Published in final edited form as:
Neuron. 2014 November 5; 84(3): 608–622. doi:10.1016/j.neuron.2014.10.038.

The evolution of preclinical Alzheimer's disease: Implications for prevention trials

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Abstract

As the field begins to test the concept of preclinical neurodegenerative disease, the hypothetical stage of disease when the pathophysiological process has begun in the brain but clinical symptoms are not yet manifest, a number of intriguing questions have already arisen. In particular, in preclinical Alzheimer's disease (AD), the temporal relationship of amyloid markers to markers of neurodegeneration and their relative utility in the prediction of cognitive decline among clinically normal older individuals remains to be fully elucidated. Secondary prevention trials in AD have already begun in both genetic-at-risk and amyloid-at-risk cohorts, with several more trials in the planning stages, that should provide critical answers about whether intervention at this very early stage of disease can truly bend the curve of clinical progression.

Introduction

The challenge in effectively treating neurodegenerative disease, and yet perhaps the greatest promise, lies in the reality that the pathophysiological process begins well more than a decade prior to the stage of clinically detectable symptoms. Recent reports from autosomal dominant forms of Alzheimer's disease (AD) suggest that amyloid-β (Aβ) accumulation may be evident 20 years before the stage of dementia, and that there is already substantial neuronal loss by the stage of mild cognitive impairment (MCI). Indeed, this long, inexorable progression of neurodegeneration, that is well entrenched by the stage of symptomatic disease, may account, at least partially, for our failure to develop successful disease-modifying therapies (Sperling et al., 2011b). The vast majority of potential disease-modifying interventions have been tested in cohorts with clinically manifest neurological illness, when there is already substantial synaptic and neuronal damage. It is likely, as in the other fields of medicine for which we have made significant inroads, in particular, cancer, cardiovascular disease, stroke, HIV/AIDS, and diabetes, that we would have a greater chance for success targeting much earlier intervention in neurodegenerative diseases. Fortunately, recent advances in molecular neuroimaging, cerebrospinal fluid assays, and other imaging and biofluid markers have greatly facilitated our ability to detect evidence of neurodegenerative pathology *in vivo*, particularly in very early AD. The critical next steps will require us to elucidate the definitive links between the biomarkers of the hallmark pathologies of AD and the earliest clinical manifestations with carefully designed natural history, observational cohort studies, and ultimately with successful early intervention trials at the preclinical stages of AD.

Convergent findings from rare autosomal dominant causative mutation carriers, non-deterministic genetic-at-risk populations, and age-at-risk cohorts indicate that the pathophysiological process of AD is detectable with cerebrospinal fluid and imaging markers many years prior to the stage of dementia (Bateman et al., 2012; Knopman et al., 2012; Mormino et al., 2014b; Reiman et al., 2012; Villemagne et al., 2013; Vos et al., 2013), and the field is active with research studies aiming to improve the accuracy of prediction of cognitive decline in at-risk individuals.

Reports from autopsy cohorts, CSF and other PET amyloid imaging studies suggest that at least 1/3 of clinically normal (CN) older individuals have evidence of substantial Aβ accumulation (see Figure 1), one of the hallmark pathologies of AD (Arriagada et al., 1992b; Bennett et al., 2006; De Meyer et al., 2010; Fagan et al., 2009; Gomperts et al., 2008; Hampel, 2013; Jack et al., 2008; Jack et al., 2014; Kantarci et al., 2012; Mintun et al., 2006; Montine, 2011; Morris et al., 1996; Rowe et al., 2010; van Harten et al., 2013; Villemagne et al., 2013). It remains unknown whether the majority of CN with evidence of cerebral amyloidosis will in fact progress to the symptomatic stages of AD and over what time frame; however, the accumulating longitudinal data suggest that many of these individuals are indeed in the “preclinical stages of AD (Sperling et al., 2011a). Recent studies suggest that older individuals designated as Aβ+ are at increased risk for cognitive decline (Lim et al., 2014b; Lim et al., 2014c; Mormino et al., 2014a) and progression towards the symptomatic AD phenotype (Knopman et al., 2012; Vos et al., 2013). The challenge is that Aβ is only one piece of the puzzle, and recent findings continue to support the hypothesis that evidence of Aβ is necessary, but not sufficient in isolation, to predict imminent decline along the AD trajectory. Thus, we must continue our efforts to characterize the biomarkers or likely the combinations of biomarkers that will more accurately predict the emergence of clinical symptoms and the rate of subsequent decline at the individual level. This information is particularly important for AD prevention clinical trial design, and for future translation to clinical practice. This review will highlight recent progress in the field of preclinical AD, and the remaining gaps in knowledge.

The amyloid debate

The predominant model of preclinical AD that has emerged from laboratory studies and longitudinal clinical investigation places Aβ peptide accumulation as a key early event in the pathophysiological process of AD, but this remains controversial. All of the known autosomal dominant, early onset forms of AD are thought to result from alterations in amyloid-precursor protein (*APP*) production or cleavage (*PSEN-1 and PSEN-2*). Similarly, trisomy-21 invariably results in AD pathology in individuals who have three intact copies of the APP coding region located on chromosome 21, and leads to AD dementia in the majority of those who live beyond age 60. In addition apolipoprotein E (*APOE)*, the major genetic risk factor for late onset AD, has been implicated in amyloid trafficking and plaque clearance.

Imaging studies in autosomal dominant AD have documented early accumulation of Aβ on PET scans beginning approximately 15-20 years prior to the average age of symptom onset in these families (Benzinger et al., 2013; Fleisher et al., 2012). Interestingly, however, there

is some evidence of early synaptic change, prior to crossing a biomarker threshold of Aβ deposition in autosomal dominant mutation carriers (Reiman et al., 2012) and APOE ε4 carriers (Filippini et al., 2009) that may reflect toxicity of Aβ oligmeric forms. PET measurements in these high genetic-risk individuals may underestimate the accumulation of diffuse plaques, and CSF measurements indicate an early rise in $A\beta_{1-42}$ levels in very young carriers that may have biological consequences in terms of synaptic function (Reiman et al., 2012). It is also possible that synaptic, mitochondrial, metabolic, or neuronal cytoskeletal alterations play an important role, in the pathogenesis of AD even in these autosomal dominant cases where Aβ peptides are overproduced since birth.

A particularly compelling finding in support of the amyloid hypothesis in late onset AD is the recent identification of a protective gene mutation (Jonsson et al., 2012). A coding mutation (A673T) adjacent to the aspartyl protease beta-site in the APP gene, which is estimated to result in approximately 40% reduction in $A\beta_{1-42}$ formation of Aβ *in vitro*, was found to be associated with a marked reduction in the prevalence of AD in several large cohorts. Interestingly, this mutation was also found to be protective against cognitive decline in CN, which also supports the hypothesis that Aβ may influence cognitive decline in the preclinical stages of AD.

Recent evidence similarly suggests that aberrant clearance of $A\beta_{42}$ may be a key etiologic event in sporadic, late-onset AD (Mawuenyega et al.). However, some researchers believe that sequestration of Aβ into fibrillar forms might serve as a protective mechanism (Lee et al., 2004; Shankar et al., 2008). Both autopsy and biomarker studies (see below), however, suggest that markers of $A\beta_{42}$ accumulation increase with advanced aging, the greatest risk factor for developing AD, are often associated with other “AD-like markers of neurodegeneration, and increased risk of progression to AD dementia. It is also clear that synaptic depletion, intracellular hyperphosphorylated forms of tau and neuronal loss invariably occur in AD, and that at autopsy, these markers appear to correlate better than plaque counts or total Aβ load with clinical impairment. Although there is increasing evidence that markers of “upstream Aβ accumulation are associated with markers of “downstream pathologic change, including abnormal tau, neural dysfunction, glial activation, and neuronal loss and atrophy, it remains to be proven in sporadic, late-onset AD that Aβ accumulation is sufficient to incite the downstream pathological cascade of AD, and to ultimately result in cognitive impairment and dementia.

Staging of preclinical Alzheimer’s disease

The National Institute on Aging–Alzheimer’s Association (NIA-AA) Preclinical Workgroup developed research criteria to aid in the study of preclinical AD (Sperling et al., 2011a). The NIA-AA workgroup proposed a hypothetical staging framework specifically to categorize clinically normal (CN) individuals thought to be on the trajectory towards the symptomatic stages of AD. These stages are applicable to both genetic at-risk and age at-risk cohorts, and are based primarily on biomarker status from the Jack et al. model (Jack et al., 2010) utilizing fluid and imaging markers of amyloid-β (Aβ) accumulation and markers of neurodegeneration (ND), including CSF tau, FDG hypometabolism, and volumetric MRI metrics of atrophy. The NIA-AA Stage 1 can be operationalized as Aβ+/ND−; Stage 2 as Aβ

+/ND+; and Stage 3 as Aβ+/ND+ with evidence of subtle cognitive and behavioral decline not yet sufficient to meet criteria for mild cognitive impairment (MCI; see Figure 2).

Since the publication of the NIA-AA Preclinical Workgroup staging schema, several amendments and additions to the proposed classifications have been suggested (Chetelat, 2013; Dubois et al., 2014; Jack et al., 2012). A "Stage 0 group, comprised of individuals who have no evidence of abnormal biomarkers (Aβ−/ND−), was formally delineated as a control group, assuming that they are unlikely to be on the AD trajectory. Perhaps the most important concept to be considered is "Suspected Non-Alzheimer Pathology (SNAP) suggested by the Mayo Clinic (Jack et al., 2012). The SNAP category encompasses individuals with biomarker or imaging evidence of neurodegeneration without exceeding the biomarker cut point for amyloidosis, and includes up to a quarter of the older individuals in clinically normal cohorts (Jack et al., 2012; Mormino et al., 2014a). As would be predicted on the basis of selection on the basis of lower Aβ deposition, the SNAP groups tend to have a lower proportion of APOE ε4 carriers (Jack et al., 2012; Mormino et al., 2014a). Interestingly, individuals classified as SNAP tend to be older, and there is also a higher proportion of males in the SNAP groups (Jack et al., 2012; Mormino et al., 2014a), perhaps indicating the higher rates of vascular co-morbidity among males.

It should be noted that the definitions of + versus − are typically based on somewhat artificial cut points in continuously distributed data (particularly for ND markers), which may have important consequences. Some data types (e.g., amyloid PET) are noisier, due largely to spatial resolution limitations, and thus may be less sensitive to subtle changes than other imaging techniques (e.g., volumetrics); thus, the error associated with the cut point differs according to data type, and the biomarker readouts (+ or −) do not in this respect have the same meaning for all biomarkers. Moreover, the defining cut points are to some extent arbitrarily designated, and may be dependent on the specific attributes of comparison group utilized to define thresholds. Finally, the ND biomarker group includes individual biomarker types that differ from each other both theoretically and empirically (see discussion below).

Nevertheless, the proportions of CN classified across these preclinical stages, utilizing operationalized cutpoints, are remarkably similar across older cohorts, with approximately 40-50% classified as Stage 0; 10-15% as Stage 1; 15% as Stage 2 (Aβ+/ND+); and approximately 25% as SNAP (Aβ−/ND+) (Jack et al., 2012; Mormino et al., 2014a; Vos et al., 2013; Wirth et al., 2013b). These findings do indicate that a non-negligible proportion of CN have biomarker evidence of ND in the apparent absence of elevated Aβ accumulation. It is possible, that SNAP does include some individuals with sub-threshold levels on Aβ markers who are early in the process of rapid accumulation, however, recent work suggests that SNAP individuals are not more likely over short intervals to subsequently accumulate Aβ, whereas Aβ+ individuals are more likely to develop subsequent increases in ND markers (Jack et al., 2014; Knopman et al., 2013).

The question as to whether SNAP individuals manifest cognitive decline at the same rate as individuals in Stage 1 or Stage 2 Preclinical remains a matter of debate. Several recent reports have suggested that SNAP (Aβ−/ND+) individuals show a greater rate of decline

than Stage 0 (Aβ−/ND−), a slightly lower rate than Stage 1 (Aβ+/ND−), and a significantly lower rate of decline than Stage 2/3 (Aβ+/ND+) (Mormino et al., 2014a; Vos et al., 2013). A subset of SNAP individuals may also be in the preclinical stages of non-AD neurodegenerative diseases. Additional large observational studies that include longitudinal markers of both Aβ and ND (ideally with more specific markers of AD-related neurodegeneration) with longer term clinical follow-up will be required to fully elucidate the temporal ordering relative contribution of these markers in predicting progression to MCI and dementia due to AD.

Relationship between markers of amyloid and neurodegeneration

Given that ND can exist in the apparent absence of elevated Aβ as highlighted by the SNAP group, it is not surprising that the results from cross-sectional studies examining the association between Aβ and ND are somewhat variable and challenging to interpret. We recently reported that Aβ+ CN were three times more likely to be classified as ND+ than Aβ − CN (Mormino et al., 2014a), which is consistent with previous work showing a similar relationship (Becker et al., 2011; Dickerson et al., 2008; Rowe et al., 2010; Storandt et al., 2009). However, other studies have not found a cross-sectional relationship between Aβ and ND (Chetelat et al., 2010; Wirth et al., 2013a). These inconsistencies may stem from differences related to cohort size and characteristics, as well as the examined measure of ND. The association between Aβ and ND is further complicated by the observation that commonly employed markers of ND are not necessarily consistent with one another (Toledo et al., 2014), and that the association between ND and Aβ status within CNs may vary depending on which measure is examined (Whitwell et al., 2013). Thus, the association between markers of Aβ and markers of ND within CN cohorts is likely subtle and influenced by methodological approaches.

Although many models suggest that neurodegenerative biology occurs downstream from Aβ dysmetabolism (Hardy and Selkoe, 2002; Jack et al., 2013a), other work suggest that pathways promoting amyloidosis and neurodegeneration might arise independently (Jack et al., 2013b; Wirth et al., 2013a). These models are not mutually exclusive, that is, Aβ and ND may initially appear to begin via separate pathways, but at some point would demonstrate an increasing biomarker association if Aβ exacerbates underlying ND (or vice versa). Longitudinal studies relating baseline levels of Aβ to change in ND biomarker over time within CNs support this claim, given that most longitudinal studies that have examined this association have revealed increased ND over time in Aβ+ CNs (Chetelat et al., 2012; Dore et al., 2013; Knopman et al., 2013; Nosheny et al., 2014; Schott et al., 2010; Storandt et al., 2009). However, there is some debate as to whether Aβ accumulation is specifically associated with atrophy of medial temporal lobe structures (Fjell et al., 2014), which may reflect the relative influence of tau rather than Aβ accumulation in this region (see below). Given the prolonged period of Aβ accumulation during preclinical AD (Villemagne et al., 2013), it is possible that different brain regions show varying degrees of vulnerability throughout the prolonged period at which Aβ accumulation occurs within CN (Mattsson et al., 2014). Finally, multiple studies have revealed that longitudinal ND is greatest in CN who have evidence of both Aβ accumulation and ND at baseline (Desikan et al., 2011; Jack et al., 2014; Knopman et al., 2013), which may be consistent with a model in which Aβ and

ND initially are observed independently, but converge to accelerate further ND. However, it is also possible that ND is a marker of how long Aβ pathology has been present within Aβ+ CNs (ie. Aβ+/ND+ CNs may be further along the AD trajectory than Aβ+/ND− CNs). In addition to promoting subsequent ND, CN that are positive for both Aβ and ND are also more likely to progress to MCI (Knopman et al., 2012; Rowe et al., 2013) from Clinical Dementia Rating (CDR) 0 to 0.5 (Desikan et al., 2012; Vos et al., 2013), as well as show cognitive decline over time (Mormino et al., 2014a; Wirth et al., 2013b). Overall, studies examining the associations between Aβ and ND suggest that ND is exacerbated after the convergence of Aβ and ND pathways, and that this convergence is consequential to behavioral outcomes.

If baseline levels of ND are not exclusively associated with Aβ accumulation within older CN, what additional factors influence biomarker readouts of ND in CNs? Recent work directly investigating characteristics of SNAP (Aβ− and ND+) have found associations with markers of cerebrovascular disease (Wirth et al., 2013b) as well as a greater proportion of men (Mormino et al., 2014a). Non-AD pathologies are also likely contributors to ND within CNs. For instance, Bennett and colleagues (Bennett et al., 2006) have found that among community dwelling CN, 21.6% show infarcts, 13.4% have Lewy bodies and approximately 5% have hippocampal sclerosis at postmortem examination. TDP-43 pathology, which is associated with frontotemporal dementia, is also prevalent in older CN (Geser et al., 2010). The relevance of TDP-43 in aging was recently highlighted in a study by Wilson and colleagues (Wilson et al., 2013b). This study followed 130 individuals that were non-demented at baseline for an average of 10 years before death and found that nearly half showed some degree of TDP-43 pathology at postmortem examination. TDP-43 pathology was most common in the medial temporal lobe, suggesting that this pathology may contribute to ND in regions typically associated with AD. Furthermore, TDP-43 pathology uniquely explained a substantial portion of cognitive decline (12%, after accounting for age and NFTs), which is on par with the amount of decline uniquely explained by NFTs. Thus, TDP-43 pathology is an important contributor of decline in aging, and may contribute to ND in regions typically associated with AD. In addition to non-AD pathologies (Jack et al., 2002), hippocampal volume has also been associated with inflammation (Marsland et al., 2008), stress (Lupien et al., 1998), and estrogen replacement therapy (Eberling et al., 2004). Individuals in their 80’s have likely accumulated many more co-morbidities than those in their 60’s, and thus are more likely to demonstrate ND markers due to other etiologies, but may also be more vulnerable to developing cognitive decline in the setting of even low levels of Aβ accumulation.

It is also possible that “normal aging processes, such as synaptic alterations (Morrison and Hof, 1997), contribute to markers of ND. Along these lines, gradual and consistent associations between chronological age and gray matter (Raz et al., 2004; Sowell et al., 2003) as well as glucose metabolism (Knopman et al., 2014) are present throughout the lifespan (occurring before the age at which levels of Aβ are clearly elevated). Given that the majority of CNs above age 60 will have some degree of medial temporal lobe neurofibrillary tangle (NFT) pathology (Nelson et al., 2012), it is possible that tau pathology contributes to variance in FDG metabolism and brain volumetry (Jagust et al., 2009; Whitwell et al., 2008) (see discussion below). Finally, it is also possible that variance in markers of ND partially

reflect developmental differences and early life brain reserve factors. Given the relatively large amount of variance that is present in markers of ND within young CN, it is possible that older CN with neuroimaging evidence of ND actually had smaller hippocampi and/or reduced glucose metabolism even in early mid-life. Thus, the increased risk of cognitive decline among older CN with both Aβ and ND markers could also reflect evidence that some individuals with lower reserve might be more vulnerable to Aβ toxicity.

The promise of Tau PET imaging

Given that our current markers of ND reflect multiple sources of variance and do not provide primary evidence of AD-related neurodegeneration, it may be useful to track the other hallmark pathology of AD: tau neurofibrillary tangles (NFT). Neuropathologic studies have long suggested that tau pathology correlates more strongly with synaptic and neuronal loss, as well as with the cognitive symptoms of AD (Arriagada et al., 1992a; Gomez-Isla et al., 1997). The application of tau-sensitive biomarker technology would therefore seem to be a potentially useful addition to preclinical AD trial designs. Existing CSF tau measures have been quite valuable in the prediction of cognitive decline among Aβ+ CN (Desikan et al., 2012; Fagan et al., 2007), and increases in CSF tau do correlate with Tau pathologic burden at post-mortem overall (Tapiola et al., 2009); however, some commonly measured Tau isoforms in CSF were not correlated with brain NFT pathology at postmortem (Buerger et al., 2007). It is possible that CSF tau measures may not have sufficient dynamic range to track progression through the spreading of NFT pathology associated with increasing cognitive impairment. The emergence of Tau PET as an AD biomarker should permit exploration of these issues and may prove to be a valuable addition to the biomarker armamentarium.

Brain Tau pathology in aging and typical AD accumulates and spreads anatomically in an orderly fashion that is frequently denoted with the ordinal staging scheme proposed by Braak and colleagues (Braak et al., 2006). The earliest of these stages (Braak Stages I–II) occurs in ~80% of all individuals by age 60 (Nelson et al., 2012). This early, medial temporal lobe (MTL) distribution of Tau likely precedes the emergence of fibrillar brain Aβ burden, and is followed in those individuals who are on the pathologic trajectory of AD, by propagation that extends the distribution of Tau pathology to limbic and neighboring temporal *neocortex* (Braak III–IV and higher) and is thought to mark the transition from asymptomatic to symptomatic pathology (Hyman et al., 2012; Nelson et al., 2012; Price and Morris, 1999). Until very recently, this critical spread and intensification of Tau pathology has been invisible to all but the neuropathologist.

Remarkable recent advances in PET imaging now allow us to image Tau pathology *in vivo* (Chien et al., 2013; Maruyama et al., 2013; Zhang et al., 2012). These Tau PET ligands are thought to selectively bind to tau and not to Aβ lesions. Although active research to fully validate these Tau PET tracers against histopathology is ongoing, the selectivity of at least one of the compounds (^{18}F-T807) for Tau over Aβ was estimated to be approximately >27 fold as measured by an autoradiographic comparison of human cortical brain sections (Xia et al., 2013).

Preliminary experience with Tau PET data with ^{18}F-T807 (see Figure 3) and other Tau tracers suggest this new technology may prove extremely valuable in the quest to elucidate the link between Aβ, Tau, and cognitive decline. Our preliminary T807 data are consistent with previous autopsy reports that medial temporal lobe Tau accumulation is very common after age 60, but it remains unknown how this pathology contributes to age-related memory change, at any level of Aβ. Despite the remarkable advances in biomarkers and cognitive research over the past decade, it remains challenging to disambiguate the trajectory of cognitive aging from the preclinical stages of Alzheimer's disease. There is continued debate in the field as to whether AD might represent an accelerated form of brain aging. This is not to say that AD should be considered normal in any way; AD is a devastating illness that should be aggressively treated, and ultimately, prevented outright. But if tau accumulation in the MTL is indeed present in nearly all individuals over the age of 60 (Nelson et al., 2012), then the distinction between the process of brain aging and at least one of the hallmark pathologies of AD may be somewhat blurred. If tau accumulation in the entorhinal cortex is associated with worse memory performance, even in the absence of supra-threshold levels of Aβ accumulation, then should this be considered part of normal aging or one of the earliest "hits in the AD pathophysiological process?

In patients with mild cognitive impairment and mild dementia due to AD with extensive Aβ deposition, our preliminary experience indicates Tau PET binding that is evident in the neocortex, particularly in the inferior temporal cortices, lateral and medial parietal cortices (see Figure 3). The biology underlying evolution of tau pathology is not completely understood, but recent work in transgenic animals suggests that tau may propagate transynaptically (de Calignon et al., 2012; Liu et al., 2012), and that the widespread cortical pattern of tau spreading may be influenced by connectivity (Ahmed et al., 2014). However, there is also evidence of Tau spreading via diffusion to more proximal locations, such as the adjacent inferior temporal cortices, as described by Braak (Braak et al., 2006). Based on our early preliminary work in Tau imaging, evidence from laboratory studies (Choi et al., 2014; Oddo et al., 2006) and previous autopsy studies (Delacourte et al., 2002; Duyckaerts and Hauw, 1997; Price and Morris, 1999), it is likely that Aβ accelerates the spread of Tau both within and beyond the MTL, disrupting function and initiating neurodegeneration in distributed brain networks, resulting in cognitive decline. This hypothetical model (see Figure 4) remains to be tested with longitudinal Aβ and Tau PET imaging in cohorts of clinically normal and very mildly impaired older individuals, and perhaps most importantly, in clinical trials with anti-Aβ therapeutic agents.

Markers of Preclinical AD, memory activity, and network dysfunction

An active line of research is the relationship of *intrinsic neural networks* and the "topographic evolution of the pathophysiological process of AD. It is possible, just as in real estate, that "location, location, location is key. The topography has been underutilized thus far in characterizing the dynamic temporal course of biomarker change (Jack et al., 2013a). Using PET molecular imaging, we now have the unprecedented opportunity to investigate the relationship of Aβ and Tau *in vivo* to the progressive disruption of functional and structural brain networks observed over the course of AD (Chhatwal et al., 2013; Chhatwal

and Sperling, 2012; Greicius et al., 2004; He et al., 2009; Hedden et al., 2009; Myers et al., 2014; Petrella et al., 2011; Sorg et al., 2007).

One of the intriguing early findings was the observation that Aβ preferentially accumulates in brain regions that overlap the topology of specific brain networks, primarily the default mode network (Buckner et al., 2005). Subsequently it has been noted that Aβ deposition occurs in multiple regions of high connectivity, designated as “cortical hubs”, that include all of the nodes of the default network but also key nodes in other intrinsic networks (Buckner et al., 2009). Using a variety of paradigms with task fMRI, older individuals with evidence of amyloid accumulation on PET imaging have demonstrated impaired ability to modulate activity in the default mode network (Kennedy et al., 2012; Rami et al., 2012; Sperling et al., 2009), similar to earlier reports in AD dementia (Lustig et al., 2003). In particular, the failure to deactivate the posterior cingulate/precuneus regions during episodic memory encoding tasks has been associated with elevated Aβ accumulation in these regions. Interestingly, a very similar pattern of disrupted posterior cingulate/precuneus activity during memory encoding has been reported in presymptomatic presenilin 1 carriers (Reiman et al., 2012) and APOE ε4 carriers (Fleisher et al., 2009; Pihlajamaki et al., 2010) suggesting that failure to modulate activity in the posteromedial cortices may be an early indicator of synaptic dysfunction that underlies impending memory impairment in very early AD.

Aβ accumulation has been less consistently associated with alterations in MTL function, at least among clinically normal older individuals. Our early cross-modality imaging work suggested that alterations in hippocampal function, manifesting as hippocampal hyperactivity, became evident at the point of the earliest clinical symptoms, perhaps at the stage of early mild cognitive impairment (MCI) (Sperling et al., 2009). Interestingly, however, hippocampal hyperactivity has been reported in asymptomatic carriers of autosomal dominant mutations (Quiroz et al., 2010; Reiman et al., 2012) and younger APOE ε4 carriers (Filippini et al., 2009) suggesting that hippocampal hyperactivity might occur earlier in the setting of virulent Aβ pathology. More recently, we reported evidence of Aβ associated disruptions in entorhinal activity (Huijbers et al., 2014), specifically failure to deactivate the entorhinal cortices, similar to the reports in the neocortical regions of the default network. Of note, the early Aβ associated disruptions in task-related activity, whether in default network regions that typically deactivate during memory encoding, or in “task-positive regions that typically activate during memory processes, tend to manifest as relative increases in activity (Sperling et al., 2010). This finding is consistent with the hypothesis that Aβ might accelerate excitotoxicity through excessive or aberrant neuronal firing (Palop and Mucke, 2010). It is also possible that the increased activity may represent evidence of attempted compensation, at least early in the pathophysiological process (Elman et al., 2014). Unfortunately, hippocampal hyperactivity may also be an indicator of network degeneration (Putcha et al., 2011) and subsequent cognitive decline (O’Brien et al., 2010).

Perhaps most intriguing is the possibility that Aβ could set up a perpetuating cycle by increasing neural activity, which in turn might increase Aβ production (Cirrito et al., 2005; Jagust and Mormino, 2011). It is also conceivable that early Tau accumulation in the medial temporal lobe might be associated with transient increases in MTL neural activity, which

could in turn increase Aβ production and result in deposition in the neocortical terminal fields of these neurons.

Similarly, there have been multiple reports of Aβ-related disruptions in resting state or task-free functional connectivity MRI, and the default network appears to be particularly vulnerable to amyloid-related alterations. The majority of these studies have reported decreases in default network activity associated with Aβ deposition (Brier et al., 2014a; Brier et al., 2014b; Hedden et al., 2009; Sheline et al., 2009; Wang et al., 2013). A similar pattern of default network disruption has also been reported in carriers of autosomal dominant genetic mutations (Chhatwal et al., 2013; Thomas et al., 2014). Interestingly, there have also been reports of increased connectivity associated with Aβ in clinically normal older individuals in the default network (Lim et al., 2014a), in prefrontal regions that comprise subcomponents of the DMN (Mormino et al., 2011) and in the salience network of APOE ε4 carriers (Machulda et al., 2011). Intriguingly, there is one report of increased default network connectivity associated with an increase in Aβ burden on longitudinal PET imaging (Jack et al., 2013b), again suggesting that there might be a complex interplay between network activity and Aβ pathology. Task-free functional connectivity MRI is already being implemented in several large-scale, secondary prevention AD trials (see below), as these relatively short MR sequences can be acquired on most scanners during safety MRI sessions. It should be noted, however, that all functional MRI techniques are still fraught with sources of variability, such as head movement, physiological noise, and analytic approaches, that may limit the utility of these techniques in longitudinal studies, and additional work is needed to optimize these methodologies.

In summary, it is striking that early Aβ deposition occurs in a stereotypic set of heteromodal cortical regions, largely overlapping the neocortical regions of the default network that are among the strongest “connection hubs”, whereas Tau accumulation begins in deep grey matter structures, prominently in the transentorhinal cortex and related structures in the MTL that are functionally connected to the default network (Celone et al., 2006). It is of particular interest that the two hallmark pathologies of AD seem to begin to accumulate at the opposite ends of the distributed brain networks supporting memory function, and progressively spread to eventually overlap as the disease progresses. Ongoing studies, combining functional MRI with both Aβ and Tau PET imaging should provide insights into the “chicken vs. egg questions regarding neural activity, network disruption, and the molecular pathology of preclinical AD.

Earliest cognitive changes

One of the most pressing questions remains the cognitive correlates of Aβ, and now Tau, accumulation among clinically normal older individuals. The early literature with cross-sectional Aβ PET data was quite mixed, with some studies reporting subtle associations between amyloid burden and neuropsychological tests (Rentz et al., 2010) and other studies reporting no difference in cognitive performance between older individuals with and without amyloid, particularly when using standard neuropsychological tests used to detect evidence of dementia (Aizenstein et al., 2008). Perhaps this should not be surprising as by definition, selecting a cognitively normal population substantially truncates the variance in test

performance. As the field has matured with large sample sizes, there have been increasing reports of significant amyloid-associated deficits in cognitive performance, even amongst the limited range observed in clinically normal older individuals (Li et al., 2014; Lim et al., 2012 [Epub ahead of print]; Sperling et al., 2013) but the cross-sectional effects remain relatively subtle. The most convincing findings, however, stem from Aβ associated decline in longitudinal studies cognition among those who were CN at baseline (Donohue et al., 2014; Doraiswamy et al., 2012; Doraiswamy et al., 2014; Kawas et al., 2013; Lim et al., 2014b; Lim et al., 2012; Mormino et al., 2014a; Mormino et al., 2014b; Resnick et al., 2010; Storandt et al., 2009). The majority of these studies have indicated that episodic memory shows the greatest vulnerability to Aβ-associated cognitive decline, but other domains of cognition including working memory and executive function have also demonstrated Aβ-associated change (Rodrigue et al., 2012). As discussed above, however, it is likely that CN with markers of Aβ in combination with markers of neurodegeneration drive the majority of this decline. In addition, several reports have suggested that Aβ-related cognitive deficits may be accelerated in the presence of one or more APOE ε4 alleles (Kantarci et al., 2012; Mormino et al., 2014b) and other genetic variants, including BDNF (Lim et al., 2013), suggesting that there may be important interactions between Aβ accumulation and genetic background in risk of cognitive decline. More sensitive cognitive and behavioral measures are currently under development in many of these longitudinal cohorts. Recent work with challenging associative memory measures (Rentz et al., 2011) and iPad computerized testing (Rentz et al., 2013) may yield useful measures that will improve our ability to track the earliest clinical changes that appear to begin years prior to the stage of mild cognitive impairment.

Also of particular interest are several reports regarding the association of Aβ accumulation with subjective cognitive concerns. Our group found that greater PiB-PET amyloid burden was related to increased report of subjective memory concerns, even when controlling for depressive sympatology (Amariglio et al., 2012). A similar report from the Berkeley group also found that high amyloid burden was associated with greater memory complaints on self-report (Perrotin et al., 2012). A recent study from Scheltens and colleagues, recruiting participants from a subjective memory complaint clinic, revealed increased cognitive decline in Aβ+ with subjective concerns compared to Aβ− with similar levels of subjective cognitive concerns (van Harten et al., 2013). Most recently, a large study from Kentucky with autopsy confirmation also found that subjective memory complaints among individuals who died prior to diagnosis of cognitive impairment were associated with greater neuritic plaque burden (Kryscio et al., 2014).

Resilience and reserve

The observation that the extent of observable AD neuropathologic changes does not always align with the degree of clinical impairment led to the concept of “reserve”. In general, reserve might be characterized as the ability to tolerate higher levels of brain injury without exhibiting clinical symptoms. The concept of reserve has continued to evolve to include both “brain reserve and “cognitive reserve (Stern, 2009). Brain reserve generally refers to the capacity of the brain to withstand pathologic insult, perhaps due to greater synaptic density or larger number of healthy neurons, such that sufficient neural substrate remains to

support normal function. Cognitive reserve is thought to represent the ability to engage alternate brain networks or cognitive strategies to withstand the effects of encroaching pathology. It is not clear, however, that the data support a sharp demarcation between these two constructs, as many factors, such as higher socio-economic status or engagement in cognitively stimulating activities, may contribute to both forms of reserve, and have been associated with lower age-adjusted incidence of clinical AD diagnosis. Recent studies suggest that high reserve may primarily influence the capability of individuals to tolerate their AD pathology for longer periods of time, but may be associated with rapid decline once a "tipping point is reached and compensatory mechanisms begin to fail (Fotenos et al., 2008; Wilson et al.). The relationship between Aβ and cognition is stronger in low reserve CNs (Rentz et al., 2010; Roe et al., 2011), suggesting that high reserve individuals may be able to maintain high levels of cognitive abilities despite underlying pathology. Furthermore, reserve has been shown to be independently associated with cognitive decline, above and beyond what is explained by AD markers such as amyloid, hippocampus volume and glucose metabolism in AD vulnerable regions (Vemuri et al., 2012), as well as common age-related pathologies as measured during post mortem examination (Wilson et al., 2013a). Thus, reserve is an important determinant of cognitive abilities in aging, and may interact with Aβ to infer additional risk of decline. However, reserve, in particular previous participation in cognitively stimulating activities, has also been associated with reduced levels of Aβ within CNs (Landau et al., 2012), which is consistent with animal work showing that an enriching environment is associated with reduced Aβ in mice (Costa et al., 2007). More recent animal data suggest that an enriched environment may also confer protection against Aβ toxicity, perhaps via beta2-adrenergic systems (Li et al., 2013). Thus, higher reserve may exert protective effects directly through influencing Aβ accumulation, and also through synaptic and neuronal capacity to influence the interaction between Aβ and downstream neurodegenerative processes.

Issues around terminology

The publication of the NIA-AA preclinical criteria raised concerns about inappropriately labeling individuals with "Alzheimer's disease who might never progress to manifest dementia, despite multiple references to the fact that not all individuals with biomarker evidence of AD will develop clinical symptoms within their lifetime. Indeed, the prefix "pre does not require that progression to the future state, merely that the "pre state occurs prior to or "before (in time, place, order, degree or importance) [Oxford English dictionary]. It is interesting that the term "precancerous lesion has not been met with the same concern, nor has "prediabetes raised any ire. The apprehension over preclinical AD terminology likely reflects the continued stigma of the clinical syndrome of AD, and the fact that more data are needed to fully understand the risk of progression at the individual level.

Although findings from both CSF and PET amyloid imaging studies are convergent that older CN with evidence of preclinical AD, particularly those with Aβ and ND markers, have a statistically greater risk of manifesting subsequent cognitive decline and progression to the symptomatic stages of AD at a group level, there are insufficient data at this time to make accurate predictions at an individual level. Despite the accumulating data that suggest older individuals with evidence of amyloid accumulation and/or markers of neurodegeneration are

at increased risk for cognitive decline and progression to AD dementia, it is becoming increasingly clear that a proportion of these individuals remain apparently resilient in the setting of early pathology. It is likely that a subset of individuals with biomarker evidence of preclinical AD will not progress to develop AD dementia during their lifetime, due to the estimated temporal lag of >15 years between the appearance of Aβ plaques sufficient to meet the neuropathological criteria for AD and the epidemiological estimates of age-adjusted dementia (Rowe et al., 2010). Recent neuropathologic studies have also highlighted specific factors that may confer resilience at the synaptic and neuronal level (Perez-Nievas et al., 2013). In addition, as noted above, there may be other protective factors, such as education and lifestyle factors, that may attenuate the progression from occult pathology to a symptomatic stage. However, the fact that there may be variable rates of progression to symptomatic AD does not negate the fact that these markers of preclinical AD are detecting evidence that the AD pathophysiological process has begun in the brain.

An international working group (Dubois et al., 2010; Dubois et al., 2007; Dubois et al., 2014), which also utilizes the overall category of preclinical AD, suggested the terminology “presymptomatic AD for individuals with autosomal dominant genetic mutations, and that “asymptomatic at-risk for Alzheimer’s disease be used to refer to individuals with biomarker evidence (CSF or PET amyloid imaging) of AD pathology but no clinical manifestations. However, this latter term is problematic as one cannot simultaneously be “at-risk for a disease”, and have “biomarker evidence that the disease has already begun”. The difficulty remains that the field uses the term “Alzheimer’s disease to refer to both the neuropathologic process in the brain and to the clinical syndrome, typically at the stage of dementia. As we move towards detecting and treating at the earliest stages of AD, the dissociation between these two connotations of “Alzheimer’s disease remains particularly salient. Both the underlying pathophysiological process of AD and its clinical symptomatology represent continua, and the evidence thus far suggests that the pathological and clinical manifestations evolve in parallel but temporally offset trajectories (Rowe et al., 2010; Sperling et al., 2011a).

The term “asymptomatic at-risk for Alzheimer’s dementia or “asymptomatic at-risk for memory decline due to AD may be preferable; however, it is also clear that a proportion of the individuals with biomarker evidence of AD pathology also demonstrate very subtle cognitive decline and subjective memory concerns as described above, thus, “asymptomatic may also be a misnomer (see section on Cognitive Studies). “Preclinical AD was originally selected by the NIA-AA workgroup as the best terminology to encompass individuals who have very subtle cognitive or behavioral changes but have not yet progressed to the point of clinically evident impairment that is diagnosed as MCI or dementia. However, as the term “preclinical also sometimes refers to the stage of animal toxicology studies in the process of drug development (also referred to as non-clinical), this term may be confusing in the setting of clinical trials. Regardless of the exact terminology, the concept that the spectrum of AD encompasses a pathophysiological phase that is detectable prior to clinically evident symptoms is important particularly for enabling clinical trials aimed at preventing the clinical expression of AD.

Implications for prevention trial design

The recognition of this long preclinical phase of AD has already enabled a number of secondary prevention trials. Secondary prevention in this context refers to testing interventions in individuals who have evidence that the disease process is already beginning in the brain aimed at preventing the onset of symptoms and progression to the clinical stages of AD. The majority of these trials are targeting presymptomatic individuals at high genetic risk for AD with anti-amyloid therapies. The Dominantly Inherited Alzheimer Network (DIAN), an international consortium trial in families with autosomal dominant mutations in PSEN1, PSEN2, and APP mutations, is currently testing two monoclonal antibodies against different forms of Aβ: solanezumab and gantereumab in a Phase 2 biomarker trial (Mills et al., 2013).The Alzheimer's Prevention Initiative (API) trial is testing another monoclonal antibody, crenezumab, in the large Colombian PSEN1 cohort (Reiman et al., 2011). The DIAN and API PSEN-1 trials utilize biomarker outcomes in the first phase of the trials, with plans to continue with longer follow-up to assess cognitive outcomes. API also plans to begin two additional trials in apolipoprotein E ε4 homozygotes, with an active vaccination against Aβ and a BACE inhibitor over the next two years. The TOMMORROW trial is testing pioglitazone, aimed at glucose metabolism, in carriers of the high-risk variant of the TOMM-40 gene.

The Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease (A4) Trial is complementary to the genetic-at-risk trials mentioned, but identifies older individuals thought to be at high risk for cognitive decline on the basis of biomarker evidence of Aβ accumulation (see Figure 5) (Sperling et al., 2014). The A4 Study will enroll clinically normal older individuals (ages 65-85) into a Phase 3 double-blind trial of solanezumab vs. placebo. The primary outcome of the A4 Study is rate of change on a cognitive composite (Donohue et al., 2014), but also includes several novel participant reported outcomes and computerized testing on an iPad using CogState technology augmented with two episodic memory measures developed on the basis of the cognitive neuroscience and fMRI literature (Rentz et al., 2013; Stark et al., 2013). The A4 Study will acquire PET amyloid imaging, structural and functional MRI on all participants, with CSF measures and Tau PET imaging in a subset. The addition of Tau PET imaging is particularly exciting, as this will allow us to directly test the hypothesis that lowering Aβ, if implemented early enough, can prevent the spread of Tau into the neocortex. If Tau PET indeed proves to be a "theragnostic marker – that is, change in rate of tau spread is predictive of and tracks eventual clinical response, this surrogate would great enhance our ability to conduct shorter, smaller prevention trials in the future. Importantly, the A4 Study also includes an observational arm, the Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) study, that will follow 500 older CN who "screen-fail falling below the threshold for Aβ positivity on screening PET amyloid imaging. The comparison of the A4 placebo arm and the LEARN cohort should provide crucial information on the individual risk of decline related to Aβ accumulation as well as other factors that may influence decline in the absence of elevated Aβ markers.

A4 is envisioned as a platform that can be adapted to test multiple potential disease-modifying therapies. The "A5 trial, which will likely test a BACE inhibitor, is currently being planned in a similar preclinical AD population. Ultimately, it is likely that we will

need combination therapies (COMBAT trial) to fully halt the progress of AD, as with every other complex disease. These combinations may be multiple mechanisms to lower Aβ burden, such as a BACE inhibitor to decrease the production of $A\beta_{1-42}$ monomer combined with an antibody that targets aggregated forms of Aβ. Recent animal studies suggest that these approaches might be synergistic in decreasing Aβ, and may have the added benefit in humans of allowing lower doses of each therapeutic to avoid treatment associated adverse events (Jacobsen et al., 2014). Ultimately, it would be ideal to combine anti-Aβ and anti-Tau treatments, particularly in early symptomatic patients. The hope of the secondary prevention trials discussed above is that intervention with an anti-amyloid therapy, if initiated early enough, might stem the spread of Tau, and slow progression of neurodegeneration and prevent memory decline. However, given the preliminary evidence of Tau spread that is present even prior to the stage of MCI, we may need to institute combination secondary prevention trials to fully arrest the development of cognitive decline.

The horns of the dilemma

The particular challenge in AD is that we may have the greatest success with disease-modifying therapy very early in the disease process, likely before the stage of clinical impairment when widespread, irreversible is already present. Perhaps the most frightening prospect is that for some therapeutic mechanisms, such as those aimed at decreasing production of Aβ, such as beta-secretase inhibitors or gamma-secretase modulators, we may ultimately need to intervene even prior to the stage of fulminant amyloidosis and early neurodegeneration.

Although several studies have now demonstrated that individuals with markers of both amyloidosis and neurodegeneration (NIA Stage 2) are at the greatest risk for rapid cognitive decline (Knopman et al., 2012; Mormino et al., 2014a; Vos et al., 2013), these are not necessarily the individuals who are most likely to respond to an anti-amyloid therapy. If indeed, the neurodegenerative process becomes increasingly amyloid-independent as the disease progresses (Hyman, 2011), the best opportunity for intervention with an anti-amyloid agent might be prior to tau spreading or significant hippocampal atrophy detectable on MRI. If on the other hand, Aβ accumulation continues to “fan the flames of tau pathology and neuronal loss, the individuals with evidence of both markers may comprise the ideal cohort for shortening the trial length. It is essential to define the “critical window for successful disease-modifying therapies.

One possibility would be to identify individuals with relatively low levels of Aβ accumulation who are in the rapid phase of accumulation but may still be years or more than a decade before reaching the plateau phase of Aβ deposition. This might be thought of as an “A3 trial – “Ante-Amyloid prevention of Alzheimer’s disease – if we could reliably identify people before the stage of Aβ positivity. The difficulty is that these individuals (perhaps they constitute a preclinical Stage 0.5) would be less likely to have Aβ-related neurodegeneration, and thus much less likely to demonstrate cognitive decline over the course of a 3-5 year secondary prevention trial. It is hoped that identifying reliable surrogate biomarkers, such as tau imaging or improved functional imaging markers if demonstrated to be theragnostic of

eventual clinical response in secondary prevention trials, would greatly facilitate these trial designs.

The future of prevention trials

Eventually we hope to begin primary prevention trials, aimed at preventing the pathology from accumulating in the first place. These trial designs would be very challenging currently, as they might require a trial length of more than two decades and medications that are demonstrated safe enough to give to very large numbers of individuals at heterogenous risk of cognitive decline, and inexpensive enough to be given for multiple years. In addition, primary prevention trials will likely require different outcomes than those employed in the current secondary prevention trials, such as web-based iPad home assessments and very short clinical assessments that can be completed in a primary care office setting. However, if the current passive immunotherapy secondary prevention trials are successful at demonstrating that anti-Aβ therapy can bend the curve of very early cognitive decline in preclinical AD, the field will surely implement more feasible trial designs and administration routes for anti-Aβ, such as active vaccination against Aβ fragments and oral medications to decrease Aβ production. Indeed, as one of the limiting factors in AD vaccine development has been raising adequate immunologic titers in older individuals, an active immunization approach may be more successful if started in 50-year-olds with booster immunizations every few years.

Similar prevention trial efforts are beginning in other neurodegenerative diseases, in particular, Huntington's disease, as risk can be reliably identified through genetic mutation testing, and an estimated date of symptom onset predicted through the number of trinucleotide repeats. As Parkinson's disease does not manifest clinically until more than 90% of the substantia nigra neurons are lost, Parkinson's also offers a tremendous opportunity for secondary prevention trials. Ongoing biomarkers efforts in Parkinson's disease are working to identify reliable markers that can be used to select asymptomatic individuals at risk for motor progression and to track response to therapies in the preclinical stages of Parkinson's disease.

Although the prospect of preventing neurodegenerative disease progression seems daunting at the moment, we should take encouragement from other fields of medicine that have seen remarkable success through secondary prevention approaches. In particular, the substantial reduction in cardiovascular disease morbidity and mortality achieved with lowering cholesterol levels came about after secondary prevention trials in familial hypercholesterolemia (Leitersdorf et al., 1995) and in older individuals with angina or after a single myocardial infarction, but who still had relatively preserved cardiac function (Group, 1994). One of the earliest challenges faced in that field was the reliable measurement of plasma lipids, and better understanding of the relationship of various cholesterol types to clinical outcomes. It is likely that our simplistic understanding of the AD pathophysiologic process based on current biomarker data will continue to evolve. In particular, the initiation of several large-scale secondary prevention trials in both genetic at-risk and amyloid at-risk older individuals will provide a wealth of data that should serve to disentangle these complex relationships.

Acknowledgments

The authors are supported by the National Institute on Aging: P01AG036694; R01 AG046396R01 AG027435; K24 AG035007; and F32AG044054, and the Alzheimer's Association. The authors also wish to thank Nayiri Arzoumanian for assistance with editing the manuscript, and all of the research participants who have contributed to our findings.

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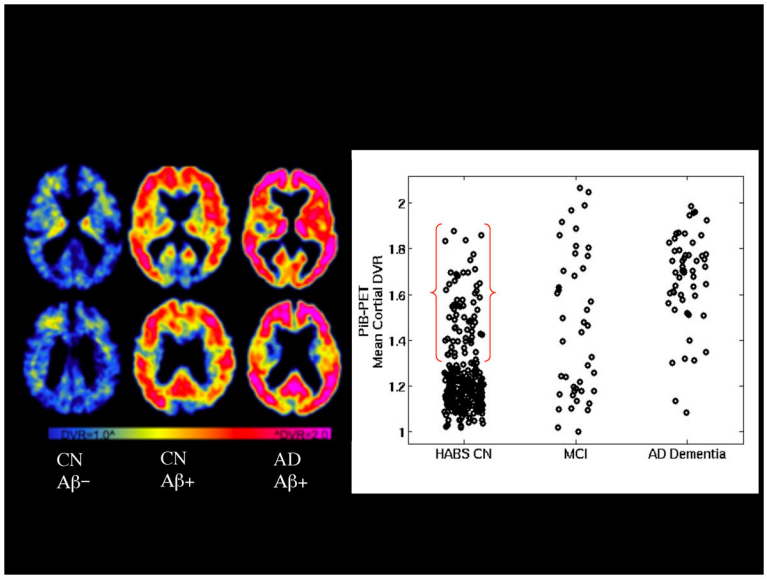

Figure 1.

PET amyloid imaging with ^{11}C-PiB. **Left:** Representative PET images from three older individuals: Clinically normal older individual without evidence of elevated Aβ accumulation (CN Aβ−), Clinically normal older individual with elevated Aβ accumulation (CN Aβ+) and patient with AD dementia with very elevated Aβ accumulation (AD Aβ+) in frontal and parietal heteromodal cortices **Right:** Scattergram of PiB distribution value ratios (DVR) by diagnostic group: Harvard Aging Brain Study Clinically normal older individuals (HABS CN), Mild Cognitive Impairment (MCI), and AD dementia. Approximately 30% of HABS CN demonstrate elevated Aβ accumulation in the range of MCI and AD dementia Aβ +.

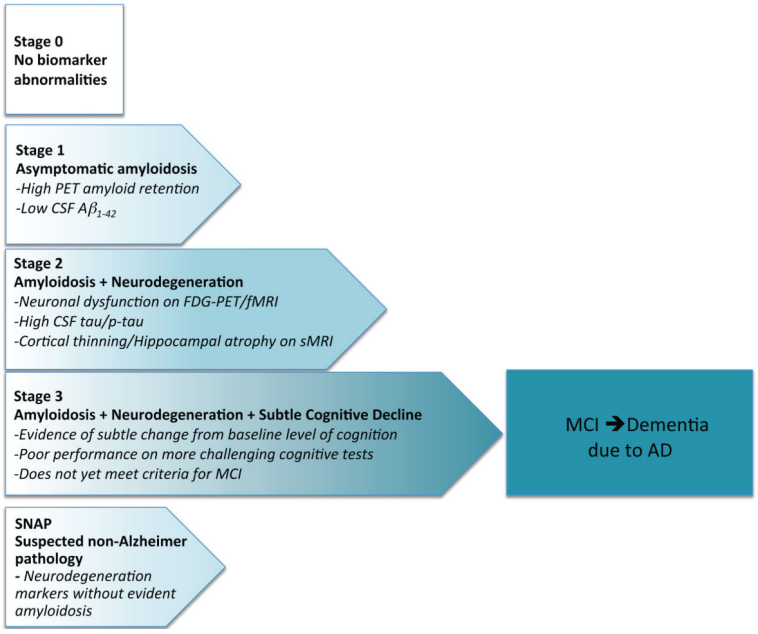

Figure 2.

Updated staging framework for preclinical AD (adapted from Sperling et al. 2011a with updates from Jack et al. 2012). Stage 0 represents individuals without biomarker abnormalities who are not thought to be on the AD trajectory. Stage 1 begins with cerebral amyloidosis; Stage 2 is amyloidosis plus markers of neurodegeneration; Stage 3 is amyloidosis + neurodegeneration + evidence of subtle cognitive and behavioral decline that is not yet sufficient to meet criteria for mild cognitive impairment or dementia due to AD. SNAP or Suspected Non-Alzheimer Pathology has evidence of neurodegeneration without apparent amyloidosis.

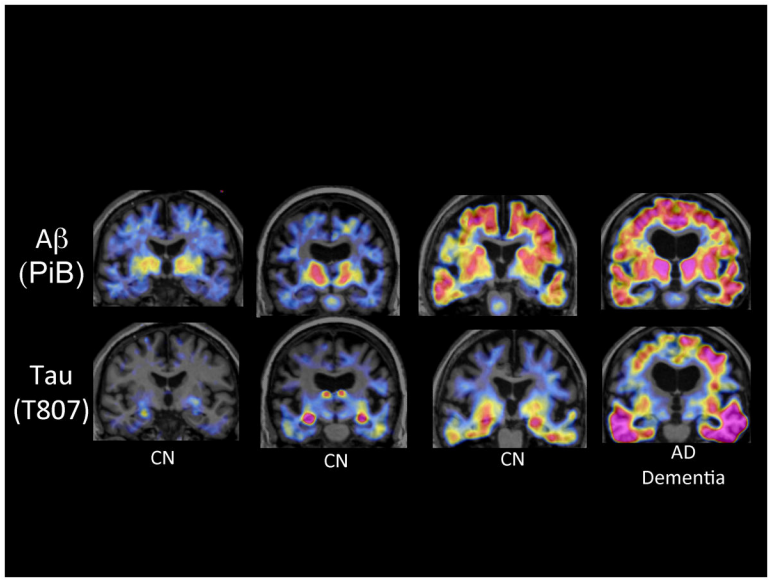

Figure 3.

Amyloid and Tau PET imaging. Coronal PET images superimposed on structural Magnetic Resonance) of PiB Aβ (upper row) and T807 Tau (lower row) acquired on 4 participants in the Harvard Aging Brain Study. The first three columns of images are from clinically normal older individuals (CN) with the far right image acquired from a patient with AD dementia. Moving from left to right exemplifies increasing levels of Aβ in necortical regions associated with increasing levels of Tau, particularly prominent in the inferior temporal cortices.

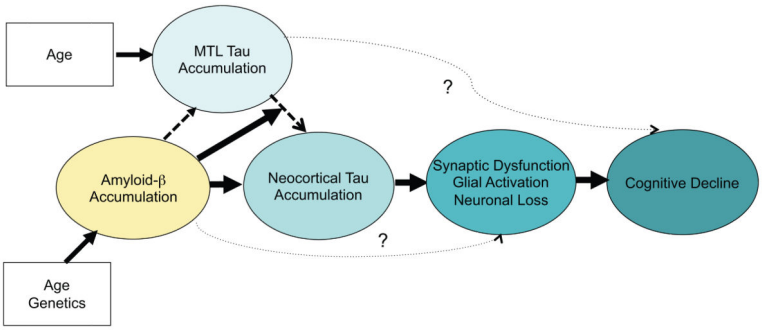

Figure 4.

Hypothetical model of the interaction of amyloid-β (Aβ) and tau accumulation. Advancing age is nearly ubiquitously associated with the gradual accumulation of Tau aggregates in medial temporal lobe (MTL), but it remains unknown whether MTL tau in isolation is associated with “age-related cognitive change. Age and genetics influence likelihood of accumulating elevated levels of amyloid-β (Aβ) aggregates. Aβ is hypothesized to increase the accumulation of Tau aggregates and in particular to accelerate the spread of Tau out of the MTL into the neocortex through local diffusion and perhaps via transynaptic spread across neural networks. Tau accumulation leads to synaptic dysfunction, glial activation, and eventually neuronal loss. Aβ may also have direct synaptic toxicity that is not mediated through Tau. The spreading of Tau into neocortex and associated neurodegenerative processes are thought to result in cognitive impairment and further progression along the clinical trajectory of Alzheimer’s disease.

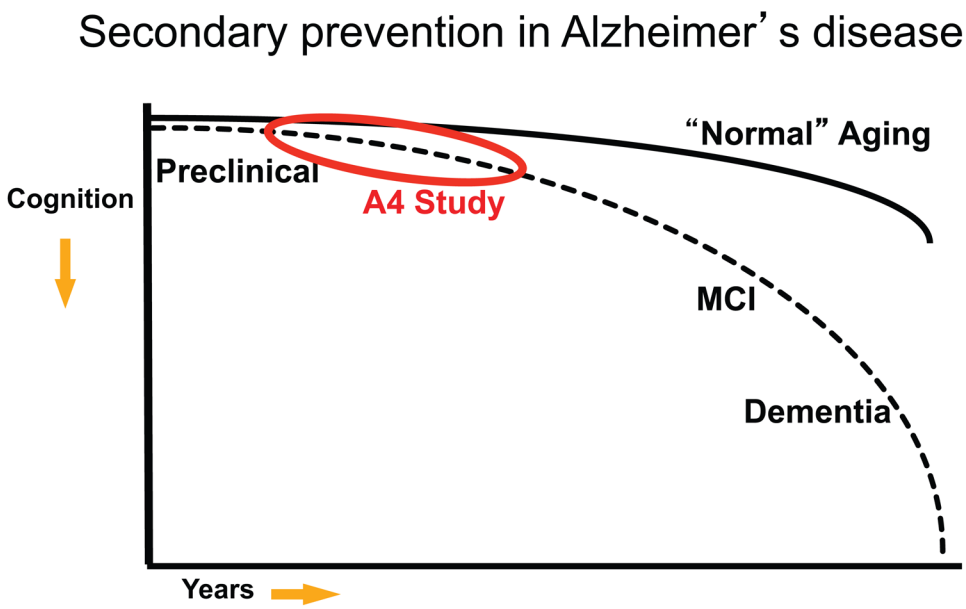

Figure 5.

Continuum of Alzheimer's disease (AD). Cognitive trajectory of "normal aging (starting in late life) demonstrates some decline over decades with increased deterioration in very late life. Preclinical stage of AD at the asymptomatic stage initially demonstrates similar cognitive trajectory as "normal aging but in later stages of preclinical AD demonstrates increased rate of cognitive decline towards mild cognitive impairment (MCI) and dementia due to AD. The Anti-Amyloid Treatment in Asymptomatic AD (A4) Study will test an anti-amyloid interview in preclinical AD aimed at slowing the rate of cognitive decline.