CHAPTER

5

The Aging Mind in Transition: Amyloid Deposition and Progression toward Alzheimer's Disease

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OUTLINE

K.W. Schaie & S.L. Willis (Eds)
Handbook of the Psychology of Aging, Eighth edition.

DOI: http://dx.doi.org/10.1016/B978-0-12-411469-2.00005-4

INTRODUCTION

Alzheimer's disease is a progressive neurologic disorder that is initially manifested as memory loss resulting from damage to mediotemporal regions in the brain, particularly the entorhinal cortex and hippocampus (Kaye et al., 1997). The disease progresses over time from memory dysfunction to inability to recognize even close family members, to loss of bodily functions, and ultimately death. The greatest risk factor for Alzheimer's disease (AD) is old age, with recent data indicating that 44% of 80-year-olds in the United States have Alzheimer's disease (Alzheimer's Association, 2015). At present, there is no cure for Alzheimer's disease. The loss of identity and dignity that AD causes, as well as the dependence it creates, has made it one of the most feared outcomes of a long life by adults of all ages. Moreover, the extended disability associated with Alzheimer's disease strains both the health care system and the loved ones of the afflicted.

Until relatively recently, the risk factors for AD were not very clear, and even now, diagnosis of AD can be quite difficult, particularly in its early stages. If an older individual is evaluated by a neurologist or neuropsychologist for memory complaints and shows below-average memory performance, the individual will receive further testing to look for the underlying cause. Possibilities include a range of neurological diseases, including AD, psychiatric disorders, and endocrine or vascular disease. The individual would likely receive a brain scan with an MRI (magnetic resonance imaging) scanner that would provide a relatively detailed image of the structure of the brain. However, the image would not have sufficient clarity to permit a diagnosis of AD. In fact, the only way to get a definitive diagnosis of AD is after death via autopsy. At autopsy, neuropathologists can diagnose Alzheimer's disease through detection of the hallmark characteristics of AD: microscopic amyloid plaques and neurofibrillary tangles in the gray matter of the brain—characteristics discovered by Aloysius Alzheimer over 100 years ago.

Diagnosis of AD in the living person has typically been one of exclusion of other disorders because it is only at autopsy that tissue can be examined microscopically for the plaques and tangles. Thus, if, after a work-up, no specific cause is isolated for the poor memory function that has been documented, the affected individual will most likely be labeled as suffering from mild cognitive impairment (MCI), and will be told that there is about a 50% chance they are in the early phases of AD. They will learn that the only way to have more confidence in a diagnosis of AD is to observe symptom progression over a period of time, possibly years, and to "wait and see." They may be offered a drug that might improve memory symptoms temporarily, although most physicians will wait until they see symptom progression and are more confident that the MCI patient is indeed afflicted with AD.

The picture presented above, however, is changing. Very recently, new imaging techniques have been developed that, for the first time in human history, provide in vivo images of the amyloid plaques (Klunk et al., 2004) and tau tangles (Villemagne, Fodero-Tavoletti, Masters, & Rowe, 2015) associated with Alzheimer's disease. Besides providing diagnostic evidence about AD, the ability to see amyloid and tau deposits in vivo, particularly when combined with other neuroimaging techniques, is providing scientists with the remarkable opportunity to understand the transition from healthy cognitive function to the earliest stages of Alzheimer's disease. The focus of this chapter is to provide an overview of what has been learned about the development of AD, beginning with older adults who are initially cognitively normal and who show no hint of any latent pathology, but who ultimately move toward a diagnosis of AD.

We first will provide a brief overview of the techniques used to measure AD pathology in healthy older adults. We will follow with two models of how individuals transition toward AD. We first will discuss the Scaffolding Model of Aging and Cognition (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014), which provides a flexible model for understanding how both subtle and frank neuropathology with age may affect cognitive function and transition an individual toward AD. Then we will present the Preclinical Model of AD (Jack et al., 2010; Sperling et al., 2011), which provides a specific sequence of detectable stages from healthy function to AD-related dementia based on underlying pathology. The latter half of the chapter will discuss what we have learned so far about the transition from healthy aging to dementia due to Alzheimer's disease, based on the above models. Finally, we will discuss factors that moderate the transition toward full-blown AD and we close with a series of critical issues and questions about cognitive aging and AD that require future study.

AMYLOID IMAGING

Great progress has been made in understanding the brain changes that lead to AD as a result of the newly found ability to image amyloid deposition in vivo. Amyloid comes from a protein found in the neurons of normal healthy brain called amyloid-precursor protein or APP (Hardy & Selkoe, 2002). In Alzheimer's disease, a piece of the APP molecule gets cleaved off. It is this protein fragment (now called amyloid) that ends up aggregating into clumps or plaques that have been a hallmark of AD since its discovery over 100 years ago. The imaging process for detecting amyloid involves injecting a radiotracer substance intravenously that travels to the brain and binds with amyloid. The radiotracer emits a signal captured by a PET scanner. The PET scanner localizes the signal to a $2\,mm^3$ voxel in 3D space, so that the produced image shows where in the brain amyloid is detected and in what quantity. Amyloid deposition is fairly widespread throughout the brain (except in primary sensory regions), but the areas with the highest concentration are typically the precuneus and the anterior and posterior cingulate cortex (Rodrigue et al., 2012). The original amyloid radiotracer was invented at the University of Pittsburgh by Bill Klunk and Chester Mathis (Klunk et al., 2004) and was named "Pittsburgh Compound B," commonly referred to as "PiB." This ligand has a limited half-life of only 20 min and can only be made on-site in a cyclotron and then must be injected immediately, thus limiting its use to a few research sites. Later, other compounds were developed with longer half-lives including F-18 florbetapir (Avid Radiopharmaceuticals/Eli Lilly; Wong et al., 2010), florbetaben (Bayer; Barthel & Sabri, 2011) and flutemetamol (GE Healthcare; Nelissen et al., 2009), that has resulted in more widespread use. The F-18 ligands were all recently approved by the FDA for diagnostic use, but only in clinical populations. It should be noted that research in fatally ill patients who underwent PET shortly before passing away confirms by autopsy that the scans accurately measure amyloid deposits (Clark et al., 2011).

It is also worth noting that it is possible to measure amyloid levels in spinal fluid retrieved during a lumbar puncture. Due to the invasiveness of this procedure, as well as the lack of information about where in the brain the amyloid has deposited, amyloid PET imaging is utilized much more heavily than lumbar puncture. Another new and potentially important development that has the potential to enhance our understanding of AD considerably is the availability of a radiotracer that binds to tau. Like amyloid, tau is a hallmark of AD, and a requirement for the definitive diagnosis of AD at autopsy. In a normal healthy brain, tau is important for the stability of

axons. In Alzheimer's disease and many other dementias, tau becomes misfolded and clumps together into tangles inside a neuron (unlike amyloid, which floats freely in the brain) (Price & Morris, 1999; Spillantini & Goedert, 2013). The tangles kill neurons (Spillantini & Goedert, 2013). The radiotracers that allow in vivo measures of tau have been developed and currently have limited availability for research. In the coming years, tau radiotracer ligands should provide a new wave of insight into AD pathology and the transition from healthy to demented (Villemagne et al., 2015). However, because of the scarcity of data on tau and the wealth of data on amyloid, the present chapter will focus primarily on what we have learned from amyloid.

MODELS OF COGNITIVE TRANSITIONS

To understand the progression from cognitive health to AD, it is useful to think of cognitive decline as having multiple causes. Broadly speaking, causality can be attributed to two major sources: normal aging and neuropathology. Below we focus on two models that are useful theoretical guides for understanding the causal factors that control the transition from a healthy mind to AD.

Scaffolding Theory of Aging and Cognition

The Scaffolding Theory of Aging and Cognition (STAC) model (Park & Reuter-Lorenz, 2009) was designed to integrate structural and functional neuroimaging data on aging with cognitive aging findings in an effort to provide a relatively complete view of how age-related changes in brain structure and function affect cognition. Importantly, the paths depicted in the model provide concrete, testable hypotheses that can be supported or disproven as relevant data become available. The original STAC model was revised recently (Reuter-Lorenz & Park, 2014) and this newer STAC-r model is shown in Figure 5.1. The model shows series constructs that are predictors of both the level of cognitive performance as well as the rate of age-related cognitive decline and individual experiences over time. Both the original model and STAC-r relate the process of biological aging directly to deterioration in brain structure and brain function, as shown by the path in Figure 5.1. Examples of biologically based, age-related declines in brain structure include dopamine depletion (Li, Lindenberger, & Sikstrom, 2001), volumetric shrinkage (Raz et al., 2005), white matter lesions (Wen & Sachdev, 2004), and cortical thinning (Salat et al., 2004). The model also shows that biological aging affects brain function, with exemplars of this including findings that show age-related decreases in hippocampal activity (Gutchess et al., 2005; Park & Gutchess, 2005), and less specialization of neural activity with age ("dedifferentiation," Park et al., 2004, 2012). The STAC-r model shown in Figure 5.1 posits that brain structure and brain function are directly related to both level of cognitive function as well as rate of cognitive change. The other important element depicted in Figure 5.1 is that STAC-r is designed to encompass the life course (depicted by the leftmost circle) in accounting for cognitive function and cognitive change. The model integrates the role of both life experiences and genetic variables that operate to enrich (e.g., exercise thickens brain tissue, Cotman & Berchtold, 2002) or deplete (e.g., obesity relates to decreased brain function, Bischof & Park, 2015) brain structure and function. Finally, both the original model and STAC-r included pathways that allow for the deleterious effects of functional and structural changes in the brain on cognition to be muted by "compensatory scaffolding," that is, as structures decline with age, an increase in neural activity is observed, primarily in frontoparietal regions of the brain (Cabeza, 2002).

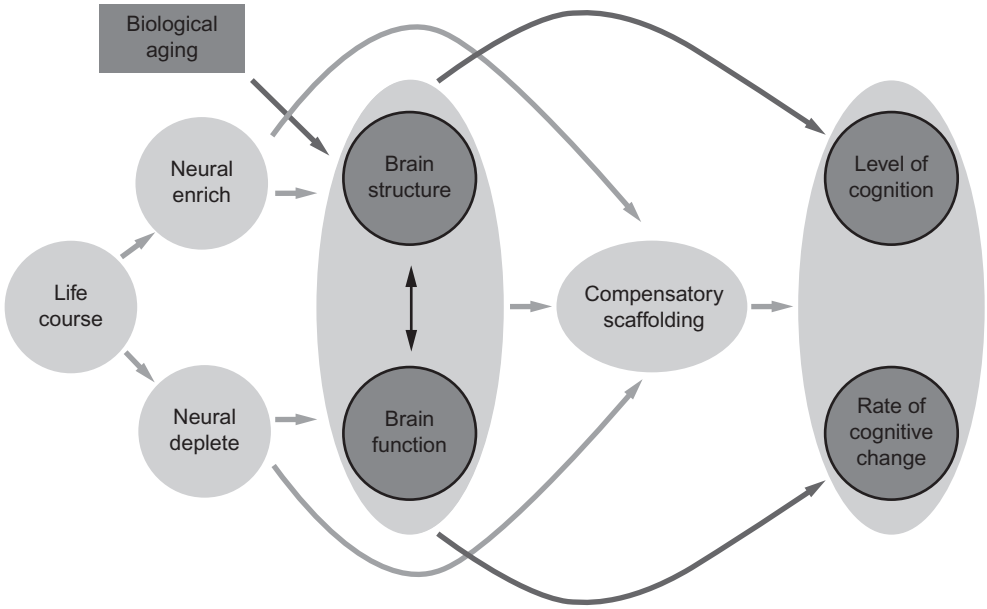

FIGURE 5.1 A schematic diagram of the Scaffolding Theory of Aging and Cognition-Revised (STAC-r). The model outlines general factors that influence adult cognition and cognitive change. Various life course events (e.g., education, physical fitness, vascular health) promote neural enrichment or neural depletion, which, along with biological aging, affect brain structure, brain function, and compensatory scaffolding. The confluence of these factors is theorized to influence one's current cognitive ability and one's rate of cognitive change. *Source: Adapted from Reuter-Lorenz and Park (2014).*

In other words, compensatory scaffolding is developed in an attempt to maintain healthy cognition in the face of a host of age-associated neural insults. There is widespread evidence that older adults recruit more neural circuitry than young on a broad range of tasks, including memory encoding (Cabeza et al., 1997; Grady, McIntosh, Rajah, Beig, & Craik, 1999), working memory (Reuter-Lorenz et al., 2000), and inhibition tasks (Huang, Polk, Goh, & Park, 2012). Finally, an important aspect of STAC and STAC-r is that the models encompass both normal aging as well as pathological aging. A normally aging individual would experience modest decreases in brain structure and function with age and evidence some compensatory scaffolding that would help maintain cognition. In contrast, a person on the path to AD would have much greater aggregation of amyloid and pronounced hippocampal shrinkage, and accordingly, would show a strong path from brain structure and function to rate of cognitive change.

One impetus for developing the STAC model and its revision was the surprising finding that many healthy older adults had no symptoms of cognitive impairment during life but had substantial amyloid deposition in their brains at autopsy (Bennett et al., 2006; Braak & Braak, 1996; Thal, Capetillo-Zarate, Del Tredici, & Braak, 2006). In fact, the autopsy data indicated that about 25–30% of deceased older adults who evidenced normal cognitive function had as much amyloid as individuals with Alzheimer's disease symptoms (Katzman et al., 1988). The constructs of both neural enrichment via experience and compensatory scaffolding provide mechanisms to explain the preservation of cognitive function in the context of declining structural integrity of the brain with aging.

A Model of Preclinical AD

The availability of amyloid imaging has greatly increased our understanding of the development of AD over time. It is known from in vitro studies and studies in rats that amyloid is neurotoxic to synapses and results in synaptic dysfunction (Cleary et al., 2005; Shankar et al., 2007; Walsh et al., 2002). The presence of amyloid in many apparently healthy individuals, including those in middle age, has resulted in the hypothesis that amyloid deposition may be one of the earliest markers of AD. This has led to the idea that AD pathology may slowly accrue over many years before cognitive symptoms are manifested. Amyloid is thought to be an initiating event that starts a cascade of neurodegeneration that eventually leads to cognitive decline and dementia (Hardy & Selkoe, 2002; Jack et al., 2010). In recent years, researchers proposed the use of various neuroimaging techniques and biomarkers to test the amyloid cascade hypothesis (Jack et al., 2010; Sperling et al., 2011).

To understand the possibility that AD pathology could be silent for many years with no manifestation of behavioral symptoms, the National Institute of Aging, in collaboration with the Alzheimer's Association, commissioned a report on the asymptomatic phase of AD. The report termed this silent phase to be "preclinical AD" (Sperling et al., 2011). Sperling et al. (2011) outlined a detailed staging of preclinical AD, relying heavily on the amyloid cascade hypothesis (Hardy and Selkoe, 2002; Jack et al., 2010). The stages of the Preclinical Model of AD proposed by Sperling et al. (2011) are described below (also see Figure 5.2):

Stage 0. No AD pathology and a healthy brain.
Stage 1. Amyloid starts to deposit.
Stage 2. Amyloid continues to accrue and evidence of neurodegeneration begins to be detectable.
Stage 3. Amyloid continues to deposit and neurodegeneration spreads, but now cognitive decline is also evident.

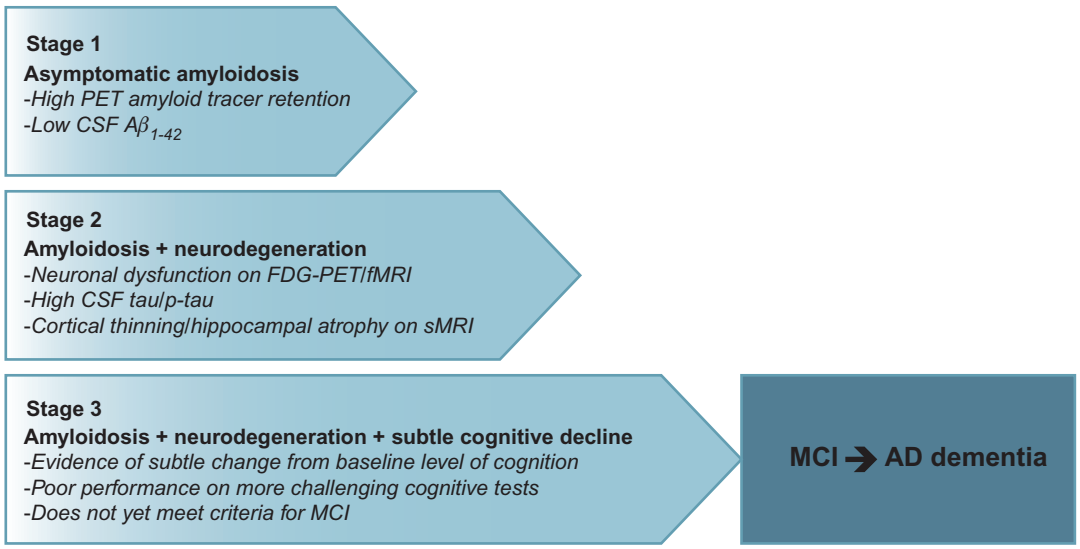

FIGURE 5.2 The Preclinical Model of Alzheimer' Disease. The above model lays out the stages of preclinical AD and the markers associated with each stage, from Stage 1 (amyloid only) to Stage 2 (amyloid + neurodegeneration) to Stage 3 (amyloid + neurodegeneration + cognitive) to MCI and finally dementia. *Source: Reproduced from Sperling et al. (2011).*

The first two stages of the model require little explanation. Stages 2 and 3 however require considerably more explication. The hypothesis is that the spread of amyloid in Stage 2 results in specific damage to neural function which then leads to neuronal loss. Then, by Stage 3, sufficient neuronal loss and damage have occurred that it results in clinical symptoms of memory decline that are detectable. Since the publication of Sperling et al. (2011), new research has been published on preclinical AD. Below, we raise three questions of critical importance to understanding the characteristic course and mechanisms underlying preclinical AD.

WHAT IS THE RELATIONSHIP BETWEEN AMYLOID DEPOSITION AND NEURODEGENERATION?

As mentioned above, the preclinical AD model predicts that amyloid deposition in healthy adults will result in a detectable relationship between amyloid burden and measures of neurodegeneration. The model suggests that amyloid deposition affects both synaptic dysfunction and neuronal loss, and we discuss each type of neurodegeneration in turn.

Neuronal Dysfunction

Studies of the link between amyloid and neuronal dysfunction have not used direct measures of neuronal activity. Rather the studies have primarily relied on how amyloid deposition affects fMRI BOLD activity in specific brain regions and metabolic activity in the brain that is measured by FDG-PET imaging. Studies have consistently demonstrated that amyloid deposition disrupts network circuitry in the brain, particularly in the default network, a network which is active at rest and suppressed at periods of high cognitive challenge (Drzezga et al., 2011; Elman et al., 2014; Mormino et al., 2011; Sheline et al., 2010). In addition to disrupting the integrity of the network, amyloid deposition also decreases the ability to modulate or control brain networks in response to task demands associated with episodic memory (Hedden et al., 2009; Huijbers et al., 2014; Kennedy et al., 2012; Sperling et al., 2009; Vannini et al., 2012, 2013). Additional evidence that amyloid may be related to dysfunction of neuronal activity can be found from FDG-PET studies. Unlike fMRI, FDG-PET does not directly measure brain activity at a specific moment in time, but rather provides an overall measure of how metabolically active different regions are by measuring how much glucose the regions are utilizing for energy. Interestingly, high amyloid burden has been associated with lower metabolic activity in temporoparietal brain regions known to be impaired in AD patients (Knopman et al., 2014; Lowe et al., 2014). In sum, fMRI and FDG-PET studies provide evidence that amyloid is related to lower brain activity in specific regions associated with AD and poorer connectivity among regions within networks. Longitudinal studies are needed to properly address cause and effect, but this supports the idea that individuals transition from healthy to demented by first depositing amyloid and then exhibiting signs of neuronal dysfunction. Based on the preclinical AD model, the next step involves detecting actual neurodegeneration in the form of losses in brain structure.

In order to fully understand the relationship between amyloid and brain function, long-term longitudinal studies are necessary, and such studies are underway. A critical question that only longitudinal studies can answer is how long individuals can show evidence of amyloid deposition before exhibiting signs of neurodegeneration and whether there are variables that hasten or slow that transition. Similar questions are relevant to tau tangles as well, but much more research is needed. Answers to these questions will unquestionably be forthcoming. It is clear from initial reports that the damage

from amyloid most likely occurs over several years, making detection difficult in the shorter 1–2-year studies completed thus far. The degradation of the brain associated with amyloid does not appear to occur rapidly.

Neuronal Loss

The second type of neurodegeneration that has been hypothesized to be related to amyloid deposition is neuronal loss. The primary measures utilized to examine neuronal loss as individuals transitions toward AD are decreases in cortical thickness across many brain regions and a specific decline in hippocampal volume. Hippocampal atrophy has long been associated with progression from healthy aging to dementia (Kaye et al., 1997), so amyloid imaging researchers quite logically have attempted to demonstrate a link between amyloid and hippocampal volume. Results have shown that, in fact, high amyloid burden has been related to lower hippocampal volume (Hedden et al., 2009; Mormino et al., 2009; Rowe et al., 2010; Storandt, Mintun, Head, & Morris, 2009), while others have failed to find a relationship (Bourgeat et al., 2010; Dickerson et al., 2009). Several studies have also found that amyloid is associated with reduced gray matter thickness in the same regions that show thinning with Alzheimer's disease (Becker et al., 2011; Dickerson et al., 2009; Dore et al., 2013; Mormino et al., 2009; Rowe et al., 2010; Storandt et al., 2009). While some studies have cast doubt that there is a consistent neuroanatomical signature associated with amyloid burden and preclinical AD (Whitwell et al., 2013; Wirth et al., 2013), it is generally accepted that amyloid is associated with cortical thinning.

Some of the inconsistent findings may be due to more individuals in studies with negative findings being in Preclinical Stage 1 (amyloid only) and positive findings occur when more participants are in Preclinical Stage 2 (amyloid + neurodegeneration).

Overall, while correlations between amyloid and measures of neuronal loss are not detected as consistently across studies as measures of synaptic dysfunction, it is likely a reflection of the more indirect relationship between amyloid and neuronal loss. Unfortunately, we are not aware of any studies to date that explicitly test the sequence from neuronal dysfunction to neuronal loss. Further research, especially longitudinal work, is necessary to establish a clearer picture of how precisely individuals transition from amyloid to synaptic dysfunction to neuronal loss.

Another important issue to consider in a discussion of neurodegeneration in the preclinical AD model is the role of tau tangles. Tau tangles literally kill neurons, so that tau deposition should be a particularly potent marker of neurodegeneration. Amyloid is known to induce the formation of tau tangles in rats (Bolmont et al., 2007), however, due to the limited data on in vivo tau in humans, little is known about the interaction of tau with amyloid and the resultant effects on neurodegeneration. While a small amount of tau is present in the medial temporal lobe in healthy adults before amyloid deposition, it is hypothesized that amyloid induces the spread of tau (and thus neurodegeneration) throughout the neocortex (Price & Morris, 1999). It is clear that tau plays a very important role in the preclinical model of AD. However, until very recently, it was only possible to measure the gross level of tau burden indirectly through CSF obtained from lumbar punctures. The very recent availability of new tracers will hopefully allow PET imaging of tau in the same way amyloid is imaged. In the coming years, tau imaging is likely to provide new insights into the transition from amyloid alone (Stage 1) to amyloid + neurodegeneration (Stage 2). It is notable that CSF studies have revealed that tau is much more predictive than amyloid of cognitive decline (Fagan et al., 2007). Thus tau imaging studies will also play an important role in understanding the transition from Stage 2 to

Stage 3, when cognitive decline becomes apparent, and from there to dementia.

DOES AMYLOID DEPOSITION INVARIABLY LEAD TO COGNITIVE DECLINE?

While the preclinical model of AD predicts that amyloid initiates a cascade that leads eventually to cognitive decline (via neurodegeneration), many early amyloid imaging studies (completed before the model was developed) sought to examine the amyloid and cognition relationship directly. In this section, we will first review the early amyloid–cognition findings, before discussing more recent studies that relate amyloid, neurodegeneration, and cognitive decline altogether, in the sequence predicted by the preclinical model of AD.

Amyloid and Episodic Memory

Due to the well-known relationship of memory dysfunction as an early symptom of Alzheimer's disease, many studies have sought to find a link between amyloid burden and episodic memory. While some cross-sectional studies have found a relationship between amyloid burden and decreased episodic memory performance (Aizenstein et al., 2008; see Hedden, Oh, Younger, & Patel, 2013 for review; Pike et al., 2011; Resnick et al., 2010; Sperling et al., 2013), others have failed to find a significant effect (Ewers et al., 2012; Rodrigue et al., 2012; Storandt et al., 2009; Tolboom et al., 2009).

One issue with these cross-sectional studies is that they attempted to relate amyloid burden to cognitive performance at a single time point, rather than to relate amyloid accumulation to cognitive decline. One way in which studies managed to get around the expense of longitudinal testing was through the use of questionnaires that collected subjective memory reports. Participants were asked to report whether they felt their memory had declined in recent years. Interestingly, greater subjective memory complaints were associated with higher amyloid burden (Amariglio et al., 2012), even in the absence of memory dysfunction.

Unlike cross-sectional studies, longitudinal studies have the potential to establish a causal relationship between amyloid deposition and cognitive decline. Importantly, initial amyloid status is predictive of future progression to MCI and dementia (Villemagne et al., 2011). While there have been few longitudinal amyloid–cognition studies to date, some studies have demonstrated that initial amyloid burden is predictive of decline in episodic memory (Ellis et al., 2013; Lim et al., 2013; Resnick et al., 2010), but others have failed to find a relationship in healthy older adults (Villemagne et al., 2011).

Impact of Amyloid on Other Cognitive Domains

Overall, results from both cross-sectional and longitudinal studies seeking to find a direct link between amyloid and episodic memory have been inconsistent. While fewer studies have evaluated the effects of amyloid on non-memory domains, the findings are just as inconsistent as the studies on episodic memory. While some cross-sectional studies find null results (Lim et al., 2012; Oh, Madison, Haight, Markley, & Jagust, 2012), others have found associations between amyloid and executive function/reasoning (Resnick et al., 2010; Rodrigue et al., 2012; Schott, Bartlett, Fox, Barnes, & Alzheimer's Disease Neuroimaging Initiative, 2010), working memory (Rentz et al., 2010; Rodrigue et al., 2012; Rolstad et al., 2011), processing speed (Rodrigue et al., 2012; Stomrud et al., 2010), and visuospatial function (Pike et al., 2011; Rentz et al., 2010). Likewise, some longitudinal studies have found a correlation between initial amyloid burden and subsequent decline in non-memory domains (Snitz et al., 2013; Wirth et al., 2013), while others have failed

to find a significant relationship (Ellis et al., 2013; Lim et al., 2014; Villemagne et al., 2011).

While some of the null findings in the amyloid–cognition literature may simply reflect insufficient power (many of the early studies had very small sample sizes), these inconsistencies may actually be explained by the preclinical model of AD. It is plausible that the inconsistencies across studies were caused by differences in how advanced the neurodegeneration was is in each study sample, with studies including subjects more advanced in amyloid deposition evidencing a relationship to cognitive function. In support of this point, Rodrigue et al. (2012) selected only the highest amyloid participants (n = 18) from a pool of 137 participants. They then treated amyloid as a continuous variable and correlated it with cognitive performance. The higher the amyloid level, the more likely subjects were in later stages of preclinical AD, and indeed, under these circumstances, increasing amyloid level was a strong predictor of decreasing performance on the speed of processing, working memory, and reasoning.

Amyloid, Neurodegeneration, and Cognitive Decline

By including measures of both amyloid and neurodegeneration, researchers can better assess predictions of the preclinical model of AD. It is expected that in order to observe cognitive decline in amyloid-positive older adults, neurodegeneration must first be present. In concordance with this, Mormino et al. (2009) demonstrated that the effect of amyloid deposition on episodic memory was fully mediated by hippocampal volume. Additionally, Mormino, Betensky, Hedden, Schultz, Amariglio, et al. (2014) demonstrated in a recent 2-year longitudinal study that only those cognitively normal adults with both amyloid and neurodegeneration at baseline exhibited cognitive decline. Thus, these studies that incorporate both amyloid and neurodegeneration support the preclinical AD model and the idea the cognitive decline is a result of a cascade from amyloid to neurodegeneration to cognitive impairment. Lastly, in another recent longitudinal study, Vos et al. (2013) reported that over 5 years the conversion rate to symptomatic Alzheimer's disease was 2% for individuals with no initial pathology (stage 0), 11% for those with amyloid only at baseline (Stage 1), 26% for those both amyloid- and neurodegeneration-positive (Stage 2), and 56% for those previously exhibiting amyloid, neurodegeneration, and cognitive decline (Stage 3). The increasing probability of conversion to dementia in later stages of the preclinical AD model provides confidence that it is an appropriate and useful heuristic for understanding how individuals transition from healthy aging to dementia.

In summary, research on the relationships among amyloid, neurodegeneration, and cognitive decline supports the preclinical model of AD. More longitudinal research, as well as research incorporating tau imaging, is needed to confirm this sequence of events.

MODIFIERS OF TRANSITION TO AD: ENRICHMENT AND DEPLETION FACTORS

Although the preclinical model does an excellent job in describing order and symptoms of a transition from cognitive health to AD, it does not address factors that speed up or slow down the rate of cognitive decline. The role of life course experiences and other individual difference variables that potentially affect brain structure and function is a key element in the STAC-r model shown in Figure 5.1. The STAC-r model distinguishes between brain enrichment and depletion factors that can result from life-course experiences (such as education) or that are biologically based (e.g., a genetic marker that enhances risk). Below we consider enrichment and depletion factors that are likely to affect the speed at which the transition to AD occurs.

Depletion Factors

There are a broad range of variables that enhance AD risk and may speed the transitions through preclinical stages. One of the highest risk factors, as noted earlier, is age itself. It has been long established from autopsy studies that amyloid plaque deposition increases with age (Braak & Braak, 1991; Braak, Thal, Ghebremedhin, & Del Tredici, 2011). Similarly, amyloid imaging studies have confirmed age as a primary risk factor for amyloid deposition (Mielke et al., 2012; Morris et al., 2010; Rowe et al., 2010). Typically, an examination of the distribution of amyloid across age reveals that most of the population is amyloid-negative, but starting around age 60 amyloid deposition reaches a sufficiently high level that a subpopulation of amyloid-positive individuals begins to appear. Interestingly, a recent study by Rodrigue et al. (2012) showed that even after removing the individuals identified as amyloid-positive from a sample of 30–89-year-olds, there was still an increase in amyloid with age. This suggests that even within the group that appears amyloid-negative, there is some sub-threshold level of amyloid that becomes increasingly common as individuals age.

Another depletion factor is the possession of the ε4 allele of the APOE gene. In comparison with other APOE alleles, the APOE ε4 allele markedly increases the risk of AD and decreases the age of onset (Corder et al., 1993). While it has been known for decades that APOE ε4 carriers transition to dementia at earlier age than non-carriers, only recently have we started to understand what this means in the context of preclinical AD. About 19% of the population in the US is APOE ε4 carriers (Strittmatter & Roses, 1996). APOE ε4 carriers are disproportionately represented in adults who are carrying amyloid (Rowe et al., 2010). Recent evidence suggests this APOE ε4-related risk is associated with impaired clearance of soluble amyloid from the brain, resulting in more rapid amyloid accumulation and deposition (Castellano et al., 2011; Deane et al., 2008). This implication of a direct relationship between APOE ε4 and amyloid deposition is supported by evidence that APOE ε4 carriers have greater amyloid deposition than non-carriers in cognitively normal older adults (Morris et al., 2010; Reiman et al., 2009; Rowe et al., 2008). Furthermore, APOE ε4 has also been associated with earlier onset of amyloid positivity (Fleisher et al., 2013), as well as an increased rate of amyloid deposition across age (Morris et al., 2010) in a dose-dependent manner. In a recent longitudinal study, Mormino, Betensky, Hedden, Schultz, Ward, et al. (2014) demonstrated that APOE ε4 carriers who were also amyloid-positive exhibited greater cognitive decline over 1.5 years than amyloid-positive APOE ε4 non-carriers, as well as amyloid-negative APOE ε4 carriers and non-carriers. Thus, these findings indicate that the APOE ε4 allele is a depleting factor that not only shifts the transition to dementia earlier in the lifespan, but also causes individuals to advance more quickly from healthy to demented.

Lifestyle variables are another particularly important depletion factor because they are potentially modifiable and thus possible targets for interventions. Greater amyloid burden has been associated with lower lifetime cognitive engagement (Landau et al., 2012), hypertension (Langbaum et al., 2012), and less physical exercise (Liang et al., 2010). Interestingly, further study has shown the impact of all of these factors is modified by the APOE ε4 allele. For example, Head et al. (2012) found that APOE ε4 carriers who engaged in low levels of exercise had greater amyloid than more physically active APOE ε4 carriers, but that in non-carriers there was no effect of exercise. Similarly, Wirth, Haase, Villeneuve, Vogel, and Jagust (2014) found being less cognitively engaged throughout the lifespan was related to greater amyloid deposition than those who were more cognitively engaged throughout their lives, but only for APOE ε4 carriers. Rodrigue et al. (2013) reported that in

APOE ε4 carriers, significantly greater amyloid burden was detected in those with uncontrolled hypertension, whereas the presence of APOE had no impact on those with controlled hypertension or without hypertension. Taken together, these studies suggest a gene–environment interaction, such that APOE ε4 carriers, while at greater risk for amyloid deposition, are also uniquely suited to intervention. Exercise, cognitive engagement, and controlling hypertension all may reduce amyloid deposition and thus delay transition to dementia.

Enrichment Factors

There is an increasingly large AD literature indicating that higher levels of education and sustained engagement in intellectually challenging activities delay the age of onset of AD (for review, see Stern, 2002). The effect of such enriching activities has also been studied with respect to levels of amyloid deposition in healthy adults (Rentz et al., 2010; Roe et al., 2008; Vemuri et al., 2011). It has been suggested that enriching experiences result in a build-up of cognitive reserve that is protective and allows individuals to withstand negative effects of pathology (Stern, 2002). In line with this argument, using education and IQ on the American National Adult Reading Test as measures of reserve (Rentz et al. (2010), demonstrated that individuals with lower cognitive reserve exhibited worse memory with increasing amyloid burden, while memory in those with higher cognitive reserve appeared to be unaffected by increasing amyloid burden. This provides evidence that enriching experiences may delay the transition from healthy aging to dementia.

It is important to recognize that the impact of these variables can be very significant. For example, research done by the Alzheimer's Association (2014) has indicated that delaying the diagnosis of AD by 5 years would reduce the number of cases diagnosed by over 40%. One also need only consider what it would mean to an AD sufferer and their family to have 5 more years of independence and vitality available to them to recognize the significance of factors that delay the transition to AD.

Conclusion and New Directions

The development of in vivo imaging of the amyloid plaques and tau tangles associated with AD is a breakthrough technology that will allow us to understand the sequence of transformations both brain and behavior undergo on what is very often a long and slow progression to the dementia associated with AD. The Preclinical Model of AD (Sperling et al., 2011) has proven to be a useful heuristic for understanding transitions. The STAC-r model of neurocognition is proving, as well, to be a flexible model that encompasses both pathological and healthy aging trajectories and allows for the integration of experiences and individual differences into our understanding of AD.

As this chapter clearly illustrates, we have much to learn about the earliest phases of AD. It is exciting to recognize that new tools are available that will provide information about causality and help isolate the most plausible timing for interventions. Key questions that remain to be answered that in our view are of pressing importance are as follows:

- More attention needs to be devoted to the study of middle age. Is it possible to isolate a neurocognitive footprint decades before symptoms of AD appear? This issue is of critical importance with respect to timing of interventions.
- What is the temporal relationship between detectable levels of amyloid and onset of cognitive symptoms? If the interval spans a decade or more, is an amyloid-positive PET scan useful information to provide to afflicted individuals? Related to this, what speeds up or slows down progression

through preclinical stages? Can we provide reliable scenarios to patients about their status and future?

- Longitudinal studies are essential to understand causal relationships and transitions. It might be useful to speed up information acquisition to develop 15-year hybrid designs where perhaps three samples were simultaneously initiated with different ages at entry (e.g., 45-, 55-, and 65-year-olds). Such a design would minimize cohort effects but provide fairly complete information regarding the lifespan from ages 45 to 80 in only 15 years.
- The study of tau is of tremendous interest and is likely to provide a significant number of missing pieces to the puzzle of AD.
- Finally, AD occurs in the context of many other disorders. Assessing total neural burden (e.g., white matter lesions, dopamine depletion, etc.) would provide critical information about how AD pathology interacts with other conditions and may be a strong predictor of rapid transitions.

Acknowledgment

Preparation of this manuscript was supported by Grant R37AGO06265-31 from the National Institute on Aging to Denise Park.

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