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Neuropathological diagnosis of alzheimer's disease: the relationship between postmortem assessment, cognitive function and functional status in centenarians

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NEUROPATHOLOGICAL DIAGNOSIS OF ALZHEIMER'S DISEASE: THE RELATIONSHIP BETWEEN POSTMORTEM ASSESSMENT, COGNITIVE FUNCTION AND FUNCTIONAL STATUS IN CENTENARIANS.

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Specific Aims

Neuritic plaques (NP) and neurofibrillary tangles (NFT) are the two major hallmarks of Alzheimer's Disease (AD) found within the brain and detectable only at autopsy (Cutler & Sramek, 1996). The presence of these lesions, in conjunction with a clinical history of dementia, is required in order to arrive at a definitive diagnosis of AD (McKhann, et al., 1984). Several sets of neuropathological criteria have been proposed and used for AD diagnosis during postmortem neuropathological assessment, although there has been little consensus regarding which protocol is the best for purposes of research. In addition, few studies have applied these protocols to neuropathological assessment of AD in the oldest old. A better understanding of the relative merits of different neuropathological criteria among centenarians, the "oldest old," is essential to answering the question of whether or not AD is an inevitable consequence of aging.

For this study, we examined a sample of centenarians, all of whom received postmortem assessments using four different neuropathological criteria that are presented in Table 1. These criteria include: 1) Khatchaturian Criteria (Khatchaturian, 1985); 2) Consortium to Establish a Registry of Alzheimer's Disease (CERAD) criteria (Mirra, Heyman, McKeel et al., 1991); 3) Braak and Braak Criteria (Braak & Braak, 1991); and 4) National Institute on Aging- Reagan Criteria (NIA-R; Hyman & Trojanowski, 1998). We investigated the relationship between neuropathological severity level and performance on measures of neuropsychological and functional performance to gain a

more comprehensive understanding of relationships between each set of neuropathological criteria and several clinical outcome measures. Four neuropsychological measures were used, as detailed in Table 2. Mini-Mental State Examination (MMSE; (Cockrell & Folstein, 1988) scores were used to measure antemortem global cognitive functioning. To assess more specific cognitive domains frequently impaired in patients with AD, a measure of executive functioning, the Behavioral Dyscontol Scale (BDS), and a measure of memory, the Fuld Object Memory Evaluation (FOME) were used. Finally, to investigate the possibility that neuropathological burden translates into impairments of daily living skills, the Direct Assessment of Functional Status (DAFS) was used. The following specific aims will be accomplished in this study:

Specific Aim 1

The goal of this aim was to determine whether the four different neuropathological assessment protocols would yield conflicting or consistent diagnostic information regarding AD severity.

Protocols to guide the neuropathological diagnosis of AD were first proposed by Khachaturian in 1985. Since that time, new protocols have been developed, with the goal of improving the accuracy of postmortem AD diagnosis. Most recently, the NIA-R criteria were published in 1997. However, no protocol has been uniformly adopted by neuropathologists (Geddes et al., 1997). As a result, the existence of multiple protocols creates a situation where a diagnosis of AD may vary, contingent upon the protocol used for assessment.

As indicated in Table 3, each protocol uses different criteria for assessing the relevance of neuropathological markers and the extent and location of neuropathological burden. Therefore, we hypothesized that discrepancies among criteria would be apparent when classifying severity of AD-related neuropathology in centenarians. Specifically, since both Khachaturian criteria and CERAD criteria quantify only NPs, we expected these protocols to differ from Braak and Braak criteria, which quantifies only NFTs. Also, since Khachaturian, CERAD, and Braak and Braak criteria measure only one AD-type brain lesion for diagnosis, we expected that these three criteria would differ from NIA-R criteria, which measures two AD-type brain lesions for diagnosis.

Specific Aim 2

The goal of this aim was to investigate the relationship between disease progression and the extent and type of cognitive and functional impairment in a sample of centenarians.

Neuropathological criteria for AD have been developed using the "younger old" (Savva, et al., 2009). Even those investigations claiming to include "older" brains in their analysis regularly used samples between the ages of 70-75 years (Prohovinik, et al., 2006). In general, the current literature is heavily skewed towards younger patients, and very little is known about the brain changes that accompany advanced or extreme age (Skoog, Nilsson, Palmertz, Andreasson, & Svanborg, 1993). However, several neuropathological indicators of AD in the oldest-old have been reported to be divergent from those found in younger brains, in both distribution and concentration of lesions (Jellinger, 2008). Arguably, the available protocols may have differential utilities for diagnosing AD in oldest old, and it is critical to examine how current post-mortem

assessments of AD relate to the ante-mortem clinical status of dementia. By using a sample of centenarians, our study will attempt to elucidate clinical correlates of the neuropathological severity criteria associated with the different classification systems. Our primary goal was to demonstrate how each neuropathological severity grading system relates to neuropsychological test performance in the oldest old. A better understanding of the relationship between each neuropathological severity grading systems and neuropsychological test performance in centenarians would identify how specific types of neuropathology impact discrete cognitive abilities in late life.

1. We hypothesized that severity grading criteria from diagnostic protocols that rely on NFTs as a neuropathological indicator of AD diagnosis would be significantly related to cognitive impairment, whereas severity gradings from protocols that emphasize SPs would not be related to cognitive impairment. Previous evidence indicates that cognitive impairment correlates more strongly with the quantity of NFTs than with SPs in individuals with AD. Therefore, the strongest relationships between neuropathological severity grade and neuropsychological test performance are expected for the NIA-R and Braak & Braak criteria, both of which quantify the presence of NFTs. In contrast, relationships between neuropathological severity grade and neuropsychological test performance would not be expected for CERAD and Khachaturian criteria, given that both sets of criteria emphasize the presence of SP.

2. It is also hypothesized that different stages of disease progression will yield distinct neuropsychological impairments. For example, it is well-known that patients in the earlier stages of AD show substantial deficits in memory, and as the disease progresses, patients begin to show additional deficits in executive function, judgment,

visuospatial capacities and language (Braak, et al., 1999). For this aim, we will investigate the association between cognitive status at the time of study entry and neuropathological severity at death, according to NIA-R criteria. This aim may help to elucidate which cognitive domains are most vulnerable across the stages of disease progression. In addition, we will also explore the possibility that certain cognitive domains might be spared, even during the most advanced stages of AD.

Background and Significance

A Brief History of AD

During a 1906 lecture to German psychiatrists, Alois Alzheimer described the case of Auguste D., a patient he treated while working as a physician in the Frankfurt Asylum (Graeber, 1999). Prior to her death at the age of 55, Auguste D. experienced a wide range of incapacitating symptoms, including progressive memory decline, paranoia, delusions, cognitive impairments and a loss of language abilities (Selkoe, 2001). After a postmortem examination, Alzheimer discovered an unusual pattern of neuropathology in Auguste D.'s brain, including the presence of both senile plaques (SP) and neurofibrillary tangles (NFT). Although plaques had been described previously, Alzheimer was the first to identify tangle pathology and assert the connection between these abnormalities and memory deterioration (Zec, 1993). Later, in 1910, Emil Kraplin assigned Alzheimer's name to the newly discovered dementia that included both clinical symptoms and specific brain changes (Cutler & Sramek, 1996).

A century later, Alzheimer's blending of astute clinical observations and systematic neuropathological examination continues to be the model for Alzheimer's disease (AD) assessment (Khachaturian, 2000). Presently, a definite diagnosis of AD

necessitates that the patient have both a clinical history of dementia and evidence of sufficient numbers of NFTs and SPs at the time of autopsy (Geddes et al., 1997).

Neuropathology in AD

Plaques. Senile plaques (also known as neuritic or amyloid plaques) are the product of dendritic and axonal damage, resulting from to amyloid deposits in the extracellular space (Selkoe, 2001). Two broad types of plaques can be categorized: diffuse and focal. Diffuse plaques involve neurons with normal axons and have been found in large numbers of patients with no clinical signs of dementia. Thus, it has been concluded that these lesions may not be directly harmful (Dickson, Crystal, Mattiace, Masur, Blau, Davies, Yen & Arronson, 1992). Focal, or neuritic plaques consist of abnormal axons, surrounded by a core of amyloid (Cutler & Sramek, 1996).

The core of the senile plaque contains several proteins, but the most abundant is a small peptide known as β-amyloid or a-beta (Aβ) that aggregates into fibrils (Anderton, 2002). Aβ is a normal cellular component and is produced in low concentrations, most likely as a waste product. However, if there is an imbalance between the production and removal of Aβ, an accumulation occurs (Duyckaerts, Delatour & Potier, 2009). This accumulation is thought to contribute to neuronal death or dysfunction through a series of events that includes the production of free radicals, mitochondrial oxidative damage, and an overall inflammatory response (Schindowski, Belarbi, & BuÈe, 2008).

Neurofibrillary Tangles. Neurofibrillary tangles are present within neurons and are a consequence of an alteration of the tau protein (Kidd, 2008). Tau proteins are associated with the microtubules of the cell and are abundant in the central nervous system, where they are expressed most often within axons (Cleveland, Hwo, &

Kirschner, 1977, (Weingarten, Lockwood, Hwo, & Kirschner, 1975). There are several well-understood functions of the tau protein, but most notably, tau binds to and stabilizes microtubules (MT) and allows for MT polymerization (Weingarten, et al., 1975). When using light microscopy, the neurofibrillary lesions of the AD brain can be stained with anti-tau antibodies, revealing paired helical filaments (PHFs) and straight filaments, composed mostly of abnormally hyperphosphorylated tau proteins (Lee, Goedert & Trojanowski, 2001). The cause of these filaments is unclear, but it is possible that the hyperphosphororylation of the tau separates it from the MT, thus increasing the amount of unbound tau in the cell. Hyperphosphororylation is thought to be an early event that transforms tau from its primary soluble form, to an insoluble form. In neurons affected by PHF, the cytoskeleton of the MT and neurofilaments disappear, leading to neuronal death (Anderton, 1997).

Neuropathological Quantification

In order to establish a definitive diagnosis of Alzheimer's Disease, neuropathologists must examine the neocortex, entorhinal cortex, hippocampus, and amygdala for evidence of SPs and/or NFTs. However, the process of making a diagnosis of AD is not without subjectivity and inconsistency on the part of the neuropathologist, leading to efforts to establish reliable diagnostic criteria (Markesbery, 1997).

Khachaturian Criteria. In 1985 the National Institute on Aging, the National Institute of Neurological and Communicative Disorders and Stroke, the National Institute of Mental Health and the American Association of Retired Persons sponsored a workshop. A major focus of this workshop was to formulate a research agenda aimed at delineating the critical issues related to the early and accurate diagnosis of AD, as well

as to develop recommendations for a more standardized approach to postmortem brain investigation (Khachaturian, 1985). As a direct result of this meeting, Khachaturian developed histological guidelines for the identification of AD based on hospital autopsy of patients with fully developed and clinically obvious signs of the disease (Ng'walali, Yonemitsu, Kibayash, & Tsunenari, 2002). This approach requires the age-corrected quantification of neocortical plaques per unit area, with at least 8 neocortical SP densities per square millimeter for patients 50-65; 10 or more for patients 66-77; and 15 or more for patients older than 75 (Giannakopoulos, Hof, Michel, Guimon, & Bouras, 1997). Sections of the frontal, temporal and parietal neocortex are reviewed, in addition to the amygdala, hippocampus, basal ganglia, cerebellum and the spinal cord (Markesbery, 1997). Although plaques are either amyloid or neuritic with tau/PHF positive neurites, the Khachaturian criteria do not provide explicit instructions in regards to the type of plaque that should be enumerated or the exact brain region that should be investigated (Jellinger, 1998).

Since the original proposal of the NIA-supported Katchaturian criteria, efforts to classify pathological features of AD have persisted, and the postmortem diagnosis has continued to evolve. This evolution is based partially on findings that non-demented older adults often meet Khatchaturian critieria for AD (Crystal, Dickson, Davies, Masur, Grober & Lipton, 2000). As a consequence, several groups have since initiated alternative ways to inform the neuropathological investigation of AD (Wisniewski & Silverman, 1998).

Braak and Braak. Braak and Braak developed a staging method to rate the degree and severity of AD disease progression (Kidd, 2008). After the investigation of

83 autopsied brains, Braak and Braak identified a reliable configuration of neurofibrillary tangles amassing in cortical and subcortical areas (Newell, Hyman, Growdon & Hedley-Whyte, 1999). These researchers, unlike Katchaturian, felt that the presence of β-amyloid did not appropriately differentiate between early and more advanced cases of AD. Consequently, their approach focused exclusively on neurofibrillary alterations in the brain, including the development of neuritic plaques, neurofibrillary tangles, and neuropil threads (Wisniewski & Silverman, 1997). More specifically, Braak and Braak proposed that as the disease process progressed, these markers developed in a predictable sequence, appearing first in the inferotemporal allocortex via the hippocampus and then spreading to the neocortical association areas (Braak & Braak, 1991). Six hierarchical levels define Braak and Braak staging. Stages I and II include few (I) or numerous (II) accumulations of NFT in entorhinal cortex, and possible rare NFTs in other brain areas. Stages III and IV include greater numbers of NFTs in the entorhinal cortex, plus the hippocampus, and a few cortical tangles can also be observed. Finally in Stages V and VI, there is severe involvement of the entorhinal cortex and the hippocampus and many tangles in the neocortex (Silver, Newell, Brady, Hedley-White & Perls, 2002).

CERAD Criteria. Formed in 1986, The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) is a longitudinal multi-center study that sought to address the need for a consistent methods of evaluating patients with AD (Gearing, et al., 1995). In 1991, CERAD responded to observed staining disparities and inter-rater counting discrepancies amongst laboratories by proposing new criteria. The new criteria were designed to enhance communication between investigators and to further facilitate

the merging of data from various medical centers (Jellinger & Bancher, 1998). CERAD criteria include assessment of neuritic plaques, using a 4-grade scale ranging from none to frequent (Mirra, 1997). Microscopic sections are required from the hippocampus and the amygdala, as well as from the frontal, temporal, parietal and occipital neocortex (Fillenbaum, et al., 2008). These plaque counts are then placed into the context of three distinct age categories: less than 50, 50-75, and over 75 (Keller, 2006). Finally, age-related NP scores are integrated with a clinical history of dementia to determine whether a diagnosis of AD is possible, probable or definite. No examination of NFT distribution or AD changes in the allocortex is necessary. Furthermore, no standardized description of NP is provided and there is no differentiation between mild or severe forms of the disease (Jelinger & Bancher, 1998).

NIA-R Criteria. In 1997, the National Institute on Aging (NIA), in concert with the Ronald Reagan Institute for the Alzheimer's Association, suggested a new procedure for postmortem diagnosis of AD, including an examination of both neuritic plaques and neurofibrillary tangles (Newell, Hyman, Growdon, & Hedley-Whyte, 1999). After exclusion of other causes of dementia, the likelihood that AD accounts for dementia is considered high, intermediate or low according to the frequency of neuritic AD lesions. lesions are quantified utilizing both the CERAD criteria and Braak staging. For example, the diagnosis of high likelihood of AD requires the combination of frequent neuritic plaques as defined by CERAD criteria, and neurofibrillary tangles in the neocortex, sufficient to warrant a Braak and Braak stage of V or VI (Hyman, 1998). This algorithm only considers the classic presentation of AD, which includes both

plaques and tangles, and thus does not identify other presentations of the disease, including the plaque-only and the tangle-only subtypes (Jellinger, 2008).

Pathological Brain Changes Associated with Age

Normal Aging. Brain changes and mental decline are commonly found in elderly individuals. An extensive body of research has confirmed that humans demonstrate an age-related loss of cognitive performance, including deterioration in fluid reasoning, processing speed, spatial ability and memory (Keller, 2006). In addition, increased age reliably brings about a reduction in dopaminergic receptors in the brain, volumetric shrinkage of brain structures, and a reduced density of while matter (Park & Reuter-Lorenz, 2009). Other universal consequences of aging include granular degeneration of myelin and axonal dystrophy (Dickson, 2005). These physiological changes may be related to the cognitive decline that is observed in aging individuals, which includes reduced abilities in processing speed, working memory, inhibition and cognitive control (West, 1996). For example, Park et al. (2002) conducted neuropsychological assessments on 345 participants, with 48-57 participants represented in each age decade, including individuals in their 20's through their 80's at the time of death. This cross-sectional investigation demonstrated gradual age related declines in cognitive abilities, including working memory, processing speed, and long term memory. Salthouse (1996) has argued that during normal aging, selective domains of cognitive abilities may be affected, with executive function and processing speed showing the greatest vulnerability to age, as compared to other domains.

Although aging is inevitably associated with alterations in the functional performance of the brain and shifts in cognitive abilities, major structural changes are usually minimal and cognitive changes gradual. Thus, the neuropathological presentation and dementia experienced by the patient with AD is not considered "normal" aging and is related to a distinct disease process (Kern & Behl, 2009).

Pathological Aging. Even though the presence of plaques and neurofibrillary tangles are compulsory for a diagnosis of AD, increasing evidence from autopsy studies suggests that the brains of healthy elderly individuals also show signs of AD related neuropathology (Keller, 2006). The presence of NFTs and SPs in non-demented subjects has been referred to as "pathological aging" or "pre-symptomatic AD," and the true significance of the neuropathological markers in otherwise healthy adults is unknown. One study found that, depending on the criteria that were used, a number of older adults with no clinical history of dementia actually possessed neuropathology sufficient to warrant a diagnosis of AD. Within their dementia-free sample, 11% of individuals met NIA-Reagan criteria for a diagnosis of intermediate likelihood of AD, 18% met CERAD criteria for possible AD, and 49% met Khachaturian criteria for AD (Schmitt, et al., 2000). In a similar study utilizing 97 brains of non-demented older adults, 47% met Khachaturian criteria, 39% met CERAD and NIA-R criteria (with all levels included), and 27% meeting Braak and Braak Stage III or higher (Price, et al., 2009). Another neuropathological investigation using 137 brains of non-demented elders, autopsied between the ages of 82 and 85 years, reported that 37.3% met NIA-R criteria for Intermediate/High likelihood of AD (Bennett et al., 2006).

The accumulated data imply a difficulty in determining whether neuropathological markers of AD represent a distinct disease process, or rather, an inevitable age related occurrence (Giannakopoulos, et al., 2007). Possibly, the presence of NFTs and SPs among non-demented older adults indicates a preliminary stage of AD that is not yet associated with the clinical signs of dementia. Perhaps some individuals require extensive neuropathology before cell damage reaches levels sufficient to produce clinical symptoms of AD (Price, et al., 2009).

Neuropathology and Neuropsychological Performance

Sufficient numbers of NFTs and SPs are necessary for a diagnosis of AD, and research indicates that these lesions correlate with the presence of dementia (Goedert, Sisodia & Price, 1991). Clinical-pathological (CP) studies seek to understand both the clinical and biological significance of AD neuropathology and are therefore indispensable for assessing the clinical significance of amyloid plaques and neurofibrillary pathology. Although CP studies have been active for several decades, the relationship between AD neuropathology and the severity of cognitive decline still remains unclear (Nelson, Braak & Markesbery, 2009). Some studies report that plaques correlate highly with dementia. For example, Dickson and colleagues (1995) demonstrated a correlation between cortical plaques and clinical symptoms of AD, as measured by the Blessed Test of Information, Concentration and Memory (BICM). On the contrary, others report that neurofibrillary tangles, and not plaques, correlate with cognitive impairments. For instance, in an investigation of 10 AD patients, dementia severity, as assessed by the Blessed Dementia Scale (BDS) was related to the number of NFTs in the neocortex, yet there was no relationship between the BDS and the presence

of SPs in the same brain region (Arriagada, Growdon, Hedley-Whyte & Hyman, 1992).

Over the years, the divergent outcomes of CP studies present a complicated disease process that has resulted in varied, yet defensible, scientific positions. Although disagreement persists, most of the recent literature asserts that plaques correlate poorly with cognitive status, whereas NFTs seem to correlate more reliably with the clinical manifestations of AD (Gunten, et. al, 2006). However, it is important to note that these recent observations do not necessarily indicate an insignificant role of amyloid plaques in AD. According to the amyloid cascade hypothesis, the disease process begins with the deposition of amyloid beta protein (AbetaP), the main component of plaques, which then leads to the formation of neurofibrillary tangles, cell loss, vascular damage and dementia (Hardy & Selkoe, 2002). However, this hypothesis has recently been called into question, partially based on data indicating the presence of amyloid in non-demented brains (Swerdlow & Khan, 2009). The mitochondrial cascade hypothesis asserts that the underlying cause of AD is early mitochondrial dysfunction and oxidative stress, which subsequently initiates neuropathological changes (Young & Bennett, 2010). Most likely plaques are somehow related to the disease process, yet the quantity of this lesion may not be a useful gauge when evaluating the cognitive status of elderly individuals (Hyman, 1998).

Neuropathology in Centenarians

It is a well-documented phenomenon that the brains of older individuals contain greater numbers of AD related neuropathology, relative to their younger counterparts. These findings, considered concurrently with the rising rates of dementia with age, have contributed to the prevailing theory that AD-type lesions are related to clinical symptoms

of dementia (Double et al 1996). In fact, several quantitative CP correlation studies have supported this theory, identifying an association between neuropathological markers of AD and dementia severity. However, the bulk of these investigations have been conducted with individuals dying in their seventh through ninth decade (Haroutunian et al., 2008). Currently, the literature reflects a paucity of neuropathological investigations of patients older than 95; the few studies that have included the oldest-old provide evidence that the brains of these individuals may be unique, making existing neuropathological severity classification standards potentially less applicable to this population.

The New England Centenarian Study, using a sample of 14 centenarians with both the presence and absence AD, compared neuropsychological assessments with postmortem brain investigations. Although relatively clear CP associations were reported for 8 out of the 14 subjects, with the extent of AD pathology positively correlating with cognitive deficits, results for the remaining 6 subjects were enigmatic. Some subjects had clinical histories of dementia but had no neuropathological evidence of AD, while other subjects had no cognitive impairment despite having substantial neuropathological disease burden. The results led the authors to conclude that dementia was not necessarily an inevitable consequence of advanced age and that AD pathology was not the only significant contributor of cognitive impairments in centenarians (Silver, Newell, Brady, Hedley-White & Perls, 2001). In another cohort-based study of demented individuals ranging from 70 to 100, clinical manifestations of dementia and underlying neuropathological findings varied with age. An association between NFT count and dementia severity was observed. However, this relationship declined with

increasing age (Savva, et al., 2009). Another investigation found that older individuals with dementia had fewer AD pathological features at death compared to younger individuals with dementia; there was no relationship between dementia severity and neuropathological markers of AD in persons over 96 years of age. These authors concluded that neuropathological markers of AD were associated with dementia in the youngest-old, but not in the oldest-old. (Prohovink, Perl, Davis, Libow, Lesser & Haroutunian, 2006).

Present Study Summary

Given the preceding review, the lack of consensus between the various neuropathological severity grading protocols used in post-mortem studies of AD may result in inconsistent diagnoses of AD, particularly in extreme old age. In addition, cognitively intact persons may also meet neuropathological criteria for AD, raising questions regarding the nature of the relationship between cognitive functioning and neuropathological burden in late life. Finally, few studies have investigated these relationships in the oldest old. Existing studies of this select group of persons of "extreme age" suggest the possibility of a different relationship between cognition and neuropathology in these successful survivors. This study will focus on comparing and contrasting similarities and differences among four different neuropathological grading protocols in a sample of persons aged 98 years and older. Relationships between these grading scales and neuropathological severity will be explored.

Method

Participants

Participants (N = 50) in this study were drawn from the Georgia Centenarian

Study (GCS), which included 244 community-dwelling and institutionalized centenarians and near-centenarians (*M* age = 100.6 years, *SD* = 2.04 years, range = 98-108 years of age). This population-based sample was randomly selected from a 44 county catchment area in northern Georgia. Potential participants were identified from a random sample of all nursing homes, assisted living facilities, and older individuals residing in the community using voters' registration records and random digit dialing. The majority of participants (73.4%) had no more than a high school education; 15.6% had a college degree. In terms of living arrangement, 37.3% of the centenarians lived in their private home or apartment, 19.7% lived in assisted living facilities, and 43% resided in skilled nursing facilities. Most centenarians (71.8%) reported that their health was either good or excellent. The average Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) score of the participants was *M* = 16.2 (*SD* = 8.81). The sample was largely female (85%). Participant ethnicity composition was 79% Caucasian and 21% African American. Depending on the number of sessions completed (total of four), participants were compensated up to $600 for their involvement. For a more comprehensive explanation of the data collection procedures used in the GCS, see (Poon, et al., 2007).

Of the 50 participants who came to autopsy, there were six (12%) males and 44 (88%) females. A total of six cases (12%) were African American, and 88% were Caucasian. A cross-tabulation of sex and race indicates that 12% of cases were African American females, 12% were Caucasian males, and 76% were Caucasian females. The mean age was 100.84 (*SD*=2.2 years, range=98 to 106 years), and the mean MMSE score was 15.8 (*SD*=9.3, range=0 to 29). Again, most participants had no more than a high

school education (77%), while 15% were college graduates. The mean number of years of education was 9.3 years (*SD*=5.8 years, range=0 to 17 years).

Neuropathological materials and methods

Approximately 30% of the overall study participants agreed to donate their brains for postmortem neuropathological investigation. All participants were autopsied by William R. Markesbery at the University of Kentucky. Dr. Markesbery quantified neuropathological markers from the brain regions necessary in order to make diagnoses according to Khachaturian, CERAD, NIA-R and Braak and Braak criteria.

Instruments

The instruments used in this study were part of a larger neuropsychological evaluation administered to participants over two two-hour sessions. Each participant participated in up to four total two-hour sessions, which also included blood chemistry analysis, a physical examination, and administration of personality questionnaires and measures of social and economic resources. Participants were typically tested in their place of residence (private home, personal care home, or skilled nursing facility).

General cognitive ability. The MMSE (Folstein et al., 1975) is a well-established measure that contains 30 items that assess orientation, memory, concentration, language and visual skills. Because of its brevity, reliability, and validity, the MMSE is commonly used to assess general cognitive ability among older adults. Research on community dwelling older adults suggests moderate internal consistency (α = .62) in a normal sample and high internal consistency (α = .81) in a sample with Alzheimer's disease (Tombaugh, McDowell, Kristjansson, & Hubley, 1996).

Executive functioning. The Behavioral Dyscontrol Scale (BDS; Grigsby &

Kaye, 1996) assesses motor-dependent executive functioning skills. This nine-item scale evaluates ability to perform bilateral alternating movements, motor inhibition, letter-number sequencing, replication of body postures and gestures, and insight into performance. BDS scores have demonstrated high internal consistency in geriatric inpatients and outpatients (Grigsby, Kaye & Robbins, 1992).

Memory. The Fuld Object Memory Evaluation (FOME; Fuld, 1981) was developed for testing memory in the elderly, and it has been standardized on nursing home residents. Ten common objects are presented in a black cloth bag (e.g., bottle, ball, key), and the examinee is instructed to identify each of the objects by touch. Afterwards, the examinee is told to remove the object from the bag and to identify the object after seeing it. Next, the objects are placed back in the bag and the examinee is distracted by a verbal fluency task. Following the distraction task, there is a second recall period, during which the examinee is asked to recall the objects from the bag. There are four more subsequent recall trials, in which the examinee is reminded of the omitted items at the end of each recall period and then is distracted using verbal tasks. Each examinee's storage efficiency (number of items recalled after each distracter task) and retrieval efficiency (number of words recalled on each trial) is assessed.

The FOME has been used in a number of studies of aging and dementia, and excellent reliability and normative data are available for the FOME, when given to older adults (Fuld, 1981; Marcopulos, McLain, & Giuliano, 1997). For example, using a sample of 96 elderly Chinese participants, test-retest reliability was found to be 0.92 and parallel-form reliability was found to be 0.96 (Chung & Ho 2009). In a sample of 104 African Americans and European-Americans, with and without dementia, it was

demonstrated that the FOME was able to accurately distinguish those with dementia 98.3% of the time (Mast, Fitzgerald, Steinberg, MacNeill, & Lichtenberg, 2001).

For the purposes of this study, the recognition, recall, and retention estimate (five-minute delayed recall and recognition) will be examined, as these measures provide a comprehensive index of retention of newly learned material when using the FOME. Also, the sum of items consistently recalled over trials (repeated retrieval) will be included in the analyses, which provide an index of immediate learning over trials and demonstrates how efficiently information is retrieved from memory during new learning.

Instrumental activities of daily living. Performance-based measures of instrumental activities of daily living were assessed using a modified version of the Direct Assessment of Functional Status (DAFS; Loewnstein et al., 1989; Loewenstein, Rubert, Arguelles, & Duara, 1995; Loewenstein et al., 1992). Importantly, the DAFS is a clinician-rated scale, which helps to eliminate the bias and inaccuracies inherent in proxy or self-report measures (Miller, et al., 2010). In order to administer the DAFS, the clinician asks the patient to perform tasks related to time orientation, communication, transportation, preparing for grocery shopping, financial skills, grocery shopping, dressing and grooming, and eating. The measure assesses both BADLs and IADLs. However, only IADL tasks were examined in the current study, given their strong relationship with cognitive functioning. Furthermore, reading transportation signs, preparing for grocery shopping, and grocery shopping tasks of the DAFS IADL items were omitted given their physical demands and low likelihood that centenarian participants performed these tasks with any regularity. Each DAFS IADL task was scored according to objective criteria that evaluated the number of correct steps

performed for each task, or the number of correct responses given for a particular task. The IADL score was calculated by summing the time orientation, communication, and financial skills scales (possible range = 0-58 points, higher scores represent higher functional status). The DAFS has been used with older adults with Alzheimer's disease (Lowenstein et al., 1989) and in community-dwelling samples (Mitchell & Miller, 2008). DAFS scores also have demonstrated inter-rater reliabilities ranging from .91 to 1.0 and three to seven week test-retest reliabilities of .92 to 1.0 in healthy older adults (.72 to .91 in older adults with memory disorders) across summary functional scales (Lowenstein et al., 1989).

Anticipated Problems and Proposed Solutions

Several study limitations were anticipated. Ideally, each subject would have had an evaluation at the same time point, near the time of death, to relate cognitive impairment to neuropathology found at autopsy. However, obtaining neuropsychological test data shortly before death was not always possible, creating some variation among the sample regarding the most recent neuropsychological evaluation and the time of death. Therefore, the relationship between the amount of time between neuropsychological testing and postmortem brain analysis was examined.

It is well established that within an elderly sample, there are many possible confounding disease processes contributing to cognitive impairment, including cerebrovascular disease (CVD), dementia with Lewy bodies, argyrophilic grain disease, and hippocampal sclerosis (Nelson et al., 2007). However, excluding brains with concurrent pathology would not necessarily enhance the understanding of the currently

used diagnostic systems, especially in a sample of the oldest old.

It is recognized that a small percentage of the larger sample agreed to brain donation, potentially resulting in a selection bias. Because the sample is disproportionately female and Caucasian, the small cell sizes for the combination of gender and ethnicity in this study precludes subgroup analysis of gender and ethnic factors. However, we compared the demographic characteristics of the larger sample to the demographic characteristics of the participants used in our study. These comparisons allowed us to identify any possible sources of demographic biases.

Finally, this study measures cognitive status, utilizing a set of measures selected by the researchers for specific reason, such that each measure is related to impairments commonly seen in patients with AD. Therefore, it is possible that there are other relevant domains of cognitive functioning not investigated with the measures used in this study. However, given the small sample size, it was necessary to restrict the number of DVs to a reasonable size.

Data Analysis

Data for this study was analyzed using Stata Statistical Software: Release 10 (StataCorp., 2007). Neuropsychological tests were screened for univariate outliers by inspecting influence plots and extreme values. In addition, for all regression analyses, regression diagnostics were used to identify overly influential observations. Values were considered for removal based on standardized residuals (if <-3 or >3), DFBetas (if >.28), and Cook's Distance (if >.08). In order to check for multicollinearity, the variance inflation factor (VIF) was examined, with values greater than ten indicating a problematic linear relationship. Overall, no data points were removed from the final

analyses.

Specific Aim 1 was analyzed using a series of McNemar-Bowker tests for correlated proportions. These analyses showed the extent to which each pair of neuropathological criteria, as applied to each person, differed with respect to their severity classifications. This statistical procedure also indicated where classification errors were most frequent (e.g., does one criteria over-predict severity or under-predict severity relative to another set of criteria). When comparisons were being made between two sets of neuropathological criteria with unequal numbers of severity levels, levels were collapsed appropriately to allow for equivalent comparisons. Both NIA-R criteria and CERAD criteria have three severity levels, Braak and Braak criteria has six severity levels, and Khachaturian criteria has two severity levels. When comparing to NIA-R and CERAD to Braak and Braak, Braak and Braak stages I and II, III and IV, and V and VI were combined in order to establish three severity levels. Khachaturian criteria has a dichotomous classification: either AD is present or absent. In order to establish two levels, Braak and Braak stages I and II were collapsed to represent the absence of AD; stages III, IV, V, and VI were collapsed to represent the presence of AD. When comparing Khachaturian to both NIA-R and CERAD, the severity level indicating the least amount of neuropathology was used to represent the absence of AD, and the reaming two levels were collapsed to represent the presence of AD. Because each set of neuropathological criteria was ordinal in nature, Spearman rho rank-ordered correlations were computed to determine the extent of agreement between each pair of criteria.

Specific Aim 2.1 was analyzed using hierarchical multiple regression analyses separately for each neuropathological grading system. Scores for each

neuropsychological test served as the dependent variables. After entering age, education, and gender, dummy coded values for the severity levels for a given neuropathological grading system were entered to determine the proportion of variance accounted for by that system. These analyses indicated to what extent neuropathological severity could predict neuropsychological test performance. Dummy coding was used, with the reference group being the neuropathological classification level indicating the least amount of pathological burden. It was anticipated that some classification systems would be better at predicting impairment, thus these systems would yield significant differences between levels. The R^2 change was examined to provide an indication of how much each neuropathological severity grading system contributes to the variation in the neuropsychological measures. Greater R^2 change provided evidence that a neuropsychological measure is sensitive to neuropathological burden.

Specific Aim 2.2 was analyzed using the Georgia Centenarian Database to establish normative data for the neuropsychological measures under study. After removing the 50 participants included in the current study, data from the remaining 194 centenarians was used to calculate the mean performance on each neuropsychological measure. Subsequently, impaired performance was defined as one standard deviation below the mean and intact performance was defined as above one standard deviation below the mean. The variables for the FOME Total Recall, Total Recognition, and Repeated Retrieval Indices were not normally distributed, and the standard deviation exceeded the mean. Therefore, these measures were excluded from the analysis. Using a Fisher's Exact Test, the proportions of intact and impaired scores on the BDS, the MMSE, the DAFS IADL and the FOME Retention Estimate Index were compared

across AD disease severity rating, using NIA-R criteria.

Results

Preliminary Analysis

Since participants included in our study were not randomly assigned to brain donation, we compared the demographic characteristics of the larger sample with the participants included in the present study. The participants that agreed to brain donation had an average age of approximately 101 years (*M* age = 100.8 years, *SD* = 2.15 years); approximately nine years of education; (*M* education=9.26 years, *SD*=5.84 years); and an average MMSE score of 15.8 (*SD*=9.34). Out of the 50 participants included in the present study, 12% were male and 12% were African-American. The remaining 194 centenarians had an average age of 100.5 years (*M* age = 100.58 years, *SD* = 2.01 years); approximately 11 years of education; (*M* education=10.67 years, *SD*=3.74 years); and an average MMSE score of 16.30 (*SD* =8.69). 16% of these participants were male and 24% were African-American. Independent sample t-tests were used to determine whether significant differences existed between the two groups. There were no significant differences in age t(72.6) = .89, *p*=.18; years of education t(59.73)= -1.32, *p*=.95; and MMSE scores t(53.11)=-.37, *p*=.64. A chi-square test indicated that the two groups did not differ in terms of race χ^2 (1)=2.86, *p*=.09 or gender χ^2(1)=.46, *p*=.50.

There was variation in our sample related to the amount of time that had elapsed between each participant's neuropsychological evaluation and their time of death. In order to address this issue, we investigated the correlation between the number of days the participant lived after completing the neuropsychological evaluation (days) and neuropsychological test performance. The number of days between testing and death was

significantly related to BDS (r=.51, p<.05); DAFS IADL (r=.43, p<.05); FOME Retention Estimate Index (r=.29, p<.05); and the MMSE (r=.38, p<.05). Days was not related to the FOME Total Recognition Index (r=.16, p=.31); FOME Total Recall Index (r=.25, p=.07); or the FOME Repeated Retrieval Index (r=.18, p=.20). Although the number of days prior to death was related to most of the neuropsychological measures, this variable was not significantly related to the any of neuropathological criteria under study.

Specific Aim 1

The goal of this aim was to determine whether the four different neuropathological assessment protocols yielded conflicting or consistent diagnostic information regarding AD severity. NIA-R criteria severity ratings departed significantly from symmetry when contrasted with the severity ratings of both CERAD (p=.03) and Khachaturian criteria (p<.01). When compared to NIA-R, CERAD over-predicted neuropathological severity. The greatest disagreement between classifications occurred between CERAD "probable" AD and NIA-R "low likelihood" of AD. When compared to NIA-R, Khachaturian also over-predicted neuropathological severity. The greatest disagreement between classifications occurred between the Khachaturian diagnosis of AD and NIA-R "low likelihood" of AD. There was symmetry among the remaining comparisons: Braak & Braak and NIA-R (p=.25), Braak & Braak and CERAD (p=.06), Braak & Braak and Khachaturian (p=.55), Khachaturian and CERAD (p=.45). Spearman rho rank-order correlations indicated that there were significant associations amongst all criteria assessed: Khachaturian and Braak and Braak (rho=.63, p<.01); Khachaturian and CERAD (rho=.64, p<.01); Khachaturian and NIA-R (rho=.73,

p<.01); NIA-R and CERAD (rho=.74, *p*<.01); NIA-R and Braak and Braak (rho=.93, *p*<.01); Braak and Braak and CERAD (rho=.59, *p*<.01). In summary, there was general agreement among most of the neuropathological grading criteria. However the NIA-R criteria differed significantly from the CERAD and the Khachaturian criteria, and a non-significant trend was observed when the Braak and Braak and CERAD criteria were compared.

Specific Aim 2

The goal of this aim was to investigate the relationship between disease progression and the extent and type of cognitive and functional impairment in a sample of centenarians.

Specific Aim 2.1. This aim hypothesized that severity grading criteria from diagnostic protocols that rely on NFTs as a neuropathological indicator of AD diagnosis would be significantly related to cognitive impairment, whereas severity gradings from protocols that emphasize SPs would not be related to cognitive impairment. After controlling for demographic variables, NIA-R criteria predicted performance on the MMSE (R^2 change=.18, F(2,32)=4.86, *p*<.05) and the FOME Retention Estimate Index (R^2 change =.18, F(2,32)=5.48, *p*<.01), the FOME Total Recall Index (R^2 change =.15, F(2,32)=3.51, *p*<.05), and the FOME Repeated Retrieval Index (R^2 change =.20, F(2,32)=4.86, *p*<.05). A similar pattern was found with the CERAD, which also predicted performance on the MMSE (R^2 change=.18, F(2,32)=4.86, *p*<.05) and the FOME Retention Estimate Index (R^2 change =.15, F(2,32)=4.25, *p*<.05), the FOME Total Recall Index (R^2 change =.18, F(2,32)=4.48, *p*<.05), and the FOME Repeated Retrieval Index (R^2 change =.19, F(2,32)=4.48, *p*<.05). Braak and Braak criteria

predicted performance on the MMSE (R^2 change=.14, F(2,32)=3.62, p<.05) and the FOME Retention Estimate Index (R^2 change =.13, F(2,32)=3.67, p<.05). Khachaturian criteria did not predict performance on any of the neuropsychological measures assessed.

Specific Aim 2.2. In this aim, we hypothesized that different stages of disease progression will yield distinct neuropsychological impairments. After removing the 50 participants who agreed to brain donation, we established normative data for the neuropsychological measures under study using the remaining 194 Centenarians (see Table 4). Impaired performance was defined as one standard deviation below the mean and intact performance was defined as above one standard deviation below the mean. A Fisher's Exact Test of the relationship between NIA-R severity rating and presence or absence of neuropsychological impairment was not significant for any neuropsychological or functional measure. However, there was a non-significant trend for the FOME Retention Estimate (p=.09, Cramer's V=.40), such that those classified as "impaired" on this index of the FOME had more severe AD neuropathology, with the greatest proportion of impaired individuals classified as having a "high likelihood" of AD. Additionally, those classified as "intact" had less severe AD neuropathology, with the greatest proportion of intact individuals classified as having a "low likelihood" of AD.

Discussion

We found that the NIA-R criteria differed significantly from both the CERAD and Khachaturian criteria. The remaining comparisons did not yield significant differences. Spearman's rho correlations ranged from .93 to .59. The strongest association was found between NIA-R and Braak and Braak, and the weakest association

was found between CERAD and Braak and Braak. These findings are consistent with recent research from Brunnstrom and Englund (2011), who compared four sets of neuropathological criteria, including: Braak and Braak, CERAD, NIA-R and the Poly-Pathology Alzheimer's Disease Assessment. Although these authors did not include centenarians in their sample, they nevertheless reported "suboptimal" correlations between the four sets of neuropathological criteria used for AD diagnosis in their study. Our work, in conjunction with the aforementioned investigation, provides additional evidence of disagreement among neuropathological diagnostic criteria. Therefore, the criteria used by a neuropathologist can ultimately have a bearing on the quantification of Alzheimer neuropathology and the subsequent diagnosis.

Although severity classifications based on NIA-R criteria were divergent from the severity classifications based on CERAD criteria, our results indicate that these two criteria both predict neuropsychological performance level on the MMSE and three FOME indices (Recall, Retention, Repeated Retrieval). In contrast, Braak and Braak criteria predicted performance on the MMSE and the FOME Retention Index, and Khachaturian criteria did not predict performance on any of the measures assessed. The observed overlap between NIA-R and CERAD was not expected. Clinico-pathological studies have provided more support for the detrimental impact of NFTs on neuropsychological test performance, compared to NPs. In general, correlations between ante-mortem cognitive dysfunction and the quantity of NPs found in the brain post-mortem are weak (Nelson, Kukull, & Frosch, 2010). It is not uncommon for individuals with considerable amounts of NPs to have no clinical signs of AD. For example, after examining 1,672 brains, one study found that NPs were the most common disease

process observed in the 242 participants who had intact cognition prior to death (Sonnen, et al., 2007). As a consequence of the accumulated research evidence indicating a limited relationship between NPs and clinical symptoms of AD, neuropathologists are particularly hesitant to interpret amyloid deposition in the brain as a harbinger for diagnosis (Giaccone, et al., 2011). Therefore, it was expected that Braak and Braak criteria would best predict neuropsychological test performance. However, the similarities between NIA-R criteria and CERAD criteria raise some questions regarding the significance of NFTs in the oldest old. Could the presence of NPs play a more detrimental role in memory as humans advance to the extremes of old age? Alternately, could the relationship between NFTs and cognition be less pronounced in centenarians, compared to the younger old? The few studies that have included the oldest old have provided some support for an age dependent relationship between cognition and neuropathology. For example, Savva et al. (2009) reported that the relationship between NFTs and dementia status in older participants was weaker, when compared to younger participants. Similarly, (Dolan, et al., 2010) conducted postmortem brain examinations in 209 elderly individuals and found that NFTs were associated with more cognitive impairment among the younger participants, but older participants with equal numbers of NFTs had fewer clinical signs of dementia. Because there is evidence that suggests that NFTs become less influential with age, it may be possible that the accumulation of NPs then becomes more influential with age. In order to refine the neuropathological assessment of AD, the association between increasing age, NPs and NFTs deserves further investigation.

The unforeseen relationship between CERAD criteria and cognitive functioning may also be supported by the "amyloid cascade hypothesis", which posits that β-amyloid is directly and indirectly responsible for the neurodegeneration observed in AD. According to this theory, the accumulation of fibrillar β-amyloid plaques in the brain eventually leads to neuronal dysfunction, neuronal death, and cognitive decline (Khairallah & Kassem, 2011). It has been suggested that β-amyloid can collect near synaptic terminals, damage the synapses, and eventually lead to the cognitive impairment seen in patients diagnosed with AD (Reddy & Beal, 2008). In addition, excess β-amyloid may interfere with mitochondrial function (Anandatheerthavarada, Biswas, Robin, & Avadhani, 2003). Because the human brain requires energy to operate, it is exceedingly sensitive to mitochondrial changes. Animal models have provided evidence that mitochondrial dysfunction is associated with cognitive impairment, and it is believed that these same mechanisms may account for the cognitive changes observed in humans with AD (Hauptmann, et al., 2009). These results are consistent with our findings, which suggest that accumulations of NPs may be significant, especially for those that reach the extremes of old age. However, it is also possible that by simply living a long life, one will invariably accumulate more β-amyloid and the subsequent neuronal changes β-amyloid is known to produce. Therefore, additional research will be necessary in order to elucidate the role of NPs and β-amyloid within the aging brain.

Contrary to expectations, our findings did not reveal a significant relationship between NIA-R AD disease severity ratings and impaired neuropsychological test performance. However, there was a non-significant trend for the FOME Retention Estimate Index. This trend was not surprising considering that the hippocampus, which

is required for memory formation, is affected during the earliest stages of the disease (Bliss & Collingridge, 1993). According to our results, greater neuropathological burden as classified by NIA-R criteria may be associated with greater memory impairment.

Limitations and Future Directions

One limitation of our study is that besides AD pathology, there are other brain and vascular dysfunctions associated with increased age and decreased cognitive performance. Therefore, it is difficult to determine if observed neuropsychological weaknesses are directly associated with a specific AD type lesion. For example, according to some estimates, hippocampal sclerosis is found in approximately 26% of the elderly population (Zarow, Sitzer, & Chui, 2008). Additionally, the vast majority of brains at the extremes of age will reveal, at the very least, signs of an emerging vascular disease. A recent investigation of 1,110 autopsied brains found that those participants who lived beyond 95 years were more likely to have hippocampal sclerosis pathology, and less likely to have AD pathology, as compared to younger participants. These authors conjecture that the positive correlation between age and dementia may be best explained by cerebrovascular pathology and hippocampal sclerosis, not by AD neuropathology (Nelson, et al., 2011).

Another limitation of our study was the variability among our participants regarding the amount of time that had elapsed between neuropsychological evaluation and time of death. When examining this relationship, we found that days prior to death was related to neuropsychological test performance, increasing the likelihood that days prior to death would have an impact on our results. We found that for several of the neuropsychological tests there was a significant association, such that the longer the

participant lived after completing a neuropsychological evaluation, the better their performance on cognitive and functional measures. This finding is consistent with the "terminal decline hypothesis", which suggests that factors that contribute to death may also interfere with cognitive functioning in the years immediately proceeding death (Kleemeier, 1962). Studies have demonstrated that older adults experience an accelerated decay in neuropsychological performance, which starts during the last three and a half years of life (Wilson, Beck, Bienias, & Bennett, 2007). But, there is some evidence to suggest that terminal decline is markedly different in centenarians. For example, one study found that the functional impairment associated with terminal decline began closer to the age of death in the oldest old, sparing cognitive abilities in this population compared to the younger old (Hitt, Young-Xu, Silver, & Perls, 1999). In addition, there is some evidence which implies that AD neuropathology may be linked to the phenomenon of terminal decline; however, there is a paucity of studies that have examined this relationship, making this theory tentative at best (Wilson, 2008). Future investigations should employ longitudinal designs to explore the association between AD neuropathology and terminal decline, in samples of the younger old and oldest old. A more comprehensive examination of these relationships could enhance our understanding of age-related cognitive changes associated with AD, which in turn could enhance end-of-life care for aging individuals.

There is a growing body of literature that seeks to identify modifiable risk factors of AD and research has indicated a possible relationship between diet and AD (Reynish, Andrieu, Nourhashemi, & Vellas, 2001). For example, epidemiological studies show evidence that serum cholesterol and saturated fats are related to an increased risk of AD,

while omega-3 fatty acids and antioxidants are related to a decreased risk of AD (Morris, 2009). Although human studies that have examined the association between dietary factors and AD have not included neuropathological data, recent research using transgenic mouse models have examined AD neuropathology as it relates to diet and nutrition (Mobbs, Yen, & Hof, 2007). For instance, one study has indicated an association between increased omega-3 intake and decreased in β-amyloid (Lim, et al., 2005). Similarly, another study found that vitamin-E levels in mice were related to reductions in β-amyloid accumulations in the brain (Sung, et al., 2004). Since our understanding of the association between diet and AD neuropathology comes largely from animal models, future research should attempt to replicate animal findings using human samples. In view of the fact that available medications are known to result in minimal improvements, understanding the influence that diet may have on the progression of AD could lead to the development of more effective interventions and symptomatic relief (Kaduszkiewicz, Zimmermann, Beck-Bornholdt, & Van Den Bussche, 2005). With animal models indicating a relationship between dietary changes and β-amyloid reductions, taken with our current findings, dietary interventions may be particularly important for those individuals who reach the extremes of old age.

Conclusions

In conclusion, our findings indicate that there are inconsistencies among the available post-mortem diagnostic criteria for AD, such that diagnoses made with NIA-R criteria may not be in agreement with diagnoses made with either CERAD or Khachaturian criteria. Further research focused on establishing a "gold standard" neuropathological diagnosis of AD is needed. A shared lexicon would encourage more

consistency among researchers, thereby enhancing collaboration and the dissemination of valuable information. In addition, development of a gold standard should rely on research that considers the way AD develops and is manifested throughout the lifespan.

Our results also indicated that NIA-R criteria and CERAD criteria were both able to predict general cognitive status and memory performance. In addition, NIA-R and CERAD criteria proved to be superior at predicting memory performance, as compared to Khachaturian and Braak and Braak criteria. This finding suggests that the preponderance of evidence indicating a significant role of NFTs relative to NPs may be related to the age of the participants under study. In addition, we also found a non-significant trend suggesting that that the FOME Retention Estimate might be sensitive to increasing amounts of neuropathology.

The present study makes important contributions to the limited literature addressing AD-type neuropathology in centenarians. Centenarians represent a unique population that may provide valuable insights into the final stages of the progression of AD. Therefore, to better understand this disease process, future research efforts should continue to examine the consequences of AD neuropathology in individuals who live to the extremes of old age.

Table 1

Independent Variables Examined in the Present Study

Neuropathological criteria	Levels	Comparisons for regression
Katchaturian	None	No evidence of AD compared to Yes, evidence of AD
Braak & Braak	Stages I,II,III,IV,V,VI	Stage I and II compared to stage III and IV and also compared to V and VI
CERAD	Possible, probable or definite (after integration of plaque count and clinical history of dementia)	Possible AD compared to probable AD and also compared to definite AD
NIA Regan	High, intermediate or low	Low likelihood of AD compared to intermediate likelihood of AD and also to high likelihood of AD

Table 2

Dependent Variables Examined in the Present Study

Neuropsychological Measure	Purpose	Score used
Mini Mental State Exam (MMSE)	General measure of cognitive status	Total score
Behavioral Dyscontrol Scale (BDS)	Assessment of motor dependant executive functioning skills	Total score
Fuld Object Memory Evaluation (FOME)	Measure of memory	Repeated Retrieval Index, Total Recall Index, Total Recognition Index, Retention Estimate
Direct Assessment of Functional Status (DAFS)	Assessment of the ability to perform tasks necessary for daily living	Instrumental Activities of Daily Living (IADL)

Table 3

Neuropathological Criteria

Neuropathological criteria	Plaques	Tangles	Location	Levels
Katchaturian	Age adjusted neocortical plaques (neuritic and diffuse) per unit	Necessary for AD diagnosis, only if patient is younger than 75	Neocortex (frontal, temporal and parietal lobes)	Yes or No
Braak & Braak	Not necessary for AD diagnosis	Assessment of neurofibrillary tangles, and neuropil threads	Inferotemporal allocortex, hippocampus, neocortical association areas	Stages I,II,III,IV, V,VI
CERAD	Assessment of neuritic plaques, using a scale from none to frequent	Not necessary for AD diagnosis	Hippocampus, amygdala, and neocortex	Possible, probable or definite
NIA Reagan	Not necessary for AD diagnosis	Not necessary for AD diagnosis	A combination of CERAD and Braak & Braak	High, intermedia te or low

Table 4

Normative Data from the Georgia Centenarian Study

Measure	*M*	*SD*	n	Minimum	Maximum	-1 SD
BDS	8.23	6.50	183	0	19	1.73
MMSE	16.22	8.74	195	0	30	7.48
DAFS IADL	26.29	18.19	182	0	58	5.1
FOME Total Recall	2.90	3.01	186	0	10	N/A
FOME Retention Est.	5.94	4.03	186	0	10	1.91
FOME Total Recognition	3.03	2.40	186	0	9	.63
FOME Repeated Retrieval	6.03	7.53	197	0	30	N/A

Note: MMSE= Mini Mental State Exam, BDS=Behavioral Dyscontrol Scale, FOME= Fuld Object Memory Evaluation, DAFS IADL=Direct Assessment of Functional Status Instrumental Activities of Daily Living

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ABSTRACT

NEUROPATHOLOGICAL DIAGNOSIS OF ALZHEIMER'S DISEASE: THE RELATIONSHIP BETWEEN POSTMORTEM ASSESSMENT, COGNITIVE FUNCTION AND FUNCTIONAL STATUS IN CENTENARIANS.

by

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Major: Psychology (Clinical)

Degree: Master of Arts

Several sets of neuropathological criteria have been used for the postmortem diagnosis of Alzheimer's Disease (AD), but few studies have examined these criteria in the oldest old. For this study, we examined a sample of centenarians, all of whom received AD assessments using four different neuropathological criteria: Khachaturian, Braak and Braak, CERAD, and NIA-R. Findings indicate that NIA-R criteria differed significantly from CERAD and Khachaturian criteria. In addition, NIA-R and CERAD criteria predicted performance on the MMSE and three FOME indices; Braak and Braak criteria predicted performance on the MMSE and one FOME index. Finally, we examined the relationship between NIA-R severity rating and the presence or absence of neuropsychological impairment. We found that neuropathological severity was not significantly related to impairment for any neuropsychological or functional measure.

AUTOBIOGRAPHICAL STATEMENT

Emily Richardson is from Teaneck, New Jersey. She received her Bachelor of Arts from the University of North Carolina at Wilmington. During her undergraduate career, she became involved in several areas of research, including the long-term cognitive consequences of cardio-pulmonary bypass surgery and animal models of fluoxetine induced hippocampal neurogenesis. After completing her undergraduate degree, she spent four years providing clinical services to children with autism and juvenile offenders, before moving to Detroit, Michigan. Currently, she is pursing a Ph.D. in Clinical Psychology at Wayne State University and studies cognitive impairment in older adults.