifically, Lim and colleagues reported an association between A β status and a composite measure of verbal memory (Logical Memory delayed recall, California Verbal Learning Test delayed recall and California Verbal Learning Test d') as well as a composite measure of visual memory (Rey Complex Figure Test 30 min delayed recall, CogState One Card Learning task, and CogState One Back task), whereas no association with A β status was found with composite measures of executive function (Stroop, Letter Fluency, and Category Fluency Switching), language (Category Fluency and Boston Naming Test), attention (Digit Symbol, CogState Detection task, and CogState Identification task) or visuospatial function (Rey Complex Figure Test Copy, and Clock Drawing) (Lim et al. 2013a). Conversely, Snitz and colleagues reported an association between A β status with cognitive decline on individual measures of visual memory (immediate and delayed recall of the Rey Complex Figure Test 30), as well as on a measure of executive function (Trials B), attention (Trials A) and language (Category Fluency) (Snitz et al. 2013). Wirth and colleagues also found associations between A β status and cognitive decline that was not specific to memory when examining a composite measure of non-memory tests (Stroop, Controlled Oral Word Association Test, Trails A, and Digit Symbol) (Wirth et al. 2013b). Inconsistencies across these studies may be due to differences in sample sizes (Lim et al.: $N=390$, Snitz et al.: $N=194$, Wirth et al.: $N=38$), as well as differences in the selection criteria used within each cohort [for instance, the cohort used by Lim and colleagues enriches for the *APOE4+* genotype and the presence of subjective cognitive complaints (Rowe et al. 2010), whereas the cohort used by Snitz and colleagues specifically enrolls CNs older than other studies investigating the relevance of A β within CNs (72–96 years of age)].

In addition to associations across memory and non-memory domains, A β + CNs also show decline in measures of global cognitive function, such as in the MMSE (Resnick et al. 2010)

and ADAS-cog (Doraiswamy et al. 2012; Landau et al. 2012b). Furthermore, A β + CNs have greater risk of progression on functional measures, such as on the clinical dementia rating scale (Roe et al. 2013) and progression to mild cognitive impairment and dementia (Villemagne et al. 2011). Overall, A β positivity within CNs increases risk of subsequent decline on both cognitive and functional measures. However, future studies are necessary to elucidate whether specific cognitive domains are selectively affected by A β status within CNs, and whether these domain specific relationships may be modified by *APOE4* status, subjective cognitive complaints, and chronological age.

Factors that may Promote Resilience to Damaging Effects of Beta-Amyloid

An additional concept that may obscure relationships between A β and markers of AD within CNs is the notion of resilience to damaging effects of A β . Specifically, it is possible that additional factors interact with A β to determine whether and how fast an individual will progress along the trajectory towards AD. Thus, it is possible that heterogeneity exists within the A β + group. In a simplified scenario, A β + CNs may be categorized into 2 types—preclinical-A β + and resilient-A β + (in actuality, it is more likely that a continuum of resilience exists with most cases falling between these 2 categories). In this framework, preclinical-A β + CNs are on the trajectory towards AD, and are concurrently cognitively normal because they are at the beginning of the AD trajectory. Longitudinal follow-up of these CNs would reveal cognitive decline and progression to AD. Conversely, longitudinal follow-up of resilient-A β + CNs would reveal that these A β + CNs have remained clinically normal, suggesting the presence of protective factors within this subgroup. The remainder of this review will discuss emerging evidence that heterogeneity within A β + CNs exists.

Greater Atrophy and Decline in CNs that are Both Positive for A β and Neurodegeneration

Recent work has suggested that longitudinal atrophy is greatest in CNs that have evidence of both A β accumulation and neurodegeneration (Fig. 2). For instance, Desikan and colleagues found greater entorhinal cortex atrophy in A β + CNs that also had elevated quantities of CSF phospho-tau (Desikan et al. 2011). Consistent with this finding, data from the Mayo Clinic Study of Aging suggests that CNs that are both A β + and ND+ at baseline show higher rates of medial temporal lobe gray matter loss and hypometabolism (Knopman et al. 2013) as well as atrophy as measured using a multivariate score derived from multiple brain regions known to be vulnerable to AD (the medial temporal lobe as well as cortical regions including lateral temporal cortex, precuneus, angular gyrus and occipital gyrus) (Jack et al. 2014). Likewise, studies investigating decline in function and cognition have also found greatest risk in CNs positive for both A β and ND. Specifically, A β +/ND+ CNs are more likely to progress to MCI (Knopman et al. 2012; Rowe et al. 2013) and from Clinical Dementia Rating (CDR) 0 to 0.5 (Desikan et al. 2012; Vos et al. 2013) than CNs negative on both markers as well as CNs positive for either A β or ND. A similar pattern has emerged when examining longitudinal cognition, such that A β +/ND+ CNs show the greatest rate of cognitive decline over time (Mormino et al. 2014; Wirth et al. 2013b).

As discussed earlier in this review, the association between A β and cross-sectional ND is often inconsistent and likely obscured by additional non-A β factors in aging (Fjell et al. 2014; Jack et al. 2013b; Jagust 2013). Thus, the observation that A β +/ND+ CNs are most at

risk for decline is consistent with the existence of heterogeneity within A β + CNs by suggesting that two separate processes must converge to direct an individual towards AD. A number of possible mechanisms exist that may underlie a synergistic interaction between A β and ND. For instance, it is possible that ND renders neurons more susceptible to toxic effects of A β . Either process alone may be insufficient to alter cognition, but the “double hit” of both processes may promote decline by overwhelming compensatory processes. Given that neurofibrillary tangles (NFTs) have been shown to mediate toxic effects of A β (Ittner and Gotz 2011), increased risk in A β +/ND+ CNs may reflect the co-occurrence of A β and NFT pathologies (assuming that ND captures NFT pathology to some extent (Jagust et al. 2009; Whitwell et al. 2008)). Although A β and NFT pathologies occur on distinct time scales, the spread of NFTs from medial temporal lobe regions to neocortex may occur in conjunction with late life A β accumulation. Thus, late life A β may induce NFT spread, which in turn promotes toxicity and cognitive decline. Regardless of the mechanism underlying increased risk in A β +/ND+ CNs, factors that reduce the likelihood of ND may offer resilience to damaging effects of A β and enable these A β + CNs to remain clinically normal.

Genetic Factors Accelerate the Effect of A β

Genetic factors, such as polymorphisms for genes encoding the Apolipoprotein E (APOE) and brain-derived neurotrophic factor (BDNF) proteins, have also been shown to interact with A β to accelerate longitudinal changes. We recently showed an interaction between the *APOE4*+ genotype and A β status in predicting cognitive decline in a large group of 490 CNs, such that *APOE4*+/A β + CNs showed greater decline over a median follow up period of 1.5 years than all other CN groups (*APOE4*-/A β -, *APOE4*+/A β -, and *APOE4*+/A β +) (Mormino et al. 2014). Although the *APOE4* genotype is known to influence AD risk through increased A β accumulation (Kok et al. 2009; Reiman et al. 2009), this genotype also affects neuronal integrity through A β -independent mechanisms (via synaptogenesis, synaptic plasticity, tau phosphorylation, mito-chondrial activity, neuroinflammation, and neurodevelopment (Wolf et al. 2013)). These A β -independent mechanisms are consistent with human imaging studies that have revealed reduced glucose metabolism (Knopman et al. 2014; Reiman et al. 2004) and gray matter (Alexopoulos et al. 2011; Shaw et al. 2007) in *APOE4*+ CNs before the age at which A β accumulation occurs. Hypometabolism and reduced resting state connectivity have also been shown in older *APOE4*+ CNs lacking evidence of fibrillar A β accumulation (the mean age in the study by Jagust and Landau was 77 years whereas the mean age in the study by Sheline and colleagues was 62 years) (Jagust and Landau 2012; Sheline et al. 2010a). It is also possible that A β and *APOE4* in conjunction impart greater levels of neuronal toxicity, given that the apoE4 protein is less effective than apoE3/2 in responding to neuronal injury (Mahley and Huang 2012). Potential mechanisms by which *APOE4* status may influence the AD trajectory is depicted in Fig. 3.

Similar to the increased risk identified in *APOE4*+/A β + CNs, in a study of 165 CNs followed over 3 years, Yen et al. demonstrated that A β + CNs that also have the val⁶⁶met *BDNF* polymorphism show greater rates of hippocampal atrophy and cognitive decline (Lim et al. 2013b). 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 (Egan et al. 2003). Thus, *BDNF* genotype is another factor that may dictate an individual's ability to tolerate underlying levels of A β .

Sex Differences and Risk of AD

Given that AD is more common in women than men (Zhang et al. 1990), sex differences may also interact with A β to effect rates of atrophy and decline within CNs. Although the mechanism underling women's heightened AD risk is unknown, it may be influenced by factors such as estrogen related changes during menopause and/or increased inflammatory processes (Carter et al. 2012), either of which may make women more susceptible to toxic effects of A β . Although the potential interaction between sex and A β in influencing downstream AD changes is currently understudied among amyloid imaging studies, it has been shown that women's elevated AD risk is modified by both the presence of the *APOE4* allele and age (Duara et al. 1996; Farrer et al. 1997). Likewise, decreased resting state functional connectivity within *APOE4+* CNs is exacerbated in women CNs (Damoiseaux et al. 2012b). Given that the *APOE4* allele and age are both associated with higher levels of A β , it is possible that interactions between sex and either *APOE4* or age is mediated by elevated A β levels. Along these lines, Pike and colleagues demonstrated that only women A β + CNs showed lower scores on a composite measure of episodic memory (comprised of the delayed recall portions of the California Verbal Learning Test, the Rey Complex Figure Test, and the Logical Memory Test from the Wechsler Memory Scale), whereas an effect of A β on this composite memory score was not present within men (Pike et al. 2011). Another study found greater entorhinal cortex atrophy in women that was independent of both A β and *APOE4* status within CNs (Holland et al. 2013). Thus, brain changes related to sex differences in aging may make women more susceptible to AD in the presence of concurrent A β accumulation.

Reserve and Risk of AD

Within the reserve framework, an individual with higher reserve is able to remain clinically normal for longer than an individual with lower reserve despite equivalent levels of underlying pathology (Stern 2012). Individuals with high reserve are thought to have either greater quantities of neurons and synapses ("brain reserve"), and/or a better ability to employ alternative strategies or compensatory mechanisms ("cognitive reserve") than individuals with low reserve.

Although estimating reserve differs across studies, proxies such as education, occupation and engagement in cognitively stimulating activities have all been shown to decrease risk of AD (Stern et al. 1994; Verghese et al. 2003). Amyloid imaging studies investigating reserve within CNs have revealed stronger relationships in low reserve participants between A β status and memory (as measured with delayed recall from the Memory Capacity Test) (Rentz et al. 2010) as well as associations between reserve and a global measure of cognition above and beyond what is explained by A β status and markers of ND (Vemuri et al. 2012). The latter study by Vemuri and colleagues is consistent with a large postmortem study of non-demented individuals that found associations between past and current cognitive activity with retrospective global cognitive decline that was independent of multiple age-related pathologies (A β , but also neurofibrillary tangles, infarcts and Lewy

bodies; associations with cognitive activity were also seen with decline in episodic memory, semantic memory, working memory, and visuospatial memory when these cognitive domains were examined separately) (Wilson et al. 2013a). These studies suggest that high levels of reserve may exert protective effects by masking downstream cognitive decline related to A β . However, high levels of reserve have been shown to be associated with reduced levels of A β within CNs (Landau et al. 2012a), which is consistent with animal work showing increased clearance of A β in mice exposed to enriching environments (Costa et al. 2007). Thus, cognitive reserve may exert protective effects both through influencing quantities of pathology, and also by preventing decline related to pathology. Interestingly, individuals with high reserve show steeper rates of decline after AD diagnosis than AD individuals with low reserve (Teri et al. 1995), suggesting that once the protection inferred by reserve is surpassed, the extensive underlying pathology exerts a large effect.

Conclusion

Evidence across multiple laboratories suggests that accumulation of A β within CNs is consequential. Specifically, A β + CNs show alterations in functional brain measures, increased brain atrophy, as well as subtle reductions in cognition and increased risk of subsequent decline. Although inconsistencies exist across studies investigating the relevance of A β in aging, it is likely that A β -related effects are superimposed upon effects related to multiple other age-related processes, making A β -related effects difficult to isolate with CN cohorts. Furthermore, detrimental effects of A β may be dampened or exacerbated by additional factors, enabling some individuals to be resilient while other CNs show heightened vulnerability to this pathology. Thus, the relevance of A β within CNs is complex and involves multiple factors. To fully elucidate these complex relationships, it is essential to investigate large cohorts that are sufficiently powered to test interactions across multiple variables at once. An important remaining question pertains to the extent to which heterogeneity within A β + CNs exists. Specifically, it will be critical to establish the average time for an A β + CN to progress to AD, and how much variance exists around this estimate. Do some A β + CNs progress within 5 years while others progress in 25 years? If so, what factors influence this variability? As we increase our understanding of these complexities, we can build multivariate models that combine A β status with additional relevant factors to derive individualized risk estimates (similar to approaches that have been used to determine individualized breast cancer risk (Amir et al. 2010)). Overall, the complex interactions between A β and additional risk factors will help elucidate the relevance of A β to the aging brain and inform strategies geared towards AD prevention.

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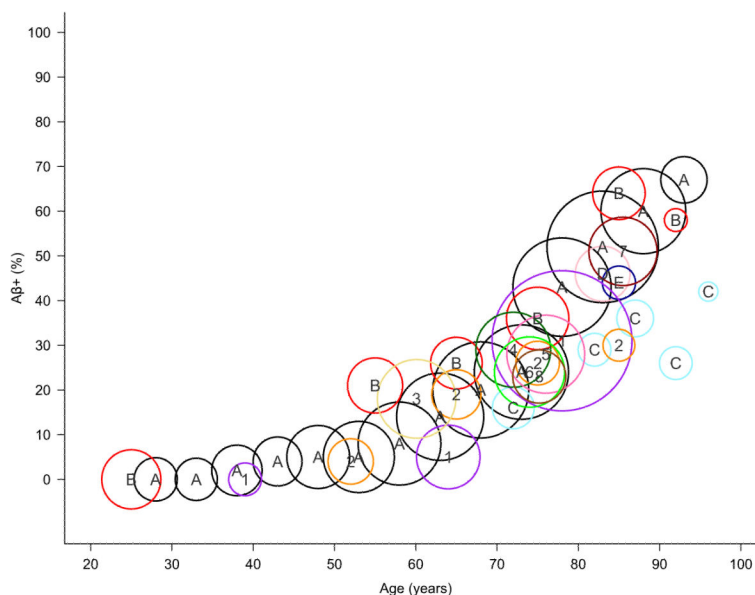


Fig. 1.

Prevalence of A β + CNs across the lifespan. Data across multiple studies are plotted by sample age and percent classified as A β + (a total of 3512 subjects from post-mortem studies and 2034 from amyloid-imaging studies are represented). The area of each bubble is scaled by group size, ranging from 12 to 639 CNs (for studies reporting A β + prevalence across multiple age groups, multiple bubbles are used). Although A β + classification is study specific, a consistent pattern emerges. These studies reveal a low proportion of A β + CNs younger than 60, followed by a linear increase in the proportion of A β + CNs after age 60 (~30 % of CNs are A β + at age 75). Post-mortem studies and A β + classification are as follows: *A/black* = Braak & Braak (CERAD B & C, $N=2661$) (Braak and Braak 1997); *B/red* = Kok et al. (CERAD moderate and frequent, $N=534$) (Kok et al. 2009); *C/light blue* = Savva et al. (CERAD moderate and severe, $N=183$) (Savva et al. 2009); *D/pink* = Bennett et al., Religious Orders Study (CERAD probable and definite, $N=98$) (Bennett et al. 2006); *E/dark blue* = Bennett et al., Memory and Aging Project (CERAD probable and definite, $N=36$) (Bennett et al. 2006). Amyloid PET studies and A β + classification are as follows: *1/purple* = Knopman et al. (>1.5 PIB SUVR with *gray* matter cerebellum, $N=806$) (Knopman et al. 2014); *2/orange* = Morris et al. (>0.18 PIB Binding Potential with *gray* matter cerebellum, $N=241$) (Morris et al. 2010); *3/yellow* = Johnson et al. 2014 (florbetapir qualitative read; $N=201$) (Johnson et al. 2014), *4/dark green* = Rowe et al. (>1.5 PIB SUVR with *gray* matter cerebellum, $N=183$) (Rowe et al. 2013), *5/hot pink* = Mormino et al. 2014, Alzheimer's Disease Neuroimaging Initiative Phase 2 study (>1.126 florbetapir SUVR *gray* and *white* matter cerebellum, $N = 198$) (Mormino et al. 2014), *6/green* = Mormino et al. 2014, Harvard Aging Brain Study (>1.196 PIB SUVR *gray* and *white* matter cerebellum, $N=161$) (Mormino et al. 2014); *7/dark red* = Mathis et al. 2013 (>1.57 PIB SUVR *gray* matter cerebellum, $N=152$) (Mathis et al. 2013); *8/brown* = Wirth et al. 2014 (>1.12 PIB DVR *gray* matter cerebellum, $N=92$) (Wirth et al. 2014)

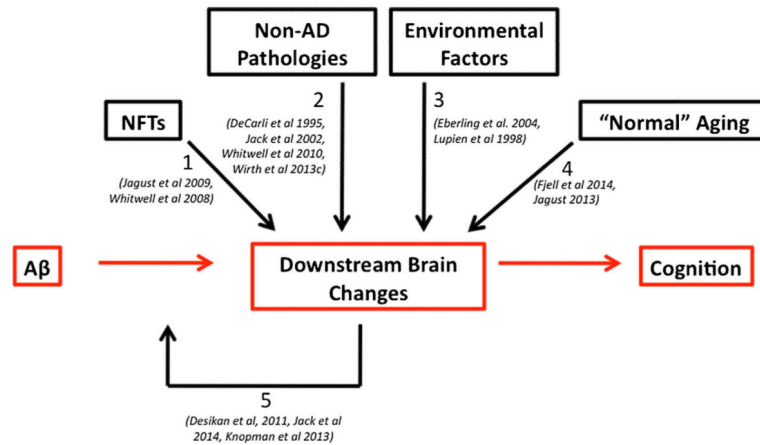


Fig. 2.

Multiple factors contribute to "downstream" brain changes in the trajectory towards Alzheimer's disease. Although many models of AD suggest that A β is an initiating event in a cascade that triggers downstream brain changes and cognitive decline (as depicted by the red boxes and arrows), emerging evidence suggests that multiple non-A β factors influence these downstream brain changes. These additional factors include non-A β pathologies (*arrows 1 & 2*), environmental factors such as stress and estrogen replacement therapy (*arrow 3*) as well as "normal" aging processes (*arrow 4*). Regardless of which factors contribute to downstream brain changes, the convergence of these changes with A β accumulation has been shown to accelerate further downstream changes (*arrow 5*)

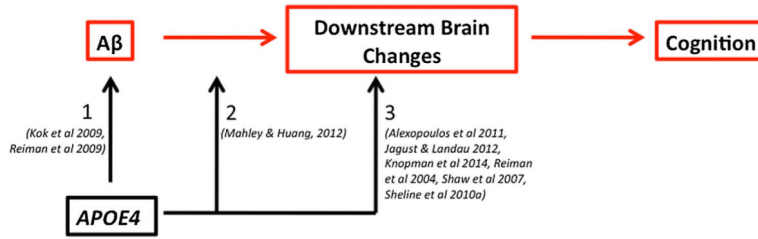


Fig. 3. Influence of *APOE4* status on the trajectory towards Alzheimer’s disease. The presence of the *APOE4* allele may affect an individual’s risk of AD through multiple mechanisms. Specifically, the *APOE4*+ genotype is consistently associated with greater levels of A β accumulation (*arrow 1*), suggesting that this genotype increases the chance of an individual becoming A β + and entering the AD trajectory. However, there is also evidence that *APOE4* interacts with A β status to impart greater synaptic damage when these events co-occur (*arrow 2*). Finally, the *APOE4* allele may exert detrimental effects by directly affecting downstream brain changes in the absence of A β (*arrow 3*), making the individual more susceptible to AD in late life when additionally confronted with elevated A β