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Normal Aging and Alzheimer's Disease: Hippocampal and Episodic Memory Differences

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Normal Aging and Alzheimer's Disease: Hippocampal and Episodic Memory Differences

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Dedication

For my mother, who brought me half of the way. For my father, who went the rest of the way. For my sister, brother-in-law, and nephew who came along for the ride.

Abstract

Normal Aging and Alzheimer's Disease: Hippocampal and Episodic Memory Differences

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Alzheimer's Disease (AD) and normal aging (NA) are characterized by structural brain changes as well as cognitive changes that appear over the lifespan. The hippocampus is an area susceptible to early atrophy in both AD and NA; however the differential causes of atrophy are not entirely clear. Hippocampal volume loss in AD is attributed to neuronal death due to underlying pathology. AD often is diagnosed years after the onset of pathology and subsequent atrophy. NA is a continuation of cognitive decline that does not become dementia. Episodic memory (EM) is processed within the hippocampus and is one of the first systems to show deficits in conjunction with both patterns of aging. This review focuses on hippocampal volume loss and EM decline in NA and AD.

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Introduction

Different neural aging patterns occur over the course of life. There are changes that are expected and follow a typical pattern of decline with age. Other changes are unexpected and develop from neuropathological processes. These pathologies can lead to dementia. The most common cause of dementia is Alzheimer's Disease (AD) (Davis et al., 2013; Mueller et al., 2010). AD is marked by the development of beta-amyloid plaques and neurofibrillary tangles (Brookshire, 2014). Normal aging (NA) can present with and without underlying pathology in the cortical tissue. Regardless, both NA and AD have patterns of cortical atrophy.

Hippocampal atrophy (HCA) occurs with or without underlying pathology, and is therefore seen in AD and NA (Apostolova et al., 2012). Moderate and severe AD atrophy can be visualized on neuroimaging and is distinguishable from NA. However, preclinical AD is difficult to differentiate from NA due to a minimal degree of HCA in each.

NA and AD have behavioral and cognitive deficits that mirror the underlying neuroanatomy. Episodic memory (EM) is a memory system affected in both NA and AD (Sexton et al., 2010). EM is processed in the HC. Consequently, EM deficits are one of the earliest hallmarks in both AD and NA (Jahn et al., 2013). Due to the similarities found in both aging patterns, understanding differences will help identify early signs of AD. The purpose of this review is to describe hippocampal atrophy patterns unique to early AD and NA and discuss how these patterns relate to EM deterioration.

Neuroanatomical Overview

CORTICAL ANATOMY

The brain is comprised of the hindbrain, midbrain and cerebral cortex (Gardner, 1968). The Rolandic fissure divides the cortex into the left and rights hemispheres with specific functions reserved for each. The hemispheres are connected by the corpus callosum, which facilitates information moving laterally to each hemisphere continuously. Each hemisphere is further divided into four parts: frontal, parietal, occipital, and temporal lobes. Each lobe supports a unique set of functions (Gardner, 1968; Gibb, 2012). Within the context of this review, the temporal lobe is the most important for the integral role the lobe has in relation to anatomical and behavioral correlates in NA and AD.

The hippocampus (HC) is a structure located deep in the medial temporal lobes and is primarily engaged in processing memory and emotions. The HC is divided into three major sections: the dentate gyrus, subiculum, and CA subfields (Amaral & Witter, 1989). On a coronal view, the subiculum lies medial and inferior to the rest of the HC. The role of the subiculum is relatively unknown, though researchers have asserted spatial concepts may be developed in that area (O'Mara et al., 2009). The dentate gyrus (DG) is the innermost structure of the HC and is responsible for neurogenesis within the HC (García-Fuster et al., 2013). The CA subiculum is further divided into CA1-3 and weaves through the HC between the DG and subiculum. This structure is responsible for temporal processing and temporal encoding (Wang & Diana, 2016). Researchers have observed that HC is an area vulnerable to atrophy with or without pathological

underpinnings (Jagust, 2013). Although a network of brain regions supports memory, the HC plays a central role. As the HC degenerates, memory functions decline.

MEMORY

Neuroanatomical correlates of memory are found throughout the cortex (Eichenbaum & Cohen, 2004). Memory is divided into short-term memory and long-term memory, which are further divided into additional facets of memory (see Figure 1). Episodic memory (EM) is an extension of long-term memory.

EM is the ability to encode and retrieve specific events, or episodes over a lifetime (Tulving & Markowitsch, 1998; Nilsson et al., 2003). An example of an event is a soccer game. Remembering the specific details of what happened during the soccer game (i.e. date, teams, location, etc.) is possible with EM. EM is processed primarily in the HC and is one of the first functions to decline in NA and AD (Jahn et al., 2013).

Deficits in EM manifest as problems remembering events that were processed beyond the time frame of STM. EM is created using encoding and retrieval. Encoding is the first step and registers incoming information from the current event and determines how that episode will be remembered (Tulving, 1983). The second and last step is retrieval and takes place when the memory of the event is recalled. The accuracy of the representation of the recalled memory is dependent on the amount of detail stored when the event took place (Tulving, 1983; Eichenbaum & Cohen, 2001). Encoding and retrieval are supported by the hippocampus and surrounding association areas (Wang and Zhou, 2002). Damage to these areas will cause distortions along with gaps in detail within the memory, which is apparent in both NA and AD.

As the brain ages, degeneration occurs throughout the cortex. Cortical atrophy occurs in several regions in tandem. For example, frontal lobe and parietal atrophy occur in conjunction with HCA in both NA and early AD (Yao et al., 2012). This review focuses on EM and HCA because of the unique vulnerability to pathology and aging observed in the HC that is not present in other cortical systems.

Figure 1: The divisions of memory. Adapted from Eichenbaum & Cohen (2001) and LaPointe (2005).

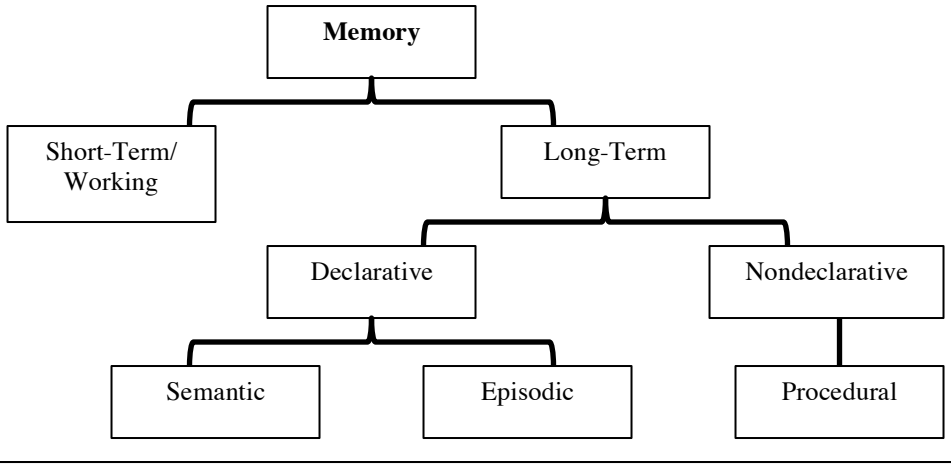

Figure 1 shows the overall breakdown of memory facets. Adapted from Eichenbaum & Cohen (2001) and LaPointe (2005)

Normal Aging

HIPPOCAMPAL ATROPHY IN NORMAL AGING

NA is characterized by noticeable declines in physical and cognitive domains such as orientation, short-term memory, and executive functioning in conjunction with cortical atrophy (Manasco, 2014). In terms of NA atrophy, there are expected and unexpected patterns that occur within the HC.

The literature surrounding HCA in NA is rapidly changing. HCA was thought to occur due to neuronal shrinkage as a result of aging (Freeman et al., 2008). However, recent research has revealed that HCA in NA is more likely caused by underlying agents such as vascular deficits or pathology (Jagust, 2013). Some atrophy has been attributed to beta-amyloid plaques, which are present in 20-40% of NA adults, but the direct effect of this underlying pathology is unclear (Jagust, 2013). AD pathology occurring in NA adults does not cause cognitive deficits as severe as the deficits in dementia. Jack et al. (2015) investigated causes of NA atrophy using gender, age, and protein deposits as variables. They found that deficits as well as atrophy existed as a function of NA rather than due to AD pathology.

The rate that HCA occurs depends on factors such as the number of synaptic connections, genetics, sex, and age (Burke & Barnes, 2006; Jack et al., 2015). Age has been shown to be the greatest contributing factor (Nilsson, 2003). Scahill et al. (2003) conducted a longitudinal investigation that focused on subjects ranging from 31 to 89 years. They found that the rate of atrophy was positively related to the age of the subjects. The degree of atrophy in NA progressed in a random nonlinear pattern among

participants that were less than 70 years of age. After 70 years of age, an accelerated atrophy pattern distinct from the younger-aged groups was noted.

After 70 years of age, the HC volume may be 7 to 8% less than the original volume (Bayles et al. et al., 1987). Barnes et al. (2009) quantified the rate at which HCA occurs in NA. The researchers analyzed longitudinal studies that had tracked the decline of HC volume. Using the average volume decreases and average length of study, the atrophy occurred at a rate of 1.4%. The slow rate of decline creates difficulties for researchers to observe and compare significant reductions of HCA to behavioral deficits because the changes would not be clinically relevant until decades later (Terry & Katzman, 2001).

Other attempts to find significant HCA patterns have been undertaken. Promising methods in Alzheimer's research have come from tracking atrophy in the individual HC subfields (De Flores et al., 2015). Researchers (Chadwick et al., 2014; Bender et al., 2013) tracked HC subfield volumes in adults with ages ranging from 52 to 82 years but failed to produce consistent results. Studies observing HC subfield measurements in NA are not common, and the results are variable. Therefore, little evidence has been found suggesting which subfields are most likely to have atrophy due to shrinkage rather than pathology.

EPISODIC MEMORY IN NORMAL AGING

Episodic memory (EM) decline is slow due to the gradual rate of atrophy in NA (Tromp et al., 2015). The changes in NA are subtle; therefore the differences in EM throughout aging are not easily followed using NA progression as the sole context for

comparison. Researchers (Davis et al., 2013; Tromp et al., 2015; Berna et al., 2012) have attempted to create methods to effectively differentiate EM decline in NA from AD. Two designs that have been found to be effective are cross-sectional and longitudinal.

Methodological Designs and Outcomes

A cross-sectional study examines a behavior across two different groups (i.e. a young group and old group with similar demographics). A longitudinal study observes changes in one group over a long period of time. Researchers have used both methods to track EM decline but they do not produce uniform results from study to study.

Berna et al. (2012) compared middle-aged adults (mean age of 55;0 years) and older adults (mean age of 73;9 years). They analyzed EM using an open-ended recall task that asked each participant to tell about three different events in their life. They concluded there were no differences in decline between the groups as a function of age. However, there are several studies that disprove this conclusion (Koen & Yonelinas, 2014).

Koen and Yonelinas (2014) found that EM deficits were greater in older adults who were considered normally aging. Nilsson (2003) and Rönnlund et al. (2005) found significant declines in EM with NA populations. Nilsson (2003) analyzed research findings related to NA and types of memory. He concluded that EM was unique because of the consistent demonstration of a temporal pattern of decline associated with NA progression. Rönnlund et al. (2005) used a cross-sectional design and longitudinal design to observe the effect NA has on EM within a 35 to 80 year age range. A battery of recall tasks (i.e. action recall, nouns, and statements) was used to measure verbal EM. Rönnlund et al. found comparable results in both designs that showed NA progression was strongly associated with EM decline after 60 years of age.

Reasons for Episodic Memory Research Differences

Berna et al. (2012) speculated that differences within the methodology, timeline, and the samples in each study were the primary cause of discrepancies between EM studies. They noted that the criterion measured and analysis methods were not identical in the studies. Berna et al. analyzed the level of detail within the recalled information. They created a list of 11 details that should be present in the participant's narratives (i.e. age, date, climate, preceding events, emotions) and assigned one point to each detail included. Rönnlund et al. (2005) used criterion measures designed to assess EM (recall of action and statements, verbal noun recognition, and verbal/action noun recall). Berna et al. (2012) analyzed details present during recall, while Rönnlund et al. (2005) analyzed recall ability across 30 to 70 years. Using the same criterion measures across studies will ensure a better comparison and eliminate effects of other variables such as timeline and sample characteristics.

The most efficacious study design is longitudinal, but is difficult to carry out (De Flores et al., 2015) due to attrition and difficulty in acquiring a sample size with a large age range. Johnson (2004) compared the two methods. Cross-sectional studies are more feasible to design, but do not provide an accurate result when observing aging processes. The manner in which individuals age are variable, which makes controlling sample characteristics difficult. Longitudinal studies allow for continuity and minimize the risk of competing demographic factors between two separate groups. Although attrition compromises the validity in longitudinal studies, this problem can be minimized with large sample sizes (Rönnlund et al., 2005).

Extreme differences in the samples from each study were the main cause of contradictory results (Berna et al., 2012; Rönnlund et al., 2005; De Flores et al., 2015; Rossler et al., 2002). Rönnlund et al. found that demographic characteristics among the participants significantly affected the outcomes. For example, they found higher educated participants had better recall regardless of age. Furthermore, studies that encompassed participants from a large age range (35 to 85 years) saw greater deficits in EM than studies with smaller age ranges (55 to 75 years) (Berna et al., 2012). Controlling for differences between cohorts and including a wider age range will increase the certainty that the results are valid estimates of EM decline in NA.

NORMAL AGING SUMMARY

Recent evidence suggests that NA age related brain volume loss is related not only to neuronal shrinkage but also to multiple underlying causes. However, the unique contributions of the underlying causes are unknown. Neurofibrillary tangles and beta-amyloid plaques have been observed within the NA HC, which may contribute to neuronal death in NA. Despite the presence of pathology, individuals considered to be NA have no significant cognitive deficits. Atrophy in NA continues at a stable rate without marked acceleration.

There have been discrepancies in studies attempting to find significant EM deficits in NA. However, there is evidence to show EM deficits can occur as a function of age independent of pathology. Reasons for these discrepancies include study design and mismatched demographic characteristics in the sample populations.

Alzheimer's Disease

Defining Alzheimer's Disease

Alzheimer's Disease (AD) is the most recognized and prevalent cause of dementia (Alzheimer's Association, 2014). AD is characterized by the aberrant presence and development of neurofibrillary tangles and beta-amyloid plaques. The culmination of these proteinopathies causes neuronal death and subsequent cortical atrophy (Brookshire, 2007; Apostolova et al., 2012). AD is incurable and results in death 5 to 20 years after diagnosis (Apostolova et al., 2012).

AD atrophy manifests as memory, cognitive, language, and behavioral impairments that increase in severity as the disease progresses. The Alzheimer's Association (2010) predicts that approximately 16 million Americans will be diagnosed with AD by 2050. On average, AD is diagnosed at 65 years of age (Mendez, 2012), but cases have seen in individuals 55 years and younger (Moon, 2015).

AD has been classified into a series of stages to help describe the progression for research and clinical purposes. Preclinical AD is characterized by development of pathology without any presenting behavioral symptoms (Tondelli et al., 2012). This stage can begin as early as 10 years before Alzheimer's dementia is diagnosed (De Flores et al., 2014; Sperling et al., 2014).

Predementia is a clinical term used to describe a stage presenting with cognitive deficits that do not impede daily activities (De Flores et al., 2015). This stage may or may not be associated with Mild Cognitive Impairment (MCI). MCI is used to describe individuals with symptoms falling between NA and AD with noticeable deficits that are

often confined to one domain (i.e. memory, executive functioning, attention) (Tang et al., 2015; Christensen & O'Brien, 2000). Individuals with MCI may progress to AD or continue without any additional cognitive decline (Petersen, 2016).

Three AD stages are used in both research and clinical settings (see Table 1). They are classified by the severity of AD pathology and symptoms present: 1) Early/Mild AD, 2) Middle/Moderate AD, and 3) Late/Severe AD (Bayles, 1975; Frisoni et al., 2009; Burke et al., 2015).

Bayles (1975) and Frisoni et al. (2009) compiled evidence that tracked AD progression. Early AD is characterized by mild cognitive deficits that impede daily activities on a basic level. The individual might need help with complex tasks (i.e. finances, cooking, driving, medical attention). They will present with poor ability to recall events that happened with complete and accurate detail.

Moderate AD presents with behaviors that are correlated with the degree of underlying atrophy. At this stage there is moderate difficulty completing basic tasks and the individual may need reminders to eat, bathe, or find an object. There are increased memory deficits for activities that happened further in the past and individuals in this stage may not recognize familiar persons or locations (Bayles, 1975; Frisoni et al., 2009; Burke et al., 2015).

Late AD atrophy is characterized by severe deficits in all behavioral and cognitive domains. The person will be withdrawn with impaired ability to control emotional responses. Help is required for completing basic activities (i.e. feeding, dressing) (Bayles,1975; Frisoni et al., 2009; Burke et al., 2015).

Table 1: Stages of Alzheimer's Disease. Adapted from Bayles, 1975; Frisoni et al., 2009; Burke et al., 2015

Stage	Early/Mild AD	Middle/Moderate AD	Late/Severe AD
Clinical Progression	• Forgets details/new information • Poor word recall • Irritability • Problem solving impaired • Spatial disorientation • Difficulty with advanced tasks ♦ Driving ♦ Finances ♦ Medicine	• Decline in long-term memory • Empty Speech • Severe logistic deficits • Misperception/loss of time • Fail to recognize friends and family. • Need reminders for basic routines: ♦ When to eat. ♦ When to bathe. ♦ Bathroom location	• Problems with one-step commands • Emotional lability • Withdrawn • Little conversation • Need assistance ♦ Dressing ♦ Feeding ♦ Bowel movement
Cumulative Atrophy	• Entorhinal Cortex • Hippocampal Association area • Cingulate gyrus	• Hippocampus • Prefrontal Gyrus • Sensorimotor Cortex	• Primary visual cortex • Visual association areas

AD behavioral deficits rarely are present at pathology onset and make early identification procedures unreliable (Sperling et al., 2014). Imaging studies provide an earlier detection method. One of the main goals of AD imaging studies is to determine structural markers to assist in early diagnosis (Scheltens et al., 1992; Sluimer et al., 2009). A strong indicator of AD is rapid and significant atrophy in the hippocampus and surrounding areas.

HIPPOCAMPAL ATROPHY IN ALZHEIMER'S DISEASE

The overall HCA rate in AD is rapid and unpredictable. Atrophy rate is affected by age, dementia onset, health factors, sex, and education level (Leoutsakos et al., 2012; Tschanz et al., 2011; Xie et al., 2009). Calculating an average HCA rate is possible (Barnes et al., 2009), but does not provide enough HCA information due to variability

among individuals with AD pathology. Direct examination of longitudinal studies tracking HCA will provide better information to identify early AD atrophy.

Fjell et al. (2009) and Apostolova et al. (2012) examined early atrophy patterns over a 2-year period. Each study employed a large sample size, which allowed generalization of the results to the population. These results replicated previous studies that observed the HC and entorhinal cortex showed the most atrophy because atrophy originated in those structures. However, overall HC volume loss is not a dependable early AD diagnostic tool (Scheltens et al., 1992; Fjell et al., 2009; Mueller et al. 2010; Apostolova et al., 2012). Examination of individual structures within the HC creates specificity and increases diagnostic accuracy.

Hippocampal Subfields

HC volume can be attributed to different atrophy combinations in hippocampal subfields. Mueller et al. (2010) found there were inherent differences in HC subfield atrophy in AD and other aging patterns (i.e. MCI and NA). The researchers compared total HCA to the atrophy in each subfield to test which volume would provide the best indicator of early AD atrophy.

The HC consists of the subiculum, dentate gyrus, and three cornu ammonis sectors labeled CA1-3 respectively (Mueller at al., 2010; De Flores et al., 2015). Mueller et al. (2010) showed HC subfields do not atrophy simultaneously or uniformly. Instead, each part atrophies at a different rate in response to pathology causing cell death. In AD, CA1, subiculum, and the entorhinal cortex showed severe atrophy while CA2 and the

dentate gyrus were relatively spared. Additionally, Mueller et al. (2010) found that CA1-2 atrophy could be an indicator of a transition from MCI to AD.

The summation of subfield atrophy resulted in a significant reduction in overall hippocampal volume in AD. The investigators also found overall HC volume in early AD was difficult to distinguish from MCI, which indicates HC subfields are a more effective diagnostic marker (De Flores et al., 2015).

AD gradually affects the entire brain (See Table 1). Using HC subfields will increase diagnostic accuracy, but including other cortical areas will continue to increase accuracy (Mueller et al., 2010). Including early memory deficits to detect AD will further increase diagnostic accuracy because a clinical component is added that can be observed without imaging (Bäckman et al., 2001). However, the onset of pathology and deficits are not simultaneous which often leads to memory deficits presenting after AD atrophy has set in (Sperling et al., 2014; De Flores et al., 2015).

EPISODIC MEMORY IN ALZHEIMER'S DISEASE

EM is one of the first behavioral symptoms to manifest in AD and presents after significant HCA has occurred. Researchers (see review by Tromp et al., 2015; Leube et al., 2008, Tomadesso et al., 2015) have attempted to remedy this ineffectiveness by conducting studies that apply what is known about preclinical AD in terms of atrophy and severity in order to detect early EM deficits.

Bäckman et al. (2001) investigated whether EM deficits associated with preclinical AD could be detected accurately. Research was unclear in terms of whether

supported or unsupported retrieval tasks were more sensitive (Bäckman et al., 2001). Therefore, the investigators used recognition (supported retrieval) and free recall (unsupported retrieval) to find the most efficacious method. They found that EM impairment is detectable over six years before AD is diagnosed. However, this was accomplished using statistical analysis. The researchers postulated that these deficits could not be detected using clinical tests alone.

Bäckman et al. (2001) found individuals in preclinical AD have difficulty encoding and consolidating episodic information. Wang and Zhou (2002) found similar results when examining individuals with MCI using visual and verbal episodic memory tasks. They found cognitively impaired individuals encoded 22.8% less information compared to age-matched peers. They attributed these weaknesses to atrophy in the entorhinal cortex, which is considered to be the source of neural encoding. Entorhinal atrophy is expressed more boldly in early AD than MCI, which suggests that EM deficits occur due to problems in cognitive consolidation of new episodes (Weintraub et al., 2012). Within the same study, Wang and Zhou (2002) found that the impaired group retrieved 6.84% less information than the control group. Although this is less than the percentage found in encoding, a measurable decrease in both processes suggests EM is impaired early.

Lange et al. (2002) discovered a longitudinal pattern of decline in EM word recall and story retell tasks that took place slowly over 3 years before AD was diagnosed. A slow behavioral decline, however, is possible despite rapid hippocampal degeneration. Relatedly, the pattern observed by Lange et al. (2002) allowed them to deduce that

individuals with mild EM deficits coupled with a sudden atrophic decline are at risk for AD. However, this fact alone does not aid in early detection; identifying factors that differentiate AD EM deficits from other cognitive decline are needed.

Tomadesso et al. (2015) conducted a study that used imaging paired with EM assessments to specifically investigate EM deficits in predementia. They compared individuals with MCI to NA adult performances in recall of recent events (within the past 10 years) and remote events (occurring 20 to 30 years prior). The researchers found each group had similar difficulty recalling remote events. More importantly, they observed that recent events were difficult for the MCI and NA groups, but were more difficult for the MCI group to recall than the NA group. Forgetting recent events is consistent with anterograde amnesia which is a deficit seen in both AD and NA. This study showed that even in predementia, there are marked differences in EM when compared to NA. However, more studies targeting MCI and predementia are needed to increase the likelihood of identifying early AD from EM decline.

ALZHEIMER'S DISEASE SUMMARY

Atrophy in AD is attributed to cell death catalyzed by underlying proteinopathies. Atrophy manifests in the HC and surrounding areas and continues to grow at a rapid rate as the amount of pathology grows. When distinguishing preclinical AD from NA, overall HCA is not an effective tool because volumes for each group are similar. A better way to distinguish the two aging patterns is to assess degeneration in the specific hippocampal subfields.

EM is processed within the HC and consequently is one of the first cognitive deficits to be observed. While EM deficits are significant and severely limit the individual's activities of daily living in moderate and severe AD, the deficits are subtler in MCI and predementia. Researchers have attempted to describe EM deficits in predementia. However, only recently have researchers identified how EM deficits in predementia differ from deficits in NA.

Normal Aging and Alzheimer's Disease Parallels

Later stages of AD are distinguishable from NA due to significant increases in rate and degree of atrophy (Scahill et al., 2003). NA and preclinical AD, however, do not have obvious differences. Overall, the two aging patterns have significant similarities in areas of atrophy, cortical makeup, and episodic deficits.

HIPPOCAMPAL ATROPHY

Neurological underpinnings are the biggest causes of confusion when distinguishing preclinical AD from NA. Freeman (2008) observed that in NA volume loss, the number of neurons remained the same without neuronal death. However, other studies have observed a marked degree of neuronal death associated with NA that closely matches that of preclinical AD (Jack et al., 2015). This adds support to the argument that NA atrophy has an underlying cause that is not simply the result of old age.

On average, AD HCA can manifest years before there is enough evidence to diagnose AD during the preclinical stage (Tondelli et al., 2012). The similarities in cortical make-up allow for a comparable rate of atrophy to occur in both NA and preclinical AD. Once AD pathology begins, the atrophy rates of NA and early AD are not comparable (Barnes et al, 2009). At the time AD is diagnosed, HCA is significantly greater in AD than NA. As AD progresses into the middle and late stages, atrophy rates increase in relation to the amount of pathology in the cortex causing increased cell death (Brookshire, 2007; Apostolova et al., 2012). Although total HC volume loss indicates the general amount of pathology present, this measure cannot be used to effectively distinguish preclinical AD from NA.

Only measuring total HC volume loss does not clearly differentiate one from the other (Mueller et al. 2010; Apostolova et al., 2012). This is because different subregions

atrophy at different rates depending on what is causing that atrophy. Therefore total HC atrophy in preclinical AD may appear similar to NA because the average volume loss is the same. While research has shown different subfields atrophy when exposed to AD proteinopathies, there are few studies that study HC subfields and NA (De Flores et al., 2015).

Hippocampal atrophy causes many deficits in both NA and AD, but the most noteworthy are episodic memory deficits. EM deficits in NA are comparable to predementia AD because they do not impede daily activities (De Flores et al., 2015). However, the parallels do not move past this stage. The degree of atrophy in NA reflects the degree of severity seen in EM deficits in NA.

EPISODIC MEMORY

Researchers found that the entorhinal cortex was one of the first areas to atrophy in AD (Mueller et al., 2010; De Flores et al., 2015). This area correlates with encoding because this process originates in the entorhinal cortex. Encoding deficits will cause the individual to incorrectly store an event or omit details from the event. Therefore, when the person goes to retrieve the event, information on when the event occurred, who was there or what happened might be missing. This is consistent with anterograde amnesia, an extension of episodic memory seen in AD (Weintraub et al., 2012, Nestor et al. (2003).

Currently, there is not a reliable manner to differentiate EM deficits in NA and AD and predict underlying atrophy (Bakkour et al., 2013; Bäckman et al., 2001). Mild EM deficits often co-occur with severe HC atrophy as well as moderate atrophy. However, function reflects structure more closely in NA than in AD (Bakkour et al., 2013). Therefore, EM deficits will often be proportional to the degree of hippocampal

atrophy in NA. Regardless, using EM alone to predict atrophy is not efficacious because there are other behavioral components in addition to EM that characterize AD and NA.

Unknown Factors Surrounding Alzheimer's Disease and Normal Aging

Research has yielded promising methods to detect AD earlier in the disease, but there are fundamental aspects of AD that are unknown. The origin of AD pathology is a factor that has not been discovered (Davis et al., 2013). Researchers have attempted to identify what causes beta-amyloid plaques and neurofibrillary tangles to develop and cause neuronal death. Individuals have been found to have genetic predisposition to familial AD. However, genetic components only account for a small percentage of AD cases and do not guarantee an AD diagnosis (Burke et al., 2015). Furthermore, because the origin of AD pathology is unknown, scientists are unable to predict when NA will progress to AD. An inadequate amount of information has lead to unanswered questions surrounding areas and causes of atrophy as well as demographic factors.

HC subfields have produced promising results to diagnose AD and even predict changes from MCI to AD (Mueller et al., 2010; De Flores et al., 2015). However, researchers have not found a subfield that predicts a change from NA to AD. This lack of information stems from inadequate study designs comparing HC subfields in NA populations. Researchers are building on these methods to increase efficient observation and comparisons. Causes of atrophy in NA are more complex than areas of atrophy.

Research has demonstrated that AD pathology occurs in NA individuals without the accompanying deficits in AD (Jagust, 2013). Within these individuals, there is reduced cortical thickness coupled with cognitive deficits that are apparent compared to NA counterparts without pathology. However, NA individuals with pathology are not comparative to individuals with early AD because neither atrophy nor behavioral decline is close in severity. NA individuals with pathology may never progress to MCI or AD, thus the trajectory from NA to AD is variable and unknown. Researchers have cited

cognitive reserve as a possible cause of the differentiation in NA and AD with shared pathology (Rentz et al., 2010).

Cognitive reserve is a term used to generalize the effect several demographic factors can have on how an individual responds to presence of AD pathology (Rentz et al., 2010). The researchers determined individuals with higher cognitive reserve had less cognitive deficits in the face of AD pathology (i.e. episodic memory measurements). However, the elements that individually make up cognitive reserve are diverse as they consist of demographic factors unique to each person. This in turn adds a degree of variability that does not identify what specifically preserves cognitive function. The effect various demographic characteristics have on formation of AD and subsequent progression is another unknown element.

The greatest demographic factors that have been shown to affect aging with AD are gender, socio-economic status (SES), and education (Seo et al., 2011; Jack eta al., 2015). Other factors such as health and IQ have also been taken into account in other studies (Stern et al., 1992). Overall, individuals with higher education levels have less cognitive deficits than those with lower levels (Rentz et al., 2010). There is, however, uncertainty in this distinction because studies have shown that education levels, gender, and SES are interrelated and affect one another. For example, men tend to have higher education levels as well as SES, and proved to have higher cognitive reserve in the study done by Rentz et al. (2010). Therefore, the actual influence of specific, individual demographic features on AD is unknown.

Although there are breakthroughs in early AD diagnostic tools, the progress is limited. This will change as researchers determine what causes AD pathology to form and then disrupt NA. Several reasons that have contributed to unknown AD origin are inadequate methods to track HC subfield atrophy in NA as well as inadequate

understanding of the effect demographic factors have on cognitive reserve in AD and NA.

Conclusion

NA and AD patterns of aging are least distinguishable during the earlier stages of AD in terms of degree of atrophy and behavioral correlates. Beyond early stages, AD atrophy and EM deficits increase rapidly due to accelerated neuronal death while NA remains stable and muted. In addition to underlying cause, subfield atrophy contributes to differentiating HCA rates in NA and AD. Although EM deficits correlate with the pattern of atrophy observed in NA and AD, they cannot accurately predict degree of atrophy in AD as in NA. EM is slowly progressive without significant observable structural damage in NA, while EM is more apparent in AD due to areas of atrophy targeting specific neurological correlates in the entorhinal cortex. As AD progresses, other facets of memory and cognition will deteriorate as more of the brain is affected. However, cortical atrophy in NA will not produce EM deficits as severe as the deficits observed in AD. Despite advances in AD treatment and diagnostics, the cause of pathology in NA and AD is unknown. Furthermore, the aspect of degeneration that causes NA to change into AD is also unknown. This is crucial information that, once discovered, will lead research to identify when AD begins to become apparent. Until then, researchers will continue to explore differential pathological patterns in NA from AD.

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