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IMPACT OF SUBJECTIVE COGNITIVE COMPLAINTS ON MCI DIAGNOSTIC CRITERIA IN ALZHEIMER'S DISEASE

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A Thesis

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ABSTRACT

Alzheimer's disease (AD) is the most commonly occurring neurodegenerative disease characterized by deficits in patient cognition. Mild cognitive impairment (MCI) is defined as an intermediate stage between cognitively normal (CN) and dementia in which the individual experiences some impairment but can function independently. Gold standard MCI criteria requires a subjective cognitive complaint (SCC) in which a patient acknowledges a decline in cognitive ability, however past findings on its validity as a measure of objective impairment have been inconsistent. Biomarkers found in cerebrospinal fluid (CSF) and indicative of neurodegeneration are also used to examine AD progression. Our study investigates if inclusion of SCC in MCI criteria improves prediction of cognitive decline over time and/or affects levels of CSF biomarkers in AD patients. This is a secondary analysis using data from the Alzheimer's Data Neuroimaging Initiative. Participants completed a battery of neurocognitive assessments and were assigned into one of 3 groups based first on MCI gold standard criteria by Petersen (2004), then on newer proposed MCI criteria by Jak-Bondi (2014): CN, MCI without SCC, or MCI with SCC. CSF biomarkers amyloid beta (AB), tau, and phosphorylated tau (p-tau) were also collected via a lumbar puncture. Multilevel modeling was used to examine whether cognitive decline along with CSF biomarker levels differed longitudinally among the 3 groups. There were no significant main effects or longitudinal differences between those with and without SCC in global cognition score or CSF biomarker

ratio levels. These findings demonstrate the inclusion of SCC in MCI criteria does not make a meaningful difference in objective performance or biomarkers of neurodegeneration.

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CHAPTER ONE

INTRODUCTION

Alzheimer's Disease

Alzheimer's Disease (AD) is the most common neurodegenerative disease occurring mostly in the elderly population in adults over 65 years of age. AD is also the most common cause of dementia, accounting for 60-80% of observed cases (Barnes & Yaffe, 2011). Dementia is defined as the loss of cognition on multiple domains that are severe enough to affect daily and social function (Arvanitakis et al., 2019). According to the Alzheimer's Association, as of 2019, 5.8 million Americans were living with dementia, and 5.6 million of those individuals were over the age of 65. One estimation made in the year 2007 predicted that by the year 2050, 1 in 85 people worldwide will be living with AD, quadrupling the estimated figures from the year prior (Brookmeyer et al., 2007). 43% of individuals with AD require living arrangements in a nursing home and a high level of care for their symptoms (Brookmeyer et al., 2007). The symptoms of AD are primarily related to cognition with the most significant deficits being observed in memory, however emotional symptoms have also been reported (Geda et al., 2013).

Currently, the outlook for AD patients is not optimistic. Pharmacological treatment utilizes cholinesterase inhibitors, but the effects are modest at best. Researchers have proposed drugs specifically targeting amyloid beta aggregation that may be more effective (Roberson & Mucke, 2006), however

drugs targeting amyloid have yet to be proven safe or efficacious. This lack of treatment options and efficacy is concerning when also considering the rapidly increasing rates of AD and subsequent dementia (Sosa-Ortiz et al., 2012).

CHAPTER TWO

ETIOLOGY

Disease Background

The symptomology and characteristics of AD were first described by Alois Alzheimer, the head of the Anatomical Laboratory at the University of Munich, and whom the disease was named after (Small & Cappai, 2006). A patient by the name of Auguste Deter complained of memory loss, delusions, and hallucinations and was placed under the care of Alzheimer (Goedert & Spillantini, 2006). After Deter's death in 1906, Alzheimer used an intravital silver staining method developed by Max Bielschowsky to examine her postmortem brain and discovered key pathological characteristics of what would eventually be known as AD (Goedert & Spillantini, 2006). He presented his observations at the Society of German Psychiatrists meeting located in Tubingen, Germany in 1906 (Small & Cappai, 2006). Alzheimer described two key brain lesions observed in patients with AD: amyloid beta plaques and neurofibrillary tau tangles (Goedert & Spillantini, 2006).

Amyloid Beta

Amyloid beta (AB) is a naturally-occurring protein that is involved in infection prevention and injury recovery (Brothers et al., 2018). Through

postmortem examination of Auguste's brain, a mysterious substance was discovered surrounding the cortex and was identified to be a peptide cleaved from a larger amyloid precursor protein (APP) (O'Brien & Wong, 2011). APP is a type 1 glycoprotein that contributes to baseline neuronal functioning and gives way to AB (Chen et al., 2017). It has since been established that AB is the main component of senile plaques observed in AD (Takahashi et al., 2017). AB plaques have been observed in elderly individuals with and without AD in the cerebral cortex, basal ganglia, and hypothalamus (Thal et al., 2006). In AD patients, they have been exclusively observed in the midbrain, brainstem, and cerebellum (Thal et al., 2006).

The Amyloid Cascade Hypothesis proposes that increased production of AB peptides is the main cause of the neurodegeneration of AD (Hardy & Higgins, 1992). AB is a normal product of APP, it is the increase in its production that is abnormal. Increased production of AB is said to be caused by mutations in APP (Citron et al., 1992). Peptides AB42 and AB40 aggregate and form insoluble plaques which in turn "cascades" into more deteriorative changes eventually resulting in cell death (Hardy & Higgins, 1992). While the Amyloid Cascade Hypothesis is the most established in AD research, it is both supported and rejected among current researchers. One review proposes a middle ground, suggesting that AB is just one of multiple factors contributing to AD (Pimplikar, 2009).

Tau

Tau is a naturally occurring protein that assists in the assembly of microtubules which make up the cytoskeleton (Spillantini & Goedert, 1998). The cytoskeleton is responsible for providing structure to a cell in order to determine its shape and is located in the cytoplasm (Torres & Coates, 1999). Tau has been identified as the main component of the neurofibrillary tangles (NFTs) observed in AD patients (Kosik et al., 1986). Similar to the mechanism in which AB plaques are formed, NFTs are a product of the aggregation of tau into filaments (Binder et al., 2005). In order to aggregate into these filaments, tau undergoes structural change, and the paired helical filaments are what comprise NFTs (Bancher et al., 1989).

NFTs have been shown to follow a consistent pattern of spread in correlation with the progression of the disease, as shown by Braak and colleagues (1998). The tangles originate in transentorhinal and entorhinal regions, then spread to the cortical and subcortical limbic system, then on to association areas of the neocortex in the late stages of AD (Braak et al., 1998). Tau's role in the degeneration of AD patients is still being investigated in current research. Interaction between tau pathologies and increased glial production has been observed (Leyns & Holtzman, 2017). It has also been found that synaptic function is disrupted at both the pre and post level in these patients as a result of NFTs (Naseri et al., 2019).

It is also worth noting the role of Alz50 in AD tau research. Alz50 is a monoclonal antibody used to detect an antigen that is common in AD patients (Carmel et al., 1996). This antibody has been shown to display exclusionary qualities, binding with only a select subset of tau proteins (Carmel et al., 1996). It has been further suggested that tau must be transformed from a coil into the more compact “Alz50 state” in order to bind with the Alz50 antibody (Binder et al., 2005). This change into “Alz50 state” may serve as a precursor to the aggregation of tau and eventual formation of NFTs (Guillozet-Bongaarts et al., 2005). These findings suggest that the initial folding of tau into “Alz50 state” may be an early indication of AD, and recognition could possibly prevent irreversible damage to the cytoskeleton (Hyman et al., 1988).

CHAPTER THREE

RISK FACTORS

Age

Age is widely recognized as the most critical risk factor in the development of AD. It is intuitive that as individuals age, they experience declines in cognition and aren't as "sharp" as they once were. In cognitively normal brains, atrophy in the temporal lobe and hippocampal volumes has been observed as individuals age (Scahill et al., 2003). These areas are known to play a significant role in learning and memory (Eichenbaum et al., 2007).

An age-based hypothesis in AD proposes that three critical steps occur at the onset of the disease, causing affected individuals to reach a demented state. First, an injury to the brain must take place, followed by an inflammatory defense response, and finally the resulting altered cell physiology which leads to synaptic dysfunction and cell loss (Herrup, 2010). Age plays a significant role in this hypothesis because due to the failure of homeostasis mechanisms in the aging brain, the second step inflammatory response is prolonged and in turn causes cell death and dementia (Herrup, 2010).

Genetics

Genetic history has been shown to provide useful information in predicting risk of AD. Apolipoprotein E (APOE) is a genotype that may predict risk of AD, with the most significant risk across all ethnic groups being associated with the allele APOE4 (Ferrer et al., 1997). APOE is mainly produced by hepatocytes in the liver and its normal function involves regulation of lipoproteins (Kockx et al., 2018). The APOE4 allele has been shown to be significantly associated with AB deposition in AD patients and increased AB production in CN individuals (Fleisher et al., 2012).

Down's Syndrome (DS) has also been known to propose genetic risk to the development of AD pathology. This syndrome is one of the leading genetic causes of learning deficiencies, and those affected make up the largest group with dementia under the age of 50 (Ballard et al., 2016). DS patients share many overlapping pathologies with AD and display a much earlier onset than non DS patients (Ballard et al., 2016). Virtually all individuals with DS are predicted to develop AD pathology by their 40s, and 70% will reach a diagnosis of dementia by 55-60 which is also their current projected lifespan (Hartley et al., 2015).

Education

While education has been identified as a correlate of cognitive functioning its effect has been shown to be controversial in the literature. Some evidence

suggests that more years of education predicts greater cognitive decline, while others have concluded that more education may have a protective effect.

In a study conducted by Roselli and colleagues (2009) an individual having completed more than 8 years of education significantly predicted cognitive decline in AD patients. This study utilized the Mini-Mental State Examination (MMSE) to assess cognitive decline, and these patients with over 8 years of schooling displayed a faster decline score over time (Roselli et al., 2009). However, another study conducted by Sando and colleagues (2008) found that more years of education showed to have a protective effect on cognitive decline in AD patients. Results of the study indicated that those with 8-9 years of schooling were better protected than those with 6-7 years, and that that effect was even further improved by having 10-18 years (Sando et al., 2008).

Cardiovascular

AD and Cardiovascular Disease (CVD) share overlapping risk factors within the elderly population. The Framingham Heart Study created a composite measure to assess risk of CVD, which was titled Framingham Cardiovascular Risk Profile (FCRP) (Harrison et al., 2014). The FRCP considered a variety of factors including age, gender, diabetes, smoking, systolic blood pressure, and cholesterol. High FRCP scores indicated risk of both CVD and cognitive decline, and demonstrated eventual progression to AD and dementia (Harrison et al., 2014). Associations have also been found between hypertension and both CVD

and AD. Occurrence of hypertension causes blood vessel walls to thicken and cerebral blood flow to be reduced, which are both pathophysiologies of CVD and AD (Santos et al., 2017).

CHAPTER FOUR

COGNITIVE SYMPTOMS

Cognitive decline commonly occurs in the elderly population, as even older adults without symptoms of dementia display problems with tasks assessing for attention and executive ability (Buckner, 2004). However these effects are accelerated in individuals with neurodegenerative disease such as AD.

Memory Deficits

Newly diagnosed AD patients seem to universally experience declines in memory as one of the earliest signs of the disease. Multiple memory systems are affected including speech, naming of objects and visual orientation (Jahn, 2022). Research indicates that episodic and working memory systems undergo the most significant decline (Kirova et al., 2015). Episodic memory refers to recall ability while working memory involves decision making and is primarily conceptualized as being a part of attention or executive functioning (Kirova et al., 2015). In the early stages of AD, lesions are observed in the medial temporal lobe with atrophy of the hippocampus and amygdala which are two areas essential to memory and recall (Braak & Braak, 1996). Consistent with findings on the association between AB and AD, one study found that high amyloid AD patients displayed

significant decline in memory-related functions compared to both low and high amyloid CN individuals (Lim et al., 2014).

Research is currently working to reveal the implications of memory decline on individual life quality. AD patients have been found to display deficits in short term memory (Parra et al., 2009). A sample of both AD patients and healthy age-matched controls were assessed for verbal short term memory of both single and bound features. A single feature refers to just one feature such as just color or shape, while bound features combine multiple single features to be unified as one. Compared to CN individuals, AD patients showed deficits in recall of bound features (Parra et al., 2009). A study conducted by Haj and colleagues (2015) indicated that declines in episodic memory lead to loss of autobiographical memory, further leading to AD patients being unable to contextualize memories. This inability to relive personal memories may promote a diminished sense of self and/or life purpose (Haj et al., 2015).

Executive Function

AD patients also demonstrate deficits in executive functioning. Executive function is defined as the complex cognitive ability for a human to self-regulate behavior and approach unfamiliarity (Gilbert & Burgess, 2008). Tests of executive function assess ability to determine relationships between objects or events (Gilbert & Burgess, 2008). The main brain region known to be involved in executive function is the frontal cortex, with various cortical areas responsible for

different functions (Aron, 2008). The inferior frontal cortex (IFC) has been shown to play a role in inhibition and the prefrontal cortex (PFC) oversees goal-making and rule following, with other subcortical areas also involved in connectivity (Aron, 2008).

A study conducted by Waltz and colleagues (2004) demonstrated impairment in establishing relationships between objects by AD patients compared to healthy controls. Participants were asked to place scrambled cards depicting images of people in descending order based on their heights. Further, this sample of individuals with AD displayed a neuropsychological profile that was consistent with dysfunction of the PFC (Waltz et al., 2004). Another study testing for ability to follow directions further confirms deficits in executive function. AD patients showed difficulty in following and keeping track of instructions on multiple measures of executive function including the Go-no-go and Set-switching tasks (Stopford et al., 2012). Participants with AD lost track of task instructions and were distracted easily (Stopford et al., 2012).

Attention

While not as widely regarded a symptom as memory deficits, individuals with AD also experience decline in attentional ability. In the brain, the parietal lobe is involved in attention-related tasks, specifically with a lot of activity observed in the intraparietal and transverse occipital sulci (IPTO) and the anterior intraparietal sulcus (AIPS) (Wojciulik & Kanwisher, 1999). Malhotra (2019)

proposed that the cognitive profile of AD patients may not be as homogenous as previously thought. While memory decline is the hallmark symptom of AD, deficits in arousal, orientation, and attention have also been observed early on in the disease (Malhotra, 2019).

Language

Language capability is another function that is negatively affected in AD patients as it is closely related to both memory and executive function. Common language deficits in AD include ability to name objects, written and auditory comprehension, speech fluency, and semantic paraphasia which is incorrectly substituting the intended word for one with a similar meaning (Szatloczki et al., 2015).

These summarized results and findings reinforce the prominence of cognitive decline in AD patients.

CHAPTER FIVE

BEHAVIORAL SYMPTOMS

Individuals diagnosed with AD experience behavioral and emotional symptoms in addition to cognitive impairment. Findings have shown that ad patients have difficulty identifying facial expressions in others, particularly those displaying sadness (McLellan et al., 2008). In addition to difficulty with recognition, these patients also display abnormal emotional symptoms.

Depression

Depression is a common comorbidity of AD. The coexistence of the two is so prevalent, that diagnostic criteria specifically for depression of AD is currently being explored and established (Olin et al., 2002). One review found rates of depression in AD patients was broad, with a range of 0-86% of AD patients exhibiting comorbid symptoms and an average of around 30% (Even & Weintraub, 2010). Depression was found to be significantly more present in the AD population compared to cognitively normal elderly individuals (Even & Weintraub, 2010). Evidence has suggested that depression precedes the onset of AD (Heun et al., 2002). Sun and colleagues (2008) found that among a sample of elderly participants, those with depression and a higher amyloid ratio, displaying greater memory impairment compared to those with depression and a lower amyloid ratio. These findings propose a subtype of depression exclusive to

AD patients known as “amyloid-associated depression” which has been suggested to be a prodromal form of AD (Sun et al., 2008).

From a cross-sectional study utilizing DSM-IV criteria to assess depression in a sample of 670 AD patients, results indicated 26% had major depression and another 26% had minor depression (Starkstein et al., 2005). Minor depression is represented by the same symptomatology associated with major depression, but less severe with only 2 required depressive symptoms compared to 5 (Fils et al., 2010). Since typical treatment for major depressive disorder utilizes antidepressant medication, these medications are being considered for use in AD patients affected by depressive symptoms. A clinical trial conducted by Lyketsos and colleagues (2003) tested the drug sertraline in a sample of 44 AD patients experiencing depressive episodes. The group treated with sertraline displayed a stronger improvement in depression score compared to the placebo group, and results concluded sertraline as superior to placebo in the treatment of AD patients with major depression (Lyketsos et al., 2003).

Delusions and Hallucinations

Delusions and hallucinations are common psychotic symptoms observed in AD patients. The occurrence of these symptoms contributes to a decline in patient and caregiver well-being, a need for institutionalization, and more rapid cognitive decline (Haj et al., 2017). A recent review found the rates of delusions to vary from 9.3% to 63% in the literature, with a median prevalence of 36%

(Ropacki & Jeste, 2005). Delusions have been found to be associated with decreased density of gray matter in the right inferior frontal gyrus and right inferior parietal lobule (Bruen et al., 2008). Pathologies observed in AD patients experiencing delusions have also been shown to overlap with those of individuals with schizophrenia, such as increased availability of striatal dopamine D2 and D3 receptors (Reeves et al., 2012). Hallucinations are also prevalent in AD patients with finding rates ranging from 4% to 76% with a median of 23% (for review see Bassiony and Lyketsos, 2003).

A cross-sectional study assessed a sample of 342 AD patients for delusions and other psychotic symptoms. Results indicated 22% of the sample were experiencing hallucinations only, 3% delusions only, and 9% both hallucinations and delusions (Bassiony et al., 2000). Along with a high prevalence of psychotic symptoms among AD patients, results also revealed associations between these symptoms and low education, older age, and depression (Bassiony et al., 2000). In a longitudinal study of 410 AD patients, annual evaluations for a 4 year period revealed hallucinations were a significant predictor of more rapid cognitive decline on every one of the 17 cognitive measures given (Wilson et al., 2000).

Irritability

Irritability is a concern among the AD population because it has been significantly reported as a chief complaint and is associated with the eventual

need for nursing home care in addition to decreased survival time (Koenig et al., 2016). From a sample of 101 AD patients, 13% displayed irritability and this was significantly associated with daily living impairments and greater depression (Starkstein et al., 1995).

In a study examining 286 individuals with mild cognitive impairment (MCI) and 393 individuals with AD, agitation and irritability were significantly higher in those with an AD diagnosis (Van der Mussele et al., 2014). Further, agitation in the AD sample was associated with more severe behavioral problems compared to the agitation observed in the MCI sample (Van der Mussele et al., 2014). Results and findings regarding behavioral and emotional symptoms including depression, irritability, and delusions indicate clinical significance in understanding and assessing AD.

CHAPTER SIX

CLASSIFICATIONS OF COGNITIVE IMPAIRMENT

Mild Cognitive Impairment (MCI)

Mild cognitive impairment (MCI) is defined as cognitive decline that does not interfere with activities of daily functioning, but is worse than average for age and education (Gauthier et al., 2006). While cognitive symptoms are not as severe as those observed in those with dementia (where cognitive impairment does interfere with daily functioning), MCI has become known as a precursor stage to eventual dementia in AD patients (Gauthier et al., 2006). The term MCI was first introduced as a stage used to assess dementia in the Global Deterioration Scale (Reisberg et al., 1982). MCI was presented as stage 3 in this scale, with the patient demonstrating subtle cognitive deficits and impairment in executive functioning that may negatively affect performance on more complex activities (Reisberg et al., 1982).

MCI is a topic of significance in AD research because it has been recognized as an intermediate stage between normal cognitive aging and dementia (Petersen, 2009). Consequently, research in this area has been expanding rapidly. One longitudinal study utilizing data from the National Alzheimer's Coordinating Center found that from a sample of 1,821 individuals with a diagnosis of MCI, 527 (28.95%) progressed to dementia (Rosenberg et al.,

2013). These findings provide support for MCI as a “stepping stone” stage, as individuals with this diagnosis seem to have an elevated risk for dementia.

Diagnostic criteria proposed by Petersen et al. (2004) has been recognized as the gold standard for diagnosing MCI. This set of criteria requires: a subjective memory complaint that is ideally confirmed by an informant, objective memory impairment, relatively normal non-memory domain performance, and a non-demented status as determined by the Clinical Dementia Rating Scale (Petersen et al., 2004). This criteria also utilizes just one cognitive assessment per domain. It is worth noting that evidence supporting the inclusion of MCI as a diagnostic stage has been inconsistent over the years, with one study that utilized the Petersen criteria finding MCI to be a poor predictor of dementia over 3 years (Ritchie et al., 2001). A review of articles investigating clinical outcomes following MCI diagnosis found that progression to dementia occurred less frequently than instances of stability and reversion back to normal cognition (Pandya et al., 2016). Additionally, MCI reversion, an individual reverting back to normal cognition after a diagnosis of MCI, poses another threat to the predictive value of MCI to dementia. One study found that of its sample of 331 individuals aged 60-95 and diagnosed with MCI, 58% reverted back to normal cognition at a 6 year follow-up, putting into question whether designating MCI as a transition stage to dementia is appropriate (Overton et al., 2019). More recently, adjustments have been proposed to existing criteria in order to address inconsistencies. Criteria by Jak and Bondi (2014) emphasizes the importance of

utilizing multiple tests to assess more than one cognitive domain, unlike the Petersen criteria which uses just one test to assess memory. The Jak-Bondi criteria also does not require subjective cognitive complaints. Research conducted by Bondi et al., (2008) concluded that rates of MCI drastically differ depending on what criteria is used, finding a range of 11-44% amongst relevant articles. Findings demonstrating amnestic multi-domain MCI, or impairment in memory and at least one other domain, to be the best predictor of subsequent dementia provide support for the multi-domain approach proposed by Jak-Bondi (Felix et al., 2016).

Subjective Cognitive Complaints (SCC)

Utilization of subjective cognitive complaints (SCC) may be another way that studies vary in terms of MCI criteria. SCC are defined as an individual or their caretaker reporting a decline in cognitive performance (Slavin et al., 2010). Since deficits in memory are the primary symptom of AD, complaints are often also referred to as subjective memory complaints (SMC) in this population. Existing literature reveals inconsistencies in definitions, terminology and methods utilized by researchers. A recent review of 44 relevant articles found there are significant differences in the definitions of SCC being used by researchers (Abdulrab & Heun, 2020). Another inconsistency was found in the method in which the presence of SCC is confirmed. A review conducted by Mendonca et al., (2015) found that while most studies incorporating SCC make the decision

based on questions asked directly to the patient, some rely solely on informant/caretaker complaints. These inconsistencies in the definition and methodology of SCC propose difficulties in its utilization in research.

The validity of SCC as a meaningful measure of objective cognitive impairment and as a predictor of future cognitive decline has also been called into question, as a result of the inconsistencies found in the literature. One study found that when SCC presence is determined with multiple questions organized by domain rather than a single-line *yes* or *no* question, it is a significantly better measure of objective impairment (Burmester et al., 2016). Consequently, the SCD-Initiative was founded in 2012 to investigate subjective cognitive decline as a useful measure in diagnosing preclinical AD (Jessen, 2013). This task force is made up of researchers who have contributed to the topic of SCC and have been working on creating a research framework to improve the efficiency in integrating SCC into preclinical AD research through improving definitions and methodology (Jessen, 2013). As part of the SCD-Initiative, guidelines for more efficient, comprehensive measures of SCC have been proposed by Rabin et al. (2015) utilizing a number of questions organized by domain (ability, change, memory, etc.) to be answered on a scale providing more variability in answer choice. An example of a self-report question of ability is “What is your ability to reason through a complicated problem?” with answer choices ranging from 1- above average to 7- severe disability (Rabin et al., 2015). The SCD-Initiative has concluded that presently available data, definitions, and measures of SCC are

not evolved enough for SCC to be of use as a clinical entity in AD research. (Jessen, 2013).

MCI and SCC

According to the gold standard of MCI criteria proposed by Petersen, SCC is a requirement, however there are inconsistencies in the operational definition of it within the literature. The inclusion of SCC in MCI diagnostic criteria has been shown to affect rates in which MCI is reported. One study estimated rates of MCI to be reduced by as much as 50% when SCC is a requirement for diagnosis (Mitchell, 2008).

SCC has been studied as a potential predictor of future cognitive decline in AD, with interest given to MCI being a transition stage from normal cognition to dementia. Past research has provided support for the role of SCC as a predictor of cognitive decline. A meta-analysis including 50 articles meeting criteria for discussion of SCC and objective cognitive function found a significant correlation between subjective memory complaints and objective memory performance, with more severe complaints associated with poorer performance (Burmester et al., 2016). One study examined predictors of cognitive decline in AD patients through a sample of 454 AD patients divided into three groups including 283 with normal cognition, 115 with MCI, and 56 with normal cognition and SCC. Results found that those with normal cognition and SCC had an elevated risk for progression to MCI, which has been established as a potential transition stage to dementia

(Donovan et al., 2013). Another study examined SCC as a predictor of cognitive decline in association with AB deposition in AD patients. These results revealed a significant relationship between SCC and the binding of AB, suggesting SCC to be an early indicator of cognitive decline in AD (Amariglio et al., 2012).

While some researchers have come to conclusions in favor of SCC being a predictor of cognitive decline in AD patients, other findings have not been supportive. A review conducted by Mitchell (2008) concluded that while SCC does have useful potential in reducing inflated rates of MCI, it does not have predictive value in predicting cognitive decline. A study assessing a sample of 152 non-demented AD patients for SCC found that complaints are not always present prior to development of AD cognitive impairment (Palmer et al., 2007). Only 50% of this sample had complaints 3 years prior to their AD diagnosis, calling into question the ability of SCC to predict cognitive decline in AD (Palmer et al., 2007).

CHAPTER SEVEN

SPECIFIC AIMS

Past findings on SCC as a useful measure in assessing cognitive impairment have been contradictory, calling for further research on the topic. Indeed, research inconsistently utilizes SCC as a criterion when classifying MCI. Similarly, there are inconsistencies in whether or not SCC predicts objective measures of cognitive performance. However, we are unaware of studies examining if utilization (or lack of utilization) of an SCC criterion in MCI classifications improves future prediction of cognitive decline or relevant biomarkers. The current study investigates the incremental validity of SCC in MCI diagnostic criteria in a longitudinal sample of AD patients. This was done using both the gold standard Petersen MCI criteria, and the newer proposed Jak-Bondi MCI criteria. Additionally, this study measures levels of biomarkers tau, p-tau, and AB from cerebrospinal fluid (CSF) to examine whether differences exist that may be attributed to the inclusion of SCC in MCI criteria. Participants were classified into one of three groups for each aim of the study: cognitively normal (CN), MCI without SCC (MCI-SCC), or MCI with SCC (MCI+SCC). The study aims to accomplish the following:

1a. Investigate if the addition of SCC in MCI criteria proposed by Petersen (2004) is associated with greater cognitive decline over time.

1b. Investigate if the addition of SCC in MCI criteria proposed by Jak-Bondi (2014) is associated with greater cognitive decline over time.

2a. Investigate if the addition of SCC in MCI criteria proposed by Petersen (2004) is associated with differences in levels of CSF biomarker ratios indicative of neurodegeneration.

2b. Investigate if the addition of SCC in MCI criteria proposed by Jak-Bondi (2014) is associated with differences in levels of CSF biomarker ratios indicative of neurodegeneration.

Our overall study hypothesis was that cognitive decline over time will be greatest in those with an MCI diagnosis and SCC, providing support for inclusion of an SCC criterion in MCI classifications. This is based on multiple past studies summarizing findings of significant association between SCC and both objective impairment and other early markers of AD such as AB deposition. Additionally, we hypothesized levels of CSF biomarkers will be most detrimental in those with an MCI diagnosis and SCC as these biomarkers are indicative of neurodegeneration in AD. In regard to predicted differences between the two sets of MCI criteria, due to the multi-domain approach utilized by Jak-Bondi we hypothesized this criteria will have better accuracy in its diagnosis and this sample will display results most consistent with the hypotheses of the two aims.

CHAPTER EIGHT

METHODS

Participants

This study utilized data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database https://adni.loni.usc.edu/data-samples/adni-data-inventory/. ADNI is a multisite longitudinal study recruiting participants across North America to examine a variety of biomarkers in order to improve detection and treatment of early-stage AD. Participants completed a cognitive assessment at baseline, after 6 months, and then once annually for a total of 4.5 years. CSF samples were also collected at baseline, and then once every 2 years for a total of 4.5 years. Participants were classified into one of three groups: cognitively normal (CN) – normal cognition, MCI without SCC (MCI-SCC) – mild cognitive impairment without a cognitive complaint, MCI with SCC (MCI+SCC) – mild cognitive impairment with a cognitive complaint. Participants were assessed for MCI using both Petersen and Jak-Bondi criteria. Due to availability of neuropsychological data from ADNI, sample sizes between the two sets of MCI criteria differ and may overlap with the same individuals.

Measures

Cognition

Participants completed the following neuropsychological assessments: Category Fluency (language), Boston Naming Test (language), Trail-Making Tests Parts A and B (executive function), Rey AVLT delayed recall and delayed recognition (episodic memory), Word List Delayed Recall (memory) and MOCA (global cognition). The MOCA was chosen as a measure of global cognition as it is a brief single page test assessing multiple cognitive domains including memory, visuospatial ability, language, attention, and executive function (Nasreddine et al., 2005).

SCC

All participants were assessed for SCC using the Everyday Cognition questionnaire completed both by the participant and an informant. This questionnaire measures 3 domains including memory, language, and executive function. Participants were classified as having SCC according to published cutoff scores (Farias et al., 2011).

CSF Biomarkers

AB, tau, and p-tau were collected from the CSF of the sample. Collection of CSF was done via lumbar puncture. 2 mL of CSF was processed at the ADNI Biomarker Core using the Roche Elecsys diagnostic assay for total protein concentration counts. These CSF biomarkers were examined as ratios (tau/AB, p-tau/AB, and p-tau/tau) to analyze whether any differences in their levels exist

between those who are CN, those with MCI+SCC, and those with MCI-SCC. Literature findings provide support for the use of ratios rather then whole values when examining CSF biomarkers in Alzheimer's Disease (Sacchi et al., 2022).

MCI Classifications

Petersen

Diagnostic criteria for MCI proposed by Petersen (2004) requires each of the following to be met: (1) an impaired memory score (defined as >1 SD below mean), (2) normal mental status (defined as a score $\geq$ 25 on the Mini-Mental State Examination (MMSE)), (3) normal daily functioning, and (4) a non-demented state (as defined by a score of <1 on the Clinical Dementia Rating Scale (CDR)). The MMSE is a brief 11 question measure used to test global cognition over 5 domains: orientation, registration, attention, recall and language with a maximum score of 30. The CDR is a rating scale of 0-3 (0- no dementia, 3-severe cognitive impairment) used to stage individuals who have been diagnosed with dementia testing 6 different cognitive domains: memory, orientation, judgment, community affairs, home performance, and personal care. Once MCI status was determined with the Petersen criteria, participants were classified as MCI+SCC or MCI-SCC dependent on scores obtained from the Everyday Cognition questionnaire.

Jak-Bondi

Diagnostic criteria for MCI proposed by Jak and Bondi (2014) requires one of the following to be met: (1) an impaired score (defined as >1 SD below the age-normative mean) on both measures within 1 or more cognitive domains, (2) an impaired score on at least 1 measure within each of the 3 cognitive domains (memory, language, or executive function), (3) or dependence in daily activities (defined as a score >9 on the Functional Assessment Questionnaire (FAQ)). Tests of the 3 different domains included Category Fluency and Boston Naming Test assessing language, Trail-Making Tests Parts A and B assessing executive function, and Rey AVLT assessing delayed recall and delayed recognition. The FAQ measures activities of daily living with a maximum score of 30 with higher scores indicating worse daily functioning. Once MCI status was determined with the Jak-Bondi criteria, participants were classified as MCI+SCC or MCI-SCC dependent on scores obtained from the Everyday Cognition questionnaire.

Statistical Analysis

Multilevel modeling was used to examine group differences in each aim of the proposed study.

Aim 1

Global cognition as measured by MOCA score served as the DV for each model. Group (CN, MCI-SCC, and MCI+SCC) was entered as the IV. Additional

covariates included age, gender, and education. This was done with separate analyses for the Petersen and Jak-Bondi criteria.

Aim 2

CSF biomarkers (tau/AB, p-tau/AB, and p-tau/tau) served as the DV for each model. Group (CN, MCI-SCC, and MCI+SCC) was entered as the IV. Each biomarker was entered as a separate analysis. Further, each biomarker analysis was run separately using Petersen and Jak-Bondi criteria.

CHAPTER NINE

RESULTS

Demographics

Petersen

The sample included 254 participants of which the majority were female (53.3%) and White (88.9%). The average age of the sample was 71.6. Additional demographic and clinical information by group can be found in Table 1.

Table 1.
Petersen Demographic and Clinical Information at Baseline

	CN (n=214)		MCI –SCC (n=6)		MCI +SCC (n=34)			
	M	**SD**	**M**	**SD**	**M**	**SD**	**p**	**Contrast**
Age	72.34	6.53	74.56	7.24	73.20	7.20	.583	--
% Male	45.8%	--	66.7%	--	73.5%	--	**.008**	MCI+SCC>CN
% White	90.7%	--	100%	--	88.2%	--	.659	--
Education	16.46	2.41	16.67	3.67	17.26	2.71	.218	--
MOCA	25.59	2.35	25.00	3.03	23.97	2.82	**.002**	CN>MCI +SCC
Category Fluency	19.63	4.29	27.00	--	19.25	5.62	.298	--

Boston Naming Test	28.69	1.40	28.00	--	28.25	2.36	.832	--
Trails A	36.75	11.49	28.00	--	43.75	14.27	.430	--
Trails B	85.76	43.09	79.67	23.24	98.03	46.43	.282	--
RAVLT Recall	5.69	2.96	5.00	--	4.25	1.89	.658	--
RAVLT Recognition	12.75	1.34	9.00	--	13.50	1.73	**.035**	CN>MCI-SCC, MCI+SCC>MCI-SCC
Logical Memory Delayed	12.79	3.32	7.50	2.59	7.09	2.22	**<.001**	CN>MCI-SCC, CN>MCI+SCC
MMSE	29.09	1.06	29.33	0.82	28.29	1.59	**<.001**	CN>MCI+SCC, MCI-SCC>MCI+SCC
FAQ	0.40	1.10	0.50	0.84	1.44	1.81	**<.001**	CN>MCI+SCC
CDRSB	0.14	0.22	0.42	0.20	0.46	0.14	**<.001**	CN>MCI-SCC, CN>MCI+SCC
Tau/AB	0.27	0.19	0.33	0.24	0.30	0.17	.447	--
P-tau/AB	0.03	0.02	0.03	0.02	0.03	0.02	.466	--
P-tau/Tau	0.09	0.01	0.09	0.01	0.10	0.01	.151	--

Jak-Bondi

The sample included 199 participants of which the majority were male (55.7%) and White (89.8%). The average age of the sample was 72.5. Additional demographic and clinical information by group can be found in Table 2.

Table 2.
Jak-Bondi Demographic and Clinical Information at Baseline

	CN (n=59)		MCI -SCC (n=19)		MCI +SCC (n=121)			
	M	**SD**	**M**	**SD**	**M**	**SD**	**p**	**Contrast**
Age	72.01	7.91	74.53	6.52	73.30	8.64	.440	--
% Male	59.3%	--	42.1%	--	59.5%	--	.350	--
% White	91.5%	--	94.7%	--	95.0%	--	.682	--
Education	15.61	2.80	15.00	3.13	15.79	2.59	.487	--
MOCA	24.61	2.94	18.61	5.05	18.47	4.96	**<.001**	CN>MCI-SCC, CN>MCI +SCC
Category Fluency	19.66	4.56	16.67	8.96	16.81	4.39	**.029**	CN>MCI +SCC
Boston Naming Test	28.07	1.71	24.67	3.06	26.62	3.24	**.004**	CN>MCI-SCC, CN>MCI +SCC

Trails A	36.61	13.13	58.67	10.69	41.31	13.18	**.011**	CN>MCI-SCC, MCI+SCC>MCI-SCC
Trails B	95.02	44.06	173.06	95.37	175.67	86.42	**<.001**	CN>MCI-SCC, CN>MCI+SCC
RAVLT Recall	6.71	3.10	1.33	0.58	2.19	2.26	**<.001**	CN>MCI-SCC, CN>MCI+SCC
RAVLT Recognition	13.44	1.52	10.00	1.73	9.19	3.10	**<.001**	CN>MCI-SCC, CN>MCI+SCC
Logical Memory Delayed	8.90	1.75	3.11	3.18	3.31	3.50	**<.001**	CN>MCI-SCC, CN>MCI+SCC
MMSE	28.14	1.63	24.68	3.15	24.83	3.13	**<.001**	CN>MCI-SCC, CN>MCI+SCC
FAQ	1.58	2.39	14.89	7.59	13.36	7.02	**<.001**	CN>MCI-SCC, CN>MCI+SCC
CDRSB	1.11	0.66	4.11	2.29	4.00	2.00	**<.001**	CN>MCI-SCC, CN>MCI+SCC
Tau/AB	0.30	0.25	0.56	0.24	0.57	0.32	**<.001**	

P-tau/AB	0.03	0.03	0.05	0.02	0.06	0.03	**<.001**	
P-tau/Tau	0.09	0.01	0.10	0.01	0.10	0.01	**.002**	

Aim 1

The first aim of this study investigates whether the addition of SCC to AD-MCI criteria predicts greater cognitive decline over time.

Petersen

There were no significant longitudinal differences in cognition between the three groups. However, there was a significant main effect of group on cognition, specifically that the CN group displayed higher scores compared to both the MCI-SCC and MCI+SCC groups. There were also significant main effects of gender, age and education such that males demonstrated lower scores, higher age was associated with lower scores, and higher education was associated with higher scores. See Table 3 for p-values and estimates. See Table 1 for means.

Table 3.

Petersen Subjective Cognitive Complaint and Cognitive Outcome

Parameter	Estimate	p-value
CN vs. MCI+SCC X Time	-0.02	0.140

MCI-SCC vs. MCI+SCC X Time	0.01	0.466
CN vs. MC-SCC X Time	-0.00	0.877
CN vs. MCI+SCC	-1.06	**< 0.001**
MCI-SCC vs. MCI+SCC	0.14	0.793
CN vs. MCI-SCC	-0.92	**0.048**
Male Sex/Gender	-0.79	**<0.001**
Age at Baseline	-0.11	**< 0.001**
Education	0.21	**< 0.001**
Occasion	0.00	0.165

CN = cognitively normal, MCI-SCC = mild cognitive impairment without subjective cognitive complaints, MCI+SCC = mild cognitive impairment with subjective cognitive complaints.

Jak-Bondi

There was a significant group x time interaction effect on cognition (see Figure 1) showing that the CN group displayed higher scores over time compared to both the MCI-SCC and MCI+SCC groups. Additionally, there was a significant main effect of group on cognition, specifically that the CN group displayed higher scores compared to both the MCI-SCC and MCI+SCC groups. There was also a significant main effect of education such that higher education

was associated with higher scores. See Table 4 for p-values and estimates. See Table 2 for means.

Table 4.

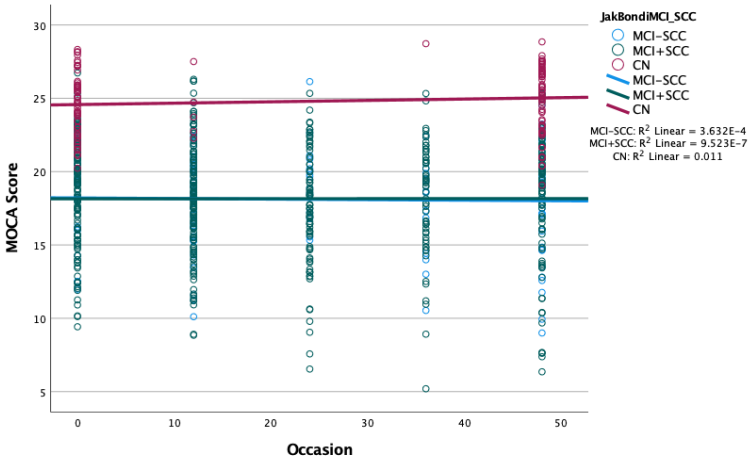
Jak-Bondi Subjective Cognitive Complaint and Cognitive Outcome

Parameter	Estimate	p-value
CN vs. MCI+SCC X Time	-0.07	**0.002**
MCI-SCC vs. MCI+SCC X Time	-0.00	0.882
CN vs. MC-SCC X Time	-0.07	**0.020**
CN vs. MCI+SCC	-5.04	**< 0.001**
MCI-SCC vs. MCI+SCC	0.16	0.832
CN vs. MCI-SCC	-4.88	**<0.001**
Male Sex/Gender	0.35	0.430
Age at Baseline	-0.03	0.290
Education	0.30	**< 0.001**
Occasion	0.02	0.292

CN = cognitively normal, MCI-SCC = mild cognitive impairment without subjective cognitive complaints, MCI+SCC = mild cognitive impairment with subjective cognitive complaints.

Figure 1.

Jak-Bondi Group X Time Interaction on Global Cognition



CN individuals performed significantly better over time

Aim 2

The second aim of this study investigates whether the addition of SCC to AD-MCI criteria is associated with differences in CSF biomarker ratios indicative of neurodegeneration.

Petersen

There were no significant longitudinal differences in any of the CSF marker ratios between the three groups. In the model with a dependent variable of tau/AB there was a significant main effect of age and time such that higher age was associated with higher levels and more time passed was associated with higher levels. In the model with a dependent variable of p-tau/AB there was a significant main effect of age and time such that higher age was associated with

higher levels and more time passed was associated with higher levels. In the model with a dependent variable of p-tau/tau there was a significant main effect of education such that higher education was associated with lower levels. See Table 5 for p-values and estimates. See Table 1 for means.

Table 5.

Petersen Subjective Cognitive Complaint and CSF Markers

	tau/AB		p-tau/AB		p-tau/tau	
Parameter	Estimate	p-value	Estimate	p-value	Estimate	p-value
CN vs. MCI+SCC X Time	0.00	0.512	0.00	0.917	-0.00	0.091
MCI-SCC vs. MCI+SCC X Time	-0.00	0.286	-0.00	0.565	0.00	0.407
CN vs. MCI-SCC X Time	-0.00	0.391	-0.00	0.556	0.00	0.977
CN vs. MCI+SCC	0.03	0.217	0.00	0.153	0.00	0.064
MCI-SCC vs. MCI+SCC	0.01	0.816	0.00	0.905	-0.00	0.513
CN vs. MCI-SCC	0.05	0.366	0.01	0.388	0.00	0.794

Male Sex/Gender	-0.03	0.130	-0.00	0.114	-0.00	0.399
Age	0.01	**<0.001**	0.00	**0.002**	0.00	0.053
Occasion	0.00	**0.002**	0.00	**0.001**	0.00	0.347
Education	-0.00	0.427	-0.00	0.330	-0.00	**0.039**

AB = amyloid beta; CN = cognitively normal, MCI-SCC = mild cognitive impairment without subjective cognitive complaints, MCI+SCC = mild cognitive impairment with subjective cognitive complaints.

Jak-Bondi

There were no significant longitudinal differences in any of the CSF marker ratios between the three groups. In the model with a dependent variable of tau/AB there was a significant main effect of group such that both MCI-SCC and MCI+SCC groups demonstrated higher levels compared to the CN group. There were also significant main effects of gender and education such that males demonstrated lower levels and higher education was associated with higher levels. In the model with a dependent variable of p-tau/AB there was a significant main effect of group such that both MCI-SCC and MCI+SCC groups demonstrated higher levels compared to the CN group. There was also a significant main effect of education such that higher education was associated with lower levels. In the model with a dependent variable of p-tau/tau there was a

significant main effect of group such that both MCI-SCC and MCI+SCC groups demonstrated higher levels compared to the CN group. There was also a significant main effect of education such that higher education was associated with lower levels. See Table 6 for p-values and estimates. See Table 2 for means.

Table 6.

Jak-Bondi Subjective Cognitive Complaint and CSF Markers

	tau/AB		p-tau/AB		p-tau/tau	
Parameter	Estimate	p-value	Estimate	p-value	Estimate	p-value
CN vs. MCI+SCC X Time	0.00	0.688	0.00	0.877	-0.00	0.470
MCI-SCC vs. MCI+SCC X Time	0.00	0.207	-0.01	0.320	-0.00	0.669
CN vs. MC-SCC X Time	0.00	0.194	0.00	0.243	-0.00	0.396
CN vs. MCI+SCC	0.23	**<0.001**	0.02	**<0.001**	0.00	**<0.001**
MCI-SCC vs MCI+SCC	-0.05	0.401	0.00	0.176	-0.00	0.910
CN vs. MCI-SCC	0.17	**0.011**	0.01	**0.031**	0.00	**0.040**

Male Sex/Gender	-0.09	**0.033**	-0.01	0.085	0.00	0.715
Age	0.00	0.327	0.00	0.519	-0.00	0.521
Occasion	0.00	0.976	0.00	0.876	-0.00	0.977
Education	-0.02	**0.025**	-0.00	**0.014**	-0.00	**0.037**

AB = amyloid beta; CN = cognitively normal, MCI-SCC = mild cognitive impairment without subjective cognitive complaints, MCI+SCC = mild cognitive impairment with subjective cognitive complaints.

CHAPTER TEN

DISCUSSION

Overall Summary

The results of this study found that those with normal cognition performed better on cognitive testing compared to those with MCI. Additionally, those with MCI displayed more detrimental levels of all three CSF biomarker ratios indicative of neurodegeneration (tau/AB, p-tau/AB, and p-tau/tau) but only when diagnosed using Jak-Bondi criteria. The presence of SCC did not lead to any identifiable differences in cognition or levels of CSF biomarker ratios.

Aim 1 Discussion

The first aim of this study investigated whether the addition of SCC to AD-MCI criteria predicts greater cognitive decline over time. Contrary to our hypothesis, there were no longitudinal differences in cognitive scores between the MCI-SCC and MCI+SCC groups. This absence of longitudinal differences was observed in both Petersen and Jak-Bondi MCI criteria. Across both sets of criteria, the CN group demonstrated higher cognitive scores compared to both the MCI-SCC and MCI+SCC groups. This suggests that the inclusion of SCC in MCI criteria is not of use in predicting cognitive decline or differentiating between worse objective impairment.

It was hypothesized that the MCI+SCC group would display significantly worse cognitive decline over time compared to the other two groups. This hypothesis was based on past studies providing evidence for SCC being a meaningful addition to MCI criteria, and its presence indicating worse cognitive performance (Burmester et al., 2016; Donovan et al., 2013). We recently conducted a study investigating the similar aims in a Parkinson's Disease patient sample in which the results were supportive of the initial hypothesis (Jones et al., 2023). Similar to the current study, the MOCA was used to measure cognitive performance over time. Results found that the MCI+SCC group displayed worse cognitive scores over time compared to the two other groups, which led to the conclusion that the inclusion of SCC in MCI criteria did make a difference in objective performance. This difference in results may be due to the fact that the previous study utilized a sample of individuals diagnosed with Parkinson's Disease (PD). While both Parkinson's and Alzheimer's cause cognitive deficits, PD patients tend to be more impaired in executive function while AD patients show greater impairment in memory (Smirnov et al., 2020). However, there has been research conducted in AD populations providing support for SCC being a meaningful predictor of MCI. The study conducted by Donovan et al. (2014) utilized an older adult sample from the Massachusetts Alzheimer's Disease Research Center to investigate progression of clinical stages within AD. They found that there was four times the risk of progression to MCI in individuals with SCC compared to those without. Similarly, a meta-analysis concluded that those

with SCC at baseline were twice as likely to develop future dementia (Mitchell et al., 2014). The Mayo Clinic Study of Aging went on to investigate SCC as a predictor of MCI using the same Ecog scale that was used to assess SCC in this study. The Ecog Questionnaire consists of 39 items to give a more thorough assessment than a single line question and researchers on this study were interested in investigating different domains of SCC to predict MCI. They found that all Ecog domains were associated with MCI risk (van Harten et al., 2018).

Despite evidence providing support for the utility of SCC, the present hypothesis was unsupported as the MCI+SCC group did not display significantly worse scores over time. There has also been past literature that has not found a meaningful association between SCC and MCI. One study examining longitudinal outcomes associated with SCC in a sample obtained from the Sydney Memory and Ageing Study concluded that this measure was not predictive of longitudinal cognitive decline (Slavin et al., 2015). Another study looking at longitudinal outcomes in an elderly population after a period of 10 years found no significant differences in cognitive and functional performance between individuals with and without SCC (Purser et al., 2006). In response to speculation that self-reported information may be inaccurate, Edmonds and colleagues (2018) investigated the relationship between SCC and objective cognitive performance. This study was conducted similarly to the present study, using a sample derived from the ADNI database and the same Ecog Questionnaire to determine SCC. After two annual follow-up visits, it was found that those with MCI were reporting stable cognitive

ability when in actuality their performance was significantly worse compared to CN and healthy controls who were over-reporting SCC with stable performance. This led to the conclusion that SCC is not a good predictor of MCI and is misleading as a measure of cognition (Edmonds et al., 2018).

In addition to investigation of the relationship between SCC and MCI, research has worked to provide insight on consistencies between SCC and objective performance on neuropsychological assessments. As previously discussed, cognitive deficits in AD affect multiple domains including memory, executive function, and language. Evidence from past research provides support for an association between SCC and cognitive testing performance. One study assessed healthy middle-aged and older adults over multiple cognitive domains including memory, perception, language, and executive function. Researchers also administered the Self-Evaluation Questionnaire to assess SCC in order to gather more specific information about different domains of complaints. It was discovered that the main domain of complaint was inability to inhibit distraction during learning which was significantly correlated with performance on the word-list recall and Digit Span tests which both assess memory (Langlois & Belleville, 2014). Markova et al. (2017) found that SCC specific to memory were significantly associated with worse memory performance in healthy older adults. Another study found that those with SCC demonstrated lower scores on tests of memory and executive functioning (Rouch et al., 2007).

Other research provides evidence against SCC as a meaningful measure of objective cognitive performance. One study found that there was no correlation between SCC specifically regarding memory and memory scores as measured by the California Verbal Learning Test (CVLT) delayed recall (Mendes et al., 2008). Similarly, another study found that there was no difference in scores across a battery of nine different cognitive tests between those with and without SCC (Minett et al., 2008). Jungwirth and colleagues (2004) examined memory performance in healthy older adults and concluded there were no differences in scores between those with and without SCC. Further, they discovered approximately 94% of individuals with objective impairment did not report SCC, further calling into question the reliability of the measure (Jungwirth et al., 2004).

Due to the conflicting evidence both in support and against the utility of SCC as a predictor of cognitive decline and measure of objective performance, further investigation is necessary. While the present study did not find any differences in cognitive decline over time between those with and without SCC others in the past have. One thing to consider is that the present study only looked at SCC in individuals already diagnosed with MCI. A study conducted by Geerlings et al. (1999) found that SCC proved to be a strong predictor of later cognitive impairment only in individuals with normal cognition at baseline, not in those already diagnosed with MCI. Future research may look to further examine the presence and role of SCC in healthy individuals in association with later development of MCI and dementia.

Aim 2 Discussion

The second aim of this study investigated whether the addition of SCC to AD-MCI criteria is associated with differences in CSF biomarker ratios indicative of neurodegeneration. In general, findings were similar to aim 1 and suggest that utilizing SCC in MCI criteria is not significantly associated with CSF biomarkers of neurodegeneration. There were no longitudinal differences in any of the three CSF ratio outcomes between the three groups across both sets of MCI criteria. Specific to Jak-Bondi MCI criteria, there were significantly higher levels of all three CSF biomarker ratios in both MCI-SCC and MCI+SCC groups compared to the CN group. Specific to Petersen MCI criteria, there were no significant group differences in any CSF outcome.

It was hypothesized that the inclusion of SCC to AD-MCI criteria would result in less favorable amounts of CSF biomarker ratios and a subsequent increase over time. While there were no significant longitudinal changes, the hypothesis was partially supported as there were significantly higher levels of all three ratios in both of the MCI groups in the Jak Bondi criteria sample. As previously discussed, aggregation of both AB and tau are observed characteristics of AD so higher levels of these biomarkers are associated with more detrimental neurodegeneration (Scheltens et al., 2021). The two proteins have even been suggested to work together synergistically toward progression of the disease (Ittner & Gotz, 2010). Further, research has shown that examining

these biomarkers as ratios instead of whole values is superior as was done in this study. CSF biomarker ratios have been shown to have higher agreement values to PET imaging compared to whole values of AB, tau, and p-tau on their own (Bouwman et al., 2022). CSF biomarker ratios have been shown to predict AD-MCI, with one study finding significantly higher levels of tau/AB and p-tau/AB in those with AD-MCI compared to both MCI alone and healthy controls at baseline and 2 year follow-up (Brys et al., 2009).

Research has provided support for a relationship between SCC and elevated levels of CSF biomarkers indicative of neurodegeneration. Edmonds and colleagues (2018) demonstrated that individuals with CSF biomarker levels consistent with that observed in AD at baseline displayed greater discrepancy in Ecog Questionnaire scores used to determine SCC. Specifically, these individuals were significantly underestimating the cognitive decline they were experiencing (Edmonds et al., 2018). A review examining 16 relevant articles on the application of SCC concluded there is an association between elevated p-tau and AB levels and the presence of SCC in preclinical stages of dementia (Webster-Cordero & Gimenez-Lort, 2022). Researchers have proposed that SCC may be one of the earliest clinical indicators of AD progression, and this idea has been further explored alongside other risk factors such as CSF biomarkers. A longitudinal study following a sample of healthy elderly adults found that those with elevated AB coupled with SCC at baseline were more likely to have diagnosis of MCI or dementia after a three year follow-up compared to individuals

with elevated AB and no SCC (Buckley et al., 2016). Another study suggests there is an existing relationship between SCC and CSF biomarkers that is independent of objective cognitive performance. Results showed an association between SCC and AB such that those with elevated AB had greater rates of SCC and additionally SCC was predictive of elevated AB (Amariglio et al., 2015).

Conversely, researchers have also demonstrated a lack of relationship between SCC and CSF biomarkers. One study determining risk factors for dementia within a sample of middle-aged and elderly patients from a memory clinic found there was a significant association between objective impairment and CSF biomarkers, but not with biomarkers and SCC (Grambaite et al., 2013). Another study's results displayed no significant differences in SCC between those with low and high levels of AB neither at baseline nor after a period of 18 months (Hollands et al., 2015).

Results from the current study did not find significant differences in CSF biomarker ratio levels between the MCI groups with and without SCC. While findings regarding the association between SCC and CSF biomarkers indicative of neurodegeneration remain controversial, evidence seems to favor the existence of a relationship between the two. Future research may look to better establish what this relationship is and its clinical significance.

Interestingly, the trend of higher CSF biomarker ratio levels in the MCI groups as compared to the CN group was only observed in the Jak-Bondi sample and was not present in the Petersen sample. A possible reason for this may be

that Jak-Bondi MCI criteria does a more accurate job of assessing true cognitive impairment. Jak-Bondi criteria differs from Petersen because it takes a multi-domain approach to cognitive deficits, assessing memory, language and executive function compared to just memory alone. In a study comparing the two sets of criteria it was similarly found that those diagnosed with MCI using Jak-Bondi criteria displayed significant CSF biomarker associations as well as greater progression to dementia (Bondi et al., 2014). Utilization of Petersen criteria to diagnose MCI has been shown to lead to false-positive results and inflated rates possibly due to a lack of heterogeneity in cognitive assessment (Edmonds et al., 2015). Another study found that when using Jak-Bondi criteria, approximately 30% less individuals qualified for an MCI diagnosis compared to Petersen criteria (Jak et a., 2016). This evidence suggests that individuals diagnosed with MCI using Jak-Bondi criteria may be a more accurate representation of objective impairment with supporting significant CSF biomarker associations to reflect that.

Limitations

This study includes a few identifiable limitations. One limitation is that the sample is predominantly white with about 89% of both the Petersen and Jak-Bondi samples identifying as Caucasian. This prevents results from being able to be generalized to more diverse populations. Another limitation of the study was the availability of necessary data from ADNI. Further, the study may have been underpowered as some groups were of a small sample size compared to others.

For example, the Petersen MCI-SCC group was composed of only 6 participants. Additionally, the Petersen sample only had a total of 40 MCI cases while the Jak Bondi sample had considerably more with a total of 140 MCI cases. These differences in sample characteristics may have contributed to the difference in results between the two sets of MCI criteria. Another limitation is the ability of the criteria available to diagnose MCI. While Jak-Bondi criteria takes into consideration multiple cognitive domains compared to Petersen's single memory measure, both sets still rely on just a few assessments to make a diagnosis when there are many more existing domains to consider.

Conclusion

The inclusion of SCC to MCI criteria did not seem to affect cognitive performance in this study. Past studies are inconsistent regarding whether or not inclusion of SCC in MCI criteria makes a meaningful difference. Considering these mixed findings on whether SCC is a meaningful measure of cognitive impairment, future research should be conducted to further investigate this topic. Additionally due to differences in results between the two sets of MCI criteria and previous findings in support of Jak-Bondi criteria over Petersen, it may be of relevance to further investigate and possibly reconsider what should be utilized as the "gold standard" to diagnose.

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