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UPDATE

Is amyloid-β harmful to the brain? Insights from human imaging studies

William Jagust

Although the amyloid-β protein associated with the Alzheimer's disease plaque has been detectable in living people for over a decade, its importance in the pathogenesis of Alzheimer's disease is still debated. The frequent presence of amyloid-β in the brains of cognitively healthy older people has been interpreted as evidence against a causative role. If amyloid-β is crucial to the development of Alzheimer's disease, it should be associated with other Alzheimer's disease-like neurological changes. This review examines whether amyloid-β is associated with other biomarkers indicative of early Alzheimer's disease in normal older people. The preponderance of evidence links amyloid-β to functional change, progressive brain atrophy, and cognitive decline. Individuals at greatest risk of decline seem to be those with evidence of both amyloid-β and findings suggestive of neurodegeneration. The crucial question is thus how amyloid-β is related to brain degeneration and how these two processes interact to cause cognitive decline and dementia.

School of Public Health and Helen Wills Neuroscience Institute, University of California, Berkeley, USA

Correspondence to: William Jagust,
Helen Wills Neuroscience Institute,
132 Barker Hall,
University of California, Berkeley,
CA 94720-3190, USA.
E-mail: jagust@berkeley.edu

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Introduction

The amyloid hypothesis of Alzheimer's disease has been the dominant theory of disease causation for decades (Selkoe, 1991; Hardy and Selkoe, 2002). This theory essentially holds that accumulation of the amyloid-β protein, the key constituent of the Alzheimer's disease plaque, is sufficient to cause a series of downstream events resulting in synaptic dysfunction, inflammation, neuronal death and eventually dementia. More recently, increasing attention has been drawn to the possibility that amyloid-β exerts deleterious effects on the brain through its interactions with the tau protein (Roberson *et al.*, 2007; Stancu *et al.*, 2014), the constituent of the neurofibrillary tangle that is more closely related to cognitive outcomes than is the amyloid-β plaque (Nelson *et al.*, 2012). Considerable evidence for the amyloid hypothesis arises from Mendelian inherited gene mutations that have enabled both animal models and studies of presymptomatic humans. Clinical research has benefitted considerably from the availability of biomarkers for amyloid-β in humans. These data show strong evidence of brain amyloid-β deposition long before neurological changes and cognitive decline occur in people who carry autosomal dominant Alzheimer's disease-causing mutations (Bateman *et al.*, 2012; Fleisher *et al.*, 2012).

A number of technical factors are important in interpreting biomarker data. Amyloid PET biomarkers have been shown to correlate well with amyloid load at autopsy (Clark *et al.*, 2012*a*; Curtis *et al.*, 2015; Murray *et al.*, 2015; Sabri *et al.*, 2015) and correlate inversely with CSF measures of amyloid-β_{1-42} (Landau *et al.*, 2013) although the information provided with both techniques may not be

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identical (Mattsson *et al.*, 2015*b*). For example, PET imaging detects aggregated, fibrillar forms of the amyloid-β protein, while abundant evidence from animal models suggests that soluble forms are most likely to be deleterious (Walsh *et al.*, 2002). While PET and CSF measures of amyloid-β occur on a continuum, it is often useful to classify individuals as 'amyloid positive' or 'amyloid negative' based on a threshold. Selection of a threshold represents a choice between sensitivity (use of a lower value to define positivity) and specificity (use of a higher value to define positivity) and thus has important effects upon how individuals are classified or misclassified (Villeneuve *et al.*, 2015). Biomarkers are also available to define downstream effects of neurodegeneration such as brain atrophy (measured with MRI), altered neural function (measured with PET and glucose metabolism or functional MRI) and impaired cognition. These neurodegeneration biomarkers are not specific for underlying pathological processes; nevertheless human data using such biomarkers have been integrated into a model in which amyloid-β is an initiating event, followed by neurodegeneration, and lastly cognitive decline (Jack *et al.*, 2010, 2013).

Biomarker studies have also generated major critiques of the amyloid hypothesis. For example, therapeutic trials of amyloid-β-directed immunotherapies have used PET scanning to demonstrate reductions in brain amyloid-β without clinical improvement in Alzheimer's disease patients (Salloway *et al.*, 2014). Another salient critique is that both neuropathological and PET data show evidence of extensive amyloid-β pathology in cognitively normal older people (Bennett *et al.*, 2006; Morris *et al.*, 2010). This evidence of amyloid-β deposition without cognitive dysfunction, and amyloid-β reduction without cognitive improvement raises substantial questions about the validity of amyloid-β as a causative agent (Herrup, 2015). In part to accommodate this evidence, a framework for the staging of preclinical Alzheimer's disease has been developed in which the deposition of amyloid-β alone is *prima facie* evidence of preclinical Alzheimer's disease in its earliest, or first stage (Sperling *et al.*, 2011) (Fig. 1A). Subsequent neurodegeneration (changes in brain structure and function) marks the second stage in preclinical Alzheimer's disease, leading to subtle, asymptomatic cognitive decline, which reflects a third stage. Therapy directed at amyloid-β, it is argued, must therefore be initiated at the earliest possible stage in order to be effective. Amyloid-β immunotherapeutic clinical trials in older people with brain evidence of amyloid-β but no cognitive symptoms are underway based on this reasoning (Sperling *et al.*, 2014).

Similarly, another test of the amyloid hypothesis is whether there is convincing evidence that amyloid-β affects brain structure, function, and cognition in normal older people well before the onset of clinically significant cognitive impairment or dementia. While there are extensive data concerning relationships between amyloid-β and such downstream effects in patients with Alzheimer's disease and mild cognitive impairment (MCI) and in those with autosomal dominantly inherited forms of Alzheimer's disease, this review is limited to studies of cognitively normal older people, with the expectation that this might represent the earliest stage of Alzheimer's disease and the appropriate window in which to detect the earliest harmful effects of amyloid-β. It seems reasonable to expect that if amyloid-β is the initiating event in the Alzheimer pathological cascade, and if normal older people with brain amyloid-β have preclinical Alzheimer's disease, then harmful effects should be detectable as Alzheimer's disease-like changes in these individuals.

Is amyloid-β associated with brain atrophy in normal older people?

Cross-sectional studies have defined a regional predilection of brain atrophy in Alzheimer's disease that, while not entirely specific, tends to follow a typical pattern. This includes volume loss of the hippocampus (Seab *et al.*, 1988; Jack *et al.*, 1992) and a pattern of atrophy involving medial and lateral parietal cortex and temporal neocortex that has been characterized as an 'Alzheimer's disease signature' (Dickerson *et al.*, 2009). Brain atrophy suggestive of Alzheimer's disease has been reported in a number of cross-sectional studies of normal older people with brain amyloid-β (Storandt *et al.*, 2009; Bourgeat *et al.*, 2010; Becker *et al.*, 2011; Dore *et al.*, 2013). CSF measures of amyloid-β_{1-42} have also been associated with whole brain atrophy (Fagan *et al.*, 2009). However, not all studies have found such relationships in cross-sectional data. In the Alzheimer's Disease Neuroimaging Initiative (ADNI), no relationship was detected between brain amyloid-β and regional brain atrophy in 280 normal older people, 30% of whom had evidence of brain amyloid deposition (Mattsson *et al.*, 2015*a*) although evidence for such associations were seen in those with MCI. Other studies have also failed to confirm cross-sectional relationships (Wirth *et al.*, 2013*a*), including some studies that reported greater atrophy progression in people with brain amyloid-β (Schott *et al.*, 2010; Andrews *et al.*, 2013). Thus, reports of associations between amyloid-β and cross-sectional measures of brain atrophy are not consistent and may also not necessarily reflect a typical Alzheimer's disease pattern (Whitwell *et al.*, 2013).

Longitudinal data have considerable advantages over cross-sectional data in progressive disorders. Many studies have shown accelerated brain atrophy rates in normal older people with evidence of brain amyloid-β by PET or CSF measurement (Schott *et al.*, 2010; Chetelat *et al.*, 2012; Ewers *et al.*, 2012; Andrews *et al.*, 2013). In one study, investigators found a relationship between the rate of accumulation of brain amyloid-β over time and the rate of hippocampal and cortical atrophy (Villemagne *et al.*, 2013). However, longitudinal results are also neither

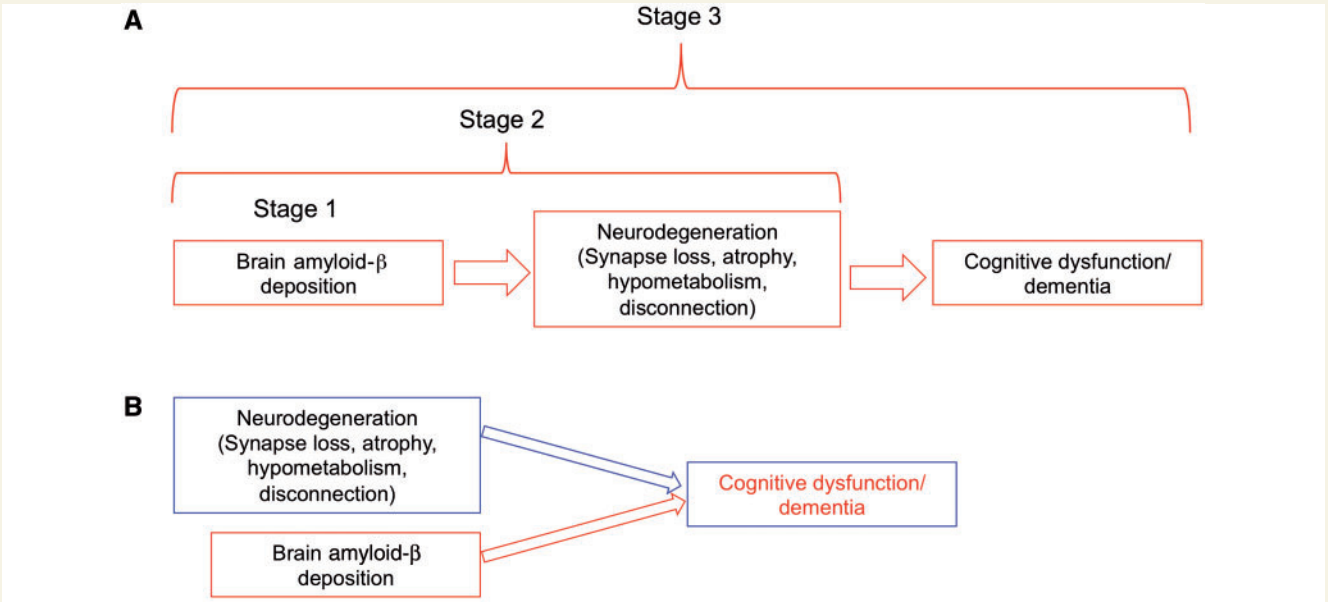

Figure 1 Two different conceptualizations of how amyloid-β affects neurological outcomes. **A** summarizes a preclinical staging scheme for Alzheimer's disease in which amyloid-β deposition is the initiating event. In this scheme, brain amyloid-β deposition alone constitutes Stage 1 of preclinical Alzheimer's disease, followed by Stage 2 in which amyloid-β leads to neurodegeneration. In Stage 3, subtle cognitive dysfunction insufficient to establish dementia or mild cognitive impairment, occurs. This scheme posits neurodegeneration as the invariable mediator between amyloid-β and cognition. **B** suggests an alternative view in which neurodegeneration and amyloid-β are independent processes. Neurodegeneration without amyloid-β has been referred to as suspected non-Alzheimer pathology (SNAP). In this scheme, either neurodegeneration or amyloid-β alone may lead to cognitive dysfunction, although the two together may produce synergistic harmful effects.

straightforward nor consistent and different methods for data analysis may produce disparate results even in subjects from the same cohort (Driscoll *et al.*, 2011; Clark *et al.*, 2012*b*). More recent studies have begun to probe subtle differences in older subjects with brain amyloid-β by classifying them according to the suggested preclinical stages of Alzheimer's disease (Sperling *et al.*, 2011) (Fig. 1A). When normal older people are categorized using this approach, an unforeseen but substantial proportion (~25%) of normal individuals show evidence of neurodegeneration without amyloid-β. These cases are often referred to as SNAP as they reflect suspected non-Alzheimer pathology (Jack *et al.*, 2012). SNAP is a complex and controversial entity as it is entirely biomarker-driven and without a clear pathological substrate; nevertheless its existence implies that amyloid-β and neurodegeneration can be independent processes (Fig. 1B). While the data are limited, some reports indicate that individuals with amyloid-β alone do not show progressive atrophy, while those with amyloid-β and evidence of neurodegeneration do (Desikan *et al.*, 2011; Knopman *et al.*, 2013). These same studies indicate that neurodegeneration without amyloid-β (SNAP) may not be progressive. These data in the aggregate suggest a relationship between brain amyloid-β and atrophy that is subtle and complex. Detection of this relationship is somewhat dependent on methods, but appears to be most robust in longitudinal data. In addition, the evidence that amyloid-β is associated with progressive atrophy may be strongest when amyloid-β is associated with other biomarkers of brain injury. This means, of course, that the best predictor of brain injury progression is not necessarily amyloid-β alone, but amyloid-β and brain injury.

Is amyloid-β associated with altered neural function in normal older people?

Glucose metabolism

Patients with Alzheimer's disease have long been known to demonstrate a characteristic pattern of hypometabolism seen on FDG-PET imaging that involves areas in temporal and parietal cortex including the posterior cingulate cortex and precuneus (Minoshima *et al.*, 1997). While this hypometabolic pattern is not entirely specific for Alzheimer's disease, it is strongly associated and has been used in much the same way as the Alzheimer's disease signature pattern of atrophy on MRI with which it shares considerable topography. Appearance of this typical pattern in older people with brain amyloid-β deposition would

therefore constitute reasonable evidence of a harmful, Alzheimer's disease-like effect on brain function.

The data indicating such an effect are limited. Some studies have suggested, in fact, that increases in brain glucose metabolism occur in older amyloid-positive cognitively normal people (Johnson *et al.*, 2014; Oh *et al.*, 2014), which has been taken as possible evidence of brain compensation. The problem of detecting effects of amyloid-β on glucose metabolism is compounded by the fact that the apolipoprotein E4 allele, the major risk genetic risk for Alzheimer's disease, is associated with both glucose hypometabolism and amyloid-β accumulation (Reiman *et al.*, 2004; Morris *et al.*, 2010). While it is unclear whether glucose hypometabolism occurs as a consequence of APOE4 or amyloid-β (Jagust *et al.*, 2012; Knopman *et al.*, 2014), one large study showed that amyloid deposition in normal ageing was associated with hypometabolism even after accounting for *APOE* genotype (Lowe *et al.*, 2014). This study enrolled over 600 normal people, and found a correlation of −0.2 between glucose metabolism in Alzheimer's disease-typical regions and retention of the PET amyloid-β tracer. These results do suggest that amyloid-β has a small deleterious effect on glucose metabolism in ageing.

Resting state functional connectivity

Another method of studying brain function uses blood oxygen-dependent imaging with functional MRI in a task-free or resting state. These studies make use of the fact that spontaneous synchrony in the functional MRI signal occurs between topographically dispersed brain regions, indicating that these regions co-activate and function together in large scale networks (Biswal *et al.*, 1995). One such network is the default mode network (DMN), so named because it is deactivated during most externally-directed cognitive tasks (Raichle *et al.*, 2001) appearing to reflect an internally directed default mode of brain function. This network is of considerable interest because it becomes disconnected in patients with Alzheimer's disease (Greicius *et al.*, 2004) and shares considerable topographic overlap with the distribution of brain amyloid-β (Buckner *et al.*, 2005). As Alzheimer's disease progresses, other brain networks also show functional disruption (Brier *et al.*, 2012).

Amyloid-β deposition has consistently been linked to alterations in DMN function in cross-sectional data. These studies have shown evidence of both decreases and increases in brain network connectivity in different parts of the DMN (Hedden *et al.*, 2009; Sheline *et al.*, 2010*b*; Mormino *et al.*, 2011) in relation to amyloid-β. It is also increasingly obvious that connectivity in multiple resting state networks, in addition to the DMN, is modified in the presence of amyloid-β deposition in normal older people (Brier *et al.*, 2014; Lim *et al.*, 2014*a*). In fact, the pattern of connectivity changes transcends specific networks and appears to align with cortical hubs, or brain regions that interconnect different neural regions and systems (Buckner *et al.*, 2009). Both the pattern of cortical hubs and the pattern of regional network connectivity that is affected by amyloid-β reflect brain regions that are hypometabolic in patients with Alzheimer's disease (Elman *et al.*, 2014*a*). This finding is congruent with other evidence that brain metabolism is related to measures of connectivity (Tomasi *et al.*, 2013; Riedl *et al.*, 2014).

While results appear to be generally consistent, a few caveats must be kept in mind. First, the approach to resting state functional MRI data analysis is far from standardized, and repeated and longitudinal measurements remain problematic. Second, the *APOE4* genotype appears to affect functional brain connectivity (Machulda *et al.*, 2011) even in the absence of detectable amyloid-β (Sheline *et al.*, 2010*a*), so that these effects probably need to be examined separately. Nevertheless, considerable existing data suggest a relationship between brain amyloid and alterations in network connectivity in normal older people.

Is amyloid-β associated with cognitive dysfunction in normal older people?

While measurement of biomarkers that reflect neurodegeneration provide important clues about the effects of amyloid-β on the brain, cognitive function is the crucial variable linking misfolded proteins to dementia. Initial cross-sectional studies investigating associations between cognition and amyloid-β in cognitively normal older people were conflicting. Because such studies define the sample *a priori* as cognitively normal, any evidence of cognitive dysfunction must be subtle and difficult to detect. Perhaps unsurprisingly while a number of studies have found evidence of cognitive deficits in association with amyloid-β (Chetelat *et al.*, 2011; Rentz *et al.*, 2011; Rodrigue *et al.*, 2012) some have failed to find this association (Aizenstein *et al.*, 2008). A meta-analysis examining data from over 3000 subjects supports a relationship, particularly between amyloid-β and episodic memory, although the strength of this relationship was very small, an unsurprising finding that likely accounts for disagreement in the literature (Hedden *et al.*, 2013).

Longitudinal studies, however, have repeatedly shown cognitive decline in people with brain amyloid-β. Initial studies examining how the presence or absence of brain amyloid-β predicted subsequent decline showed that older people with amyloid-β experienced more decline than those without, regardless of whether amyloid-β was indicated by increased retention of PET tracers or reduced CSF measurements (Fagan *et al.*, 2007; Resnick *et al.*, 2010; Landau *et al.*, 2012; Lim *et al.*, 2014*b*). In one study, rates of amyloid-β deposition correlated with rates of episodic memory decline (Villemagne *et al.*, 2013). With the publication of criteria for preclinical staging of Alzheimer's disease, studies have increasingly examined how the presence

of amyloid-β and neurodegeneration, together and separately, affect cognitive decline. Investigators studying several large cohorts from ADNI (Toledo *et al.*, 2014), Amsterdam (van Harten *et al.*, 2013), Harvard (Mormino *et al.*, 2014), the Mayo Clinic (Knopman *et al.*, 2012), and Washington University (Vos *et al.*, 2013) have used this approach to contrast progression by preclinical stage of Alzheimer's disease. In general, advancing stage was associated with a greater risk of progressive cognitive decline so that those with evidence of amyloid-β with neurodegeneration (i.e. preclinical stages 2/3) had the highest risk. The situation for those in Stage 1, with only evidence of amyloid-β is not as straightforward; two studies found that such individuals with CSF evidence of low amyloid-β alone declined (van Harten *et al.*, 2013; Vos *et al.*, 2013) while in the three other cohorts using PET measures of amyloid-β, decline in those with Stage 1 was less evident. These studies differ in many ways besides the method of amyloid-β measurement; they used different outcomes, sample selection and length of follow-up. However as a group they indicate that the risk from amyloid-β alone, while likely important, is lower than the risk from amyloid-β in the presence of additional abnormal biomarkers. This has, in fact, been seen as an interaction between amyloid-β and neurodegenerative biomarkers in other studies, suggesting that the joint effect of abnormal amyloid-β and neurodegeneration is greater than the additive contribution of either marker alone (Wirth *et al.*, 2013*b*; Mormino *et al.*, 2014).

Summary

Is amyloid-β harmful to the brain? The literature is replete with evidence that individuals who harbour amyloid-β show a number of neurological effects that are similar to those seen in Alzheimer's disease. While studies are sometimes contradictory, there is substantial evidence that amyloid-β is associated with cross-sectional and progressive brain atrophy, cross-sectional network dysfunction and longitudinal cognitive decline. A closer examination of the data indicates that simply classifying individuals based on the presence or absence of amyloid-β does not give the full picture. Studies that have categorized normal older people according to preclinical stages of Alzheimer's disease strongly indicate that those with evidence of both amyloid-β and biomarkers suggesting neurodegeneration show the greatest evidence of decline. Thus examining individuals simply in terms of the presence or absence of amyloid-β is not as informative as defining where they stand along a putative pathway of preclinical Alzheimer's disease progression.

Many of these studies, especially those that are cross-sectional, demonstrate associations but do not prove causality. Scientific inquiry, especially in human research, benefits from studies of association especially when results converge across different methods and laboratories. However, traditional views of the scientific method hold that disproving a hypothesis is more valuable than accumulating positive evidence. In this regard, the only true human experiments manipulating amyloid-β levels—clinical trials of amyloid-lowering therapies—refute the importance of amyloid-β in Alzheimer's disease. This has not, however, disproven the amyloid hypothesis primarily because it is not a true hypothesis but rather a complex model of disease causation. Over time, this model has been refined and generated numerous hypotheses, one of which is that Alzheimer's disease has a prolonged incubation period during which amyloid-β promotes neurological damage. Failure of clinical trials in late stage disease is fully compatible with this model and begs for studies to be done in early and presymptomatic individuals. The limitations of cross-sectional association studies are in part ameliorated through longitudinal studies that permit observation of the evolution of disease from asymptomatic stages. While incomplete, the studies reviewed here show that amyloid-β deposition is a very early event that appears to play a harmful role in brain ageing especially when it is associated with neurodegeneration.

In this setting, the appropriate question, therefore, may not be whether amyloid-β is harmful to the brain, but how amyloid-β is harmful to the brain. The mechanisms that link amyloid-β to neurodegeneration are poorly understood and perplexing. For example, in Alzheimer dementias with focal features such as posterior cortical atrophy or progressive aphasia, the pattern of amyloid-β deposition does not reflect the pattern of brain degeneration (Rabinovici *et al.*, 2008; Rosenbloom *et al.*, 2011). Individuals may respond differently to amyloid-β deposition based on the ability to compensate (Elman *et al.*, 2014*b*) or the presence of genetic factors that influence immunity and inflammation (Tanzi, 2015). Multiple biomarkers must be measured to characterize neurodegeneration, which could be important for 'staging' individuals by defining how progressed they are—an important factor for selection of individuals in clinical trials. The addition of tau imaging offers the potential of more specific biomarkers for degenerative brain processes (Villemagne *et al.*, 2015) that may shed light on these issues.

Cross-sectional association studies also have the disadvantage that they reflect brain biomarkers of structure and function that do not necessarily reflect neurodegeneration but could indicate a variety of non-progressive processes. The time between the appearance of brain amyloid-β and the development of dementia is potentially decades (Villemagne *et al.*, 2013) during which a multitude of pathological mechanisms may be operating. We need longitudinal studies to define relationships between amyloid-β, neurodegeneration, and cognition, and to better infer causation from temporal associations. How often is neurodegeneration preceded by amyloid-β, and how often might it arise independently and interact with amyloid-β to result in decline? Is Fig. 1A or Fig. 1B closer to the evolution of Alzheimer's disease? In Fig. 1A, dementia occurs via amyloid-β-induced neurodegeneration, while

in Fig. 1B dementia could evolve in relation to either amyloid-β or neurodegeneration independently. This is one of the key controversies in Alzheimer's disease research today, but it is not simply an academic exercise. Our ability to target the right interventions to the correct processes at the appropriate time point depends on a more precise understanding of the complex chain of events that occurs over many years to produce dementia.

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