

Identification of earlier biomarkers for Alzheimer's disease: A neuroimaging study of individuals with subjective cognitive decline

by

Ashleigh Parker  
B.Sc. (Hons), University of British Columbia, 2017

A Thesis Submitted in Partial Fulfillment  
of the Requirements for the Degree of

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in the Department of Psychology

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## **Supervisory Committee**

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Jodie R. Gawryluk, Department of Psychology  
**Supervisor**

Colette M. Smart, Department of Psychology  
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## Abstract

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**Background:** Given that individuals with subjective cognitive decline (SCD) report a change that is not yet measurable with standard neuropsychological assessment measures, they are thought to be the earliest along the cognitive continuum between healthy aging and Alzheimer's disease (AD). The current study used a neuroimaging approach to examine differences in brain function and structure between individuals with SCD and healthy controls (HC). **Method:** 3T resting state functional MRI and high resolution anatomical images were retrieved from 23 individuals with SCD (mean age = 72.9 years, SD = 5.4, 12 females) and 23 HC (mean age = 74.3 years, SD = 5.0, 12 females) from the screening time point from the AD Neuroimaging Initiative database. All data were processed using the FMRIB Software Library. Seed-based analyses of the default mode network (DMN) were used to compare differences in brain function between SCD and HC groups ( $Z > 2.3$ ; cluster significance:  $p < 0.05$ , corrected). Voxel-based morphometry (VBM) was used to examine differences in grey matter volume between the SCD and HC groups. **Results:** The SCD and HC groups were not significantly different in age or education level. Results revealed significantly greater activity in the DMN including the bilateral precuneus cortex, bilateral thalamus, and right hippocampal regions in individuals with SCD relative to controls. Conversely, those with SCD showed decreased activation in the bilateral frontal pole, caudate, angular gyrus, lingual gyrus, right superior frontal gyrus, right occipital pole, right superior temporal gyrus, left superior

temporal gyrus in the posterior division, left precuneus cortex, left precentral gyrus, left occipital fusiform gyrus, left temporal pole, and left cerebellum compared to HC. Finally, VBM results did not show significant differences in grey matter volume between the groups. **Conclusion:** Findings revealed changes in brain function but not structure between individuals with SCD and HC. Overall, this study represents a crucial step in characterizing individuals with SCD, a group recognized to be at increased risk for AD. It is imperative to identify biomarkers prior to significant decline on clinical assessment, so that disease-delaying interventions may be delivered at the earliest possible time point.

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## **Dedication**

I dedicate this thesis to my mom, who has always provided me with the simple message that comes from the heart – to believe in myself.

## **Chapter 1**

In Canada, more than 500,000 people are currently living with dementia and it is estimated that with the aging population, this number will reach 937,000 by the year 2031 (Alzheimer Society of Canada, 2018). Consequently, the current estimated cost to Canadians to care for those living with dementia is \$10.4 billion annually, which is expected to rise to \$16.6 billion in the next 12 years (Alzheimer Society of Canada, 2018). Congruently, 56% of Canadians are reportedly concerned about acquiring Alzheimer's disease (AD), the most common type of dementia (Alzheimer Society of Canada, 2018). Given that there is no cure for AD, it is imperative for current research to focus on the detection of neuropathology prior to symptom onset and preventative interventions.

### **Neuropathological Hallmarks of AD**

AD is a neurodegenerative disorder characterized by changes in the brain that occur both intra- and extra- cellularly. The neuropathological hallmarks of AD were first described by Alois Alzheimer in 1906; hence the name Alzheimer's disease. Alzheimer's discovery emanated from both the clinical observation and neuropathological examination of his patient Auguste D. Given that Alzheimer was intrigued by Auguste D.'s behaviours and believed she was suffering from an illness yet to be classified, he evaluated her brain post-mortem, which showed evidence of atrophy as well as arteriosclerotic changes. Using Bielchowsky's silver staining method, Alzheimer was also able to examine specimens of her brain cells. Upon evaluation, Alzheimer described what is known today as the pathological hallmarks of AD, including extracellular build-

up of beta-amyloid plaques which interfere with neuron communication at synapses and intracellular accumulation of tau tangles which interfere with the transport of chemicals within the neuron itself (Bloom, 2014). Together these changes are thought to lead to neural degeneration. These neuropathological changes are thought to occur over time, thus AD is considered to be a slowly progressive brain disease, with research suggesting that such changes in the brain may occur over decades prior to the emergence of clinical symptoms (Jack et al., 2011; Villemagne et al., 2013).

To capture the changes that occur in AD over time, Braak and Braak (1995) described a six-stage model of AD-related neurofibrillary changes, based on post-mortem research. The first two stages comprise the accumulation of the tau protein in the transentorhinal area (stage 1) and entorhinal region (stage 2). Stage 3 includes lesions that extend into the neocortex of the fusiform and lingual gyri. Stage 4 is characterized by the disease spreading to neocortical association areas such as the temporal lobe and the medial temporal gyrus. Stage 5 is characterized by the disease process extending to the frontal, superolateral, and occipital regions in a fanlike projection; this stage also includes the peristriate area within the occipital lobe. Finally, stage 6 is characterized by the disease reaching both secondary and primary areas of the neocortex as well as to the striate area in the occipital lobe. Understanding the pattern of changes that occur in AD may be helpful in the search for the earliest in vivo markers of neurodegeneration as well as understanding the pattern of symptoms that emerge in the clinical presentation of the disorder.

Although Braak and Braak's model focused on the accumulation of tau, other studies have focused on the amyloid cascade hypothesis. The idea of the amyloid cascade

hypothesis originated from Hardy and Higgins in 1992, where they postulated that beta-amyloid protein deposits contributed to mechanisms of cell death and the formation of neurofibrillary tangles. This hypothesis theorized that beta-amyloid accumulation and tau neurofibrillary tangles is what produces AD pathology. Since 1992, research focusing on the mechanism of AD has found that different forms of beta-amyloid can cause neurodegeneration (Ricciarelli & Fedele, 2017). Recent findings have found soluble beta-amyloid peptides to correlate more strongly with symptoms and severity of AD compared to insoluble beta-amyloid peptides (Ferreira, Lourenco, Oliveira, & De Felice, 2015; Muck & Selkoe, 2012). In contrast, some studies have revealed instances where levels of beta-amyloid do not correlate with neurodegeneration or cognitive decline, as PET studies have found individuals with higher beta-amyloid levels to remain cognitively unimpaired (Aizenstein et al., 2008; Klunk et al., 2009; Villemagne et al., 2011). To sum, many studies have evaluated the amyloid cascade hypothesis, yielding mixed results, with data showing both support and opposition for the hypothesis (Ricciarelli & Fedele, 2017).

Despite these mixed findings, the neuropathological hallmarks of beta-amyloid plaques, neurofibrillary tangles, and neural degeneration are thought to occur prior to and underlie the clinical presentation of AD.

### **Clinical Presentation of AD**

Clinically, the continuum of AD falls along two diagnostic categories; mild cognitive impairment (MCI), and AD dementia (Jessen et al., 2014; Sperling et al., 2011).

MCI is characterized by multiple criteria. First, either the patient, an informant, or clinician must be concerned regarding a change in cognition; second, there must be

objective evidence of cognitive impairment in one or more cognitive domains (informed through standardized cognitive testing). Finally, individuals with MCI lack of difficulties completing activities of daily living independently, and do not have significant impairment in social or occupational settings (Langa & Levine, 2014).

For research purposes, Jack et al. (2018) developed a numeric clinical staging schedule (comprised of six stages) for those on the AD continuum ranging from unimpaired individuals (stage 1) to severe dementia (stage 6). Individuals with MCI would fall at stage 3 (Jack et al., 2018). This stage is the first stage where the individual would perform in impaired or abnormal limits on neuropsychological assessments. This decline from normal to impaired functioning would need to be documented either by the individual, an observer, or by longitudinal neuropsychological testing. An individual at stage 3 in the Alzheimer's continuum would still be able to carry out their daily activities but may struggle cognitively or take more time to complete activities with increased complexities. Notably, past research has found the diagnosis of amnesic MCI – that is MCI with primary impairment in memory – to be related to a greater risk of developing AD over time (Stoub et al., 2005). A number of longitudinal studies have examined the conversion rates from amnesic MCI to AD. Although estimates vary, conversion rates range from 8.1% in clinical samples to 6.8% in community settings (Mitchell & Shiri-Feshki, 2009).

AD dementia is diagnosed when the patient experiences a progressive decline over months or years, has shown a history of cognitive decline either through report or observation, and experiences either an amnesic presentation that may involve other domains (e.g. executive function, visuospatial skills; McKhann et al., 2011). Within the

diagnostic category of AD, symptoms are expected to progress over time. Previous research suggests the time of survival following the diagnosis of AD ranges from 3 to 10 years, which mainly depends on the patient's age at the time of diagnosis (Brookmeyer, Corrada, Curriero, & Kawas, 2002; Helzner et al., 2008). Symptoms of mild AD include evidence of memory loss or an impaired ability to learn and recall new information, language problems including skills such as reading, writing, or speaking, fluctuations in mood, personality changes, and poor judgment. Using research-based criteria, mild AD would be characterized as stage 4 by Jack et al. (2018). At this stage of decline, individuals are less able to carry out daily activities independently and will sometimes require assistance with their instrumental activities (Jack et al., 2018). As this disease process worsens, individuals progress to moderate AD (stage 5; Jack et al., 2018). The symptoms experienced in moderate AD include substantial changes in behaviour and personality style, an inability to learn and recall recently learned information, impaired long term memory, wandering, experience feelings of agitation, aggression, or confusion, and requires assistance with instrumental activities of daily living. In the sixth and final stage, individuals are considered to have severe dementia (Jack et al., 2018). The symptoms experienced in the most severe stage of AD include disturbances in gait and motor skills, incontinence, being bedridden, the inability to perform instrumental activities of daily living, and the individual requiring support in long-term care.

Currently, there is no cure for AD and available pharmacological treatments aim to provide symptomatic relief (Wilkinson, 2012). Notably, pharmacological treatments are not capable of halting the progression of AD, but some newly developed drugs such as Aricept and Namenda are able to temporarily slow down symptoms, for a limited time;

approximately 6 to 12 months (Sevigny et al., 2016). Advancing early detection methods is critical, as research suggests that an intervention aimed to eliminate the effects of beta-amyloid in the stage of MCI will not change the clinical course of this disease, as substantial neurodegeneration has already occurred (Sperling, Jack, & Aisen, 2011). Unsuccessful clinical trials aimed at decelerating the progression of AD at the mild to moderate stages (Doody et al., 2014; Salloway et al., 2014) have fostered increasing interest in the earlier pre-clinical stages of AD (Epelbaum et al., 2017). It is imperative to identify individuals who are likely to progress to AD before measureable symptoms develop and there is evidence that studying individuals with subjective cognitive decline (SCD) can advance this objective.

### **SCD**

SCD was initially conceptualized as an early stage of dementia by Reisberg and colleagues in 1982. Although their work was conducted over 30 years ago, the identified characteristics of SCD are the same today. Specifically, individuals with SCD report changes in their cognition, although their scores on clinical neuropsychological assessment measures are not indicative of significant decline (findings are in the normal range). Although the concept of SCD has existed for some time, there have been relatively few studies focusing on SCD, to date. The slow progression of research on SCD has been attributed to a lack of common terminology and research standards across studies. A review by Rabin, Smart, and Amariglio (2017) reported multiple variations in the terminology used to describe SCD, such as but not limited to, subjective cognitive complaints, subjective memory concerns, and subjective memory impairment. In order to allow for greater comparability across studies, an international working group on SCD

was formed to propose a framework for research on SCD (Jessen et al., 2014). Jessen and colleagues (2014) established the term *Subjective Cognitive Decline or SCD*; herein, I will refer to this concept as SCD. The word *subjective* was chosen to demonstrate that one's view of their cognitive performance is self-perceived and independent of performance on a cognitive measure. The word *cognitive* was chosen to encompass any cognitive domain. The word *memory* was not chosen, as initial symptoms of AD are not restricted solely to the cognitive domain of memory. Finally, the term *decline* was selected to suggest a worsening of cognitive abilities to emphasize the progressive course of this disease (Jessen et al., 2014).

The SCD-I defines two specific requirements to consider someone to be experiencing pre-MCI SCD. The first criterion states that SCD is “self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event.” The second criterion states that there must be “Normal age-, gender-, and education-adjusted performance on standardized cognitive tests, which are used to classify MCI or prodromal AD” (Jessen et al., 2014). Given that these guidelines are relatively new, studies on conversion rates based on these criteria are forthcoming. However, previous longitudinal studies estimate that as many as 60% of older adults with SCD will decline over a 15-year period to MCI and AD (Reisberg & Gauthier, 2008; Reisberg et al., 2008), suggesting that in some cases, SCD is a prodromal phase of the disease process.

In terms of the AD continuum, SCD appears to fit with the definition of stage 2 of the numeric staging schedule by Jack et al. (2018). Stage 2 is described to be a transitional stage from asymptomatic, cognitively unimpaired individuals to mild

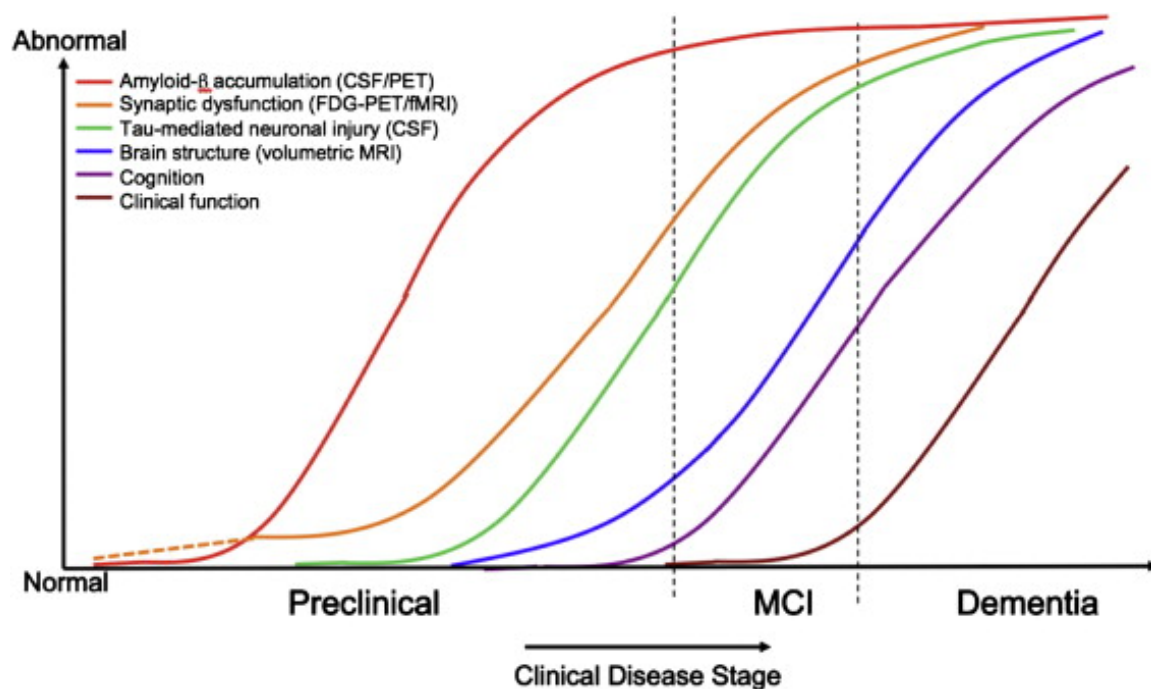
impairment. Individuals in stage 2 show a decline in cognitive abilities compared to previous levels of cognitive functioning but still perform within normal limits (Jack et al., 2018). This transitional stage of cognitive decline may be recorded through self-report from the individual expressing a concern about a subjective decline in their cognition within the last 1 to 3 years and has persisted for a minimum of 6 months. Although individuals at stage 2 are reporting subjective or subtle decline from their normal baseline, this decline in cognitive abilities does not interfere with their functioning or every day activities (Jack et al., 2018).

Notably, the International Working Group (IWG), US National Institute of Aging – Alzheimer’s Association (NIA-AA), and SCD-Initiative (SCD-I) agree that this pre-clinical stage of AD is likely to have detectable biomarkers (Jack et al., 2018; Jessen et al., 2014; Sperling et al., 2011).

## **Biomarkers**

A biomarker is a measurable biological characteristic that can be identified in vivo and is indicative of risk or presence of a disease (Alzheimer’s Association, 2018; Jack et al., 2011). Given that biomarkers have potential to advance the diagnosis of AD, the NIA-AA released revised guidelines on the diagnosis of AD to include pathological criteria in addition to clinical observations (McKhann et al., 2011; Sosa-Ortiz et al., 2012). Currently, the diagnostic criteria for AD has integrated five different biomarkers, including 1) accumulation of beta-amyloid (as measured by positron emission tomography (PET) imaging), 2) low levels of beta-amyloid in the cerebrospinal fluid, 3) elevations of cerebrospinal fluid tau, 4) levels of glucose metabolism, and 5) brain

atrophy (as measured by structural magnetic resonance imaging (MRI); Jack et al., 2011).



*Figure 1.* Hypothetical model of dynamic biomarkers in the preclinical stages of AD (Sperling et al., 2011)

Recently, the NIA-AA released an article outlining an updated research framework aiming to conceptualize AD as a biological construct (Jack et al., 2018). This proposed research framework (Jack et al., 2018) delineates permutations of biomarkers that contribute to the progression of AD. These biomarkers include aggregated beta-amyloid, aggregated tau, and neurodegeneration. The biomarker grouping of aggregated beta-amyloid (or associated pathologic state) is measured by CSF  $A\beta_{42}$ ,  $A\beta_{42}/A\beta_{40}$  ratio, or by amyloid PET. Next, the biomarker group of aggregated tau (neurofibrillary tangles or associated pathologic state) is classified by the measurement of CSF phosphorylated tau or through tau PET. The third and final biomarker grouping listed by Jack et al. (2018) is neurodegeneration (or neuronal injury) which is measured through anatomic MRI, FDG-PET, or CSF total tau. The addition of the separate neurodegeneration

biomarker is an extension from the previous 2011 guidelines from the NIA-AA (Sperling et al., 2011), which was previously grouped in the tau biomarker category.

Importantly, this research framework is endorsing the use of biomarkers to create distinct groups of research participants based on their presenting neuropathological profiles (Jack et al., 2018). Furthermore, this research framework uses these biomarker groups for hypothesis testing by generating unique pathways to represent the mechanism of how these biomarkers may lead to cognitive decline (Jack et al., 2018). Jack et al. (2018) illustrated multiple possible pathways for the mechanism of cognitive decline in the context of AD, but the most supported biomarker sequence is that of a modified amyloid cascade hypothesis. This revised hypothesis postulates that amyloidosis is what influences the production of pathologic tau which subsequently leads to neurodegeneration and ultimately cognitive decline (as seen in AD; Jack et al., 2018).

Another research group that has championed the use of biomarkers to conceptualize the AD continuum is the IWG. Similar to the NIA-AA, the IWG requires an individual to show AD symptoms and to have one positive biomarker associated with AD (Dubois et al., 2014). In contrast to the work of Jack et al. (2018), the IWG guidelines (Dubois et al., 2014) only reported definitions of diagnostic and progression biomarkers of AD, not listing *specific* AD biomarkers (such as those seen in Jack et al. (2018)). In 2016, Dubois et al. listed the *in vivo* detection of amyloidosis and tau as specific *in vivo* biomarkers to allow for the diagnosis of preclinical AD, when they declared that in light of these biomarkers, a cognitively unimpaired individual could still be considered for the diagnosis of AD. This shift in the IWG's (Dubois et al., 2016) conceptualization of AD at the preclinical stage represents the cooperative movement to

strengthen the idea of AD as being a biological construct, as stated by Jack et al. (2018). Moreover, the IWG (Dubois et al., 2016) differs from the 2018 NIA-AA framework (Jack et al., 2018) in their labeling schemes where the IWG will consider a cognitively unimpaired individual at risk for AD whether they present with either positive beta-amyloid (A+T-) or tau (A-T+), while Jack et al. (2018) will label someone to have Alzheimer's pathologic change if they show positive beta-amyloid (A+T-) and label someone with positive tau (A-T+) to have non-Alzheimer's pathologic change. Finally, these two research groups will use the term "at risk" very differently where the IWG (Dubois et al., 2016) will use this term to refer to being at risk for AD while the NIA-AA (Jack et al., 2018) will refer to the individual as being at risk for subsequent cognitive decline.

Importantly, the main thrust of biomarker research has focused on the preclinical stage, which is believed to be the period during which disease-modifying treatments are most effective (Berti et al., 2016; Sperling et al., 2011). There are currently, a number of potential biomarkers that have been identified, as described above, however, an ideal pre-clinical biomarker would be easily repeatable, non-invasive, and widely available, as is MRI.

### **Magnetic Resonance Imaging Measures and their Application in SCD**

MRI meets the criteria for an ideal technique for biomarker detection because it does not include exposure to radiation or result in any known negative side effects and it is available in nearly every hospital setting. MRI can also be used to acquire various types of data, with different contrast (e.g., T1-weighting, T2-weighting), as well as diffusion-weighted imaging, and functional MRI, through the use of different MRI

sequences. 3 Tesla T1-weighted MRI provides high resolution structural images of the brain which can be used to identify regional atrophy. As a result, T1-weighted imaging is regularly used in the clinical detection of AD, through the identification of hippocampal and medial temporal lobe atrophy (Frisoni, Fox, Jack, Scheltens, & Thompson, 2010). Congruently, the gold standard MRI biomarker for AD is based on the identification of brain atrophy in medial temporal lobe structures using voxel-based morphometry analyses on T1-weighted data (Teipel et al., 2013). To date, the vast majority of MRI based research on SCD has focused on the detection of similar changes in brain structure. These studies have provided evidence that individuals with SCD exhibit atrophy in multiple grey matter structures. For example, many studies have found the hippocampus to show reduced grey matter density in those with SCD (Cherbuin et al., 2015; Saykin et al., 2006; Stewart et al., 2011; Striepens et al., 2010). Additionally, results from Saykin et al. (2006) found evidence of atrophy in the left medial frontal gyrus and right precentral gyrus. Finally, areas such as the amygdala (Killiany et al., 2000) and entorhinal cortex (Dickerson et al., 2001; Jessen et al., 2006; Killiany et al., 2000; Meiberth et al., 2015; Striepens et al., 2010) have been associated with patterns of reduced grey matter density.



*Figure 2.* An example of Voxel Based Morphometry results when individuals with AD are compared to healthy controls (Mayo et al., 2015)

A more advanced imaging technique that is not used much clinically is fMRI, measured through the blood oxygen level-dependent (BOLD) signal within each voxel of the brain (Heeger, 2002). In particular, resting state fMRI records spontaneous fluctuations in the BOLD signal, when individuals are “at rest” in the MRI scanner (Van den Heuvel & Hulshoff Pol, 2010). Resting state fMRI scans are advantageous over task-based fMRI scans when working with clinical populations because no minimum level of cognitive understanding is needed to carry out the scan. This is important as these types of scans can be given to anyone along the AD continuum.

Resting state fMRI can be analyzed to examine functional connectivity networks, using specific seeds. The most commonly studied network to date is the default mode network (DMN). The DMN is comprised of the dorsal medial prefrontal cortex, ventral medial prefrontal cortex, and the posterior cingulate cortex (including the precuneus and

lateral parietal cortex; Raichle, 2015). These areas are associated with different types of functioning such as performance on self-referential tasks, emotional processing through the integration of external sensory stimuli, and recollection of previously learned information (Raichle, 2015). The DMN becomes active when an individual is at rest (Fig. 3)



*Figure 3.* DMN co-activation in healthy elderly controls during resting state fMRI (Koch et al., 2012)

To date, very few studies have used fMRI to better understand SCD. Specifically, three studies have used resting state fMRI to compare individuals with SCD to healthy aging controls. Wang and colleagues (2013) found decreased DMN connectivity, relative to healthy controls, whereas Hafkemeijer et al (2013) found relatively increased functional connectivity in the DMN in individuals with SCD. Dillen et al. (2017) used a slightly different analytical approach and found “de-coupling” of the DMN in individuals with SCD compared to healthy controls. Therefore, a few examinations of functional connectivity in the DMN in individuals with SCD have yielded mixed results.

In comparison, many studies have examined functional connectivity in the DMN in groups with MCI and AD. For example, a study by Jin, Pelak, and Cordes (2012) found those with amnesic MCI to show both increases and decreases in functional connectivity in the brain compared to healthy individuals. Those with amnesic MCI showed increased functional activity in the medial prefrontal cortex, middle cingulate cortex, and left cortex; and decreased functional connectivity in the medial temporal lobe, posterior cingulate cortex, precuneus, and lateral prefrontal cortex. Findings have been similarly mixed in studies focused on AD, with regional increases and decreases in connectivity in different regions (e.g., Wang et al., 2006).

Overall, more research is needed that combines both structural and functional approaches in the same groups to better understand this relationship and what each technique may contribute to understanding biomarkers for SCD; this is the objective of the current study.

### **Current Study**

The aim of the current study is to use MRI to investigate whether individuals with SCD show differences in brain tissue density and/or activation compared to healthy controls.

### **Research Questions**

1. Are there differences in brain tissue density between those with SCD and healthy controls?
2. Are there differences in resting state functional MRI activation between those with SCD and healthy controls?

## Chapter 2

### Identification of earlier biomarkers for Alzheimer's disease: A multimodal neuroimaging study of individuals with subjective cognitive decline

Globally, the number of individuals aged 60 and older are expected to double to nearly 2.1 billion, by 2050 (United Nations, 2017). Although increased longevity can create opportunities for positive and active community engagement for older adults, these can be hampered by health issues associated with aging. Indeed, research suggests that age is the strongest risk factor the development of Alzheimer's disease (AD), the most common form of dementia (Barker et al., 2002; Wilson et al., 2012). Consistently, mirroring the aging population, the number of individuals with dementia, currently estimated at 50 million, is expected to more than double and reach 131.5 million by 2050 (Prince et al., 2015). AD is a neurodegenerative disorder which includes clinical impairments in memory and other cognitive domains (e.g. executive functions; Alzheimer's Association, 2018). In addition to impairing the patient's quality of life, AD can lead to burdens for caregivers (Svendsboe et al., 2016; Yu, Wang, He, Liang, & Zhou, 2015) and economic consequences, societally (Dodel et al., 2015; Maresova, Mohelska, Dolejs, & Kuca, 2015; Wimo et al., 2017).

Clinically, the continuum of AD falls along two diagnostic categories; mild cognitive impairment (MCI) and AD dementia, distinguished by multiple significant cognitive impairments and difficulties with activities of daily living (Jessen et al., 2014; Sperling et al., 2011).

At this time, there is no cure for AD and the available pharmacological treatments only provide temporary symptomatic relief (Wilkinson, 2012). Unsuccessful clinical

trials aimed at decelerating the progression of AD at the mild to moderate stages (Doody et al., 2014; Salloway et al., 2014) have fostered increasing interest in the earlier pre-clinical stages of AD (Epelbaum et al., 2017). It is imperative to identify individuals who are likely to progress to AD before measureable symptoms develop and there is evidence that studying individuals with subjective cognitive decline (SCD), who are considered to fall earlier along the continuum – between healthy aging and MCI – can advance this objective.

Individuals with SCD have a self-perceived decline in a cognitive domain over time but perform within normal limits on standardized cognitive tests (Jessen et al., 2014). Importantly, research to date has found that as many as 60% of individuals with SCD are likely to convert to a diagnosis of MCI and AD over a 15-year period (Reisberg & Gauthier, 2008; Reisberg et al., 2008). In light of these findings, the International Working Group (IWG), US National Institute of Aging – Alzheimer’s Association (NIA-AA), and SCD-Initiative (SCD-I) agree that this pre-clinical stage of AD is likely to have detectable biomarkers (Jack et al., 2011; Jack et al., 2018; Sperling et al., 2011).

An ideal biomarker for AD at the stage of SCD would be non-invasive and easily repeatable, as is magnetic resonance imaging (MRI). To date, the vast majority of MRI based research on SCD has focused on changes in brain structure. This is likely because the gold standard MRI biomarker for AD is based on the identification of atrophy in medial temporal lobe structures (Ma et al., 2016). Similar studies focused on individuals with SCD have revealed atrophy in multiple grey matter structures, including the hippocampus (Cherbuin et al., 2015; Saykins et al., 2006; Stewart et al., 2011; Striepens et al., 2010;), left medial frontal gyrus (Saykin et al., 2006), right precentral gyrus

(Saykin et al., 2006), entorhinal cortex (Dickerson et al., 2001; Jessen et al., 2006; Killiany et al., 2000; Meiberth et al., 2015; Striepens et al., 2010), and the amygdala (Killiany et al., 2000). However, findings have been mixed, with some studies finding no differences between individuals with SCD and healthy controls, using voxel-based morphometry (VBM) techniques (Wang et al., 2013).

An additional potential MRI biomarker, which has been less studied, is resting state functional connectivity (Jack et al., 2011). Early on in the disease process of AD, the brain may be able to compensate for neuropathological changes, allowing an individual to function as they normally would and perform within normal limits on standardized cognitive testing (Sperling et al., 2011). As a result, it is possible that changes in functional MRI (as a result of compensation) may be detectable prior to changes in brain structure.

Thus far, few studies have examined both brain structure and function in individuals with SCD. Notably, Hafkemeijer et al. (2013) and Wang et al. (2013) examined both brain atrophy and resting state functional connectivity in individuals with SCD compared to healthy controls with mixed results. Specifically, Hafkemeijer et al. (2013) found that individuals with SCD showed structural atrophy in regions including the right amygdala, bilateral precuneus, cuneus, anterior cingulate cortex, and medial prefrontal cortex along with increased levels of functional connectivity in the default mode network (DMN) compared to healthy controls. In contrast, the study conducted by Wang and colleagues (2013) found individuals with SCD had no significant differences in brain structure, but decreased DMN connectivity, relative to healthy controls.

To date, more research is needed that combines both structural and functional approaches in the same groups to better understand this relationship and what each technique may contribute to understanding biomarkers for SCD. Therefore, the current project focused on the following two research questions and hypotheses:

- 1) Are there differences in brain tissue density between those with SCD and healthy controls? It was hypothesized that those with SCD would show decreased brain tissue density compared to healthy controls.
- 2) Are there differences in resting state functional MRI activation between those with SCD and healthy controls? It was hypothesized that those with SCD would show increased resting state functional MRI activation in the DMN compared to healthy controls.

## **Methods and Materials**

### **Data Collection**

Data used in the present study were obtained from the Alzheimer's Disease Neuroimaging Initiative 2 (ADNI-2) database ([adni.loni.usc.edu](http://adni.loni.usc.edu)). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see [www.adni-info.org](http://www.adni-info.org). All ADNI participants or their authorized representatives provided written informed consent approved by the Institutional Review Board at each acquisition site. For the current study, secondary use of the data was

approved by the Human Research Ethics Board at the University of Victoria (Victoria, BC, Canada).

### **Participant Selection**

All participants were selected from the ADNI-2 database. 23 individuals with SCD (mean age = 72.9 years, SD = 5.4) and 23 healthy elderly controls (mean age = 74.3, SD = 5.0) were included (Please see Figure 1 for a flow chart of participant selection and Table 1 for participant demographics). The SCD group was drawn from the significant memory complaints (SMC) cohort that was included in ADNI-2 to focus on the gap between healthy elderly controls and individuals with MCI. All participants within the SMC cohort self-reported a significant memory concern and achieved a score of  $\geq 16$  on the Cognitive Change Index (from the first 12 questions) and a score of 0 on the Clinical Dementia Rating (CDR). All control participants were free of memory complaints and deemed cognitively normal based on clinical assessments by the site physician showing an absence of significant impairment in cognitive functioning and performance of daily activities.

Both the participants in the control and SMC cohorts exhibited normal memory function on the Logical Memory II subscale of the revised WMS ( $\geq 9$  for 16 years of education and above,  $\geq 5$  for 8-15 years of education, and  $\geq 3$  for 0-7 years of education), a MMSE score between 24 and 30 (inclusive), and a Clinical Dementia Rating of 0. For more information on group classifications, including all additional eligibility criteria, please consult the ADNI-2 procedures manual (Alzheimer's Disease Neuroimaging Initiative, 2008).

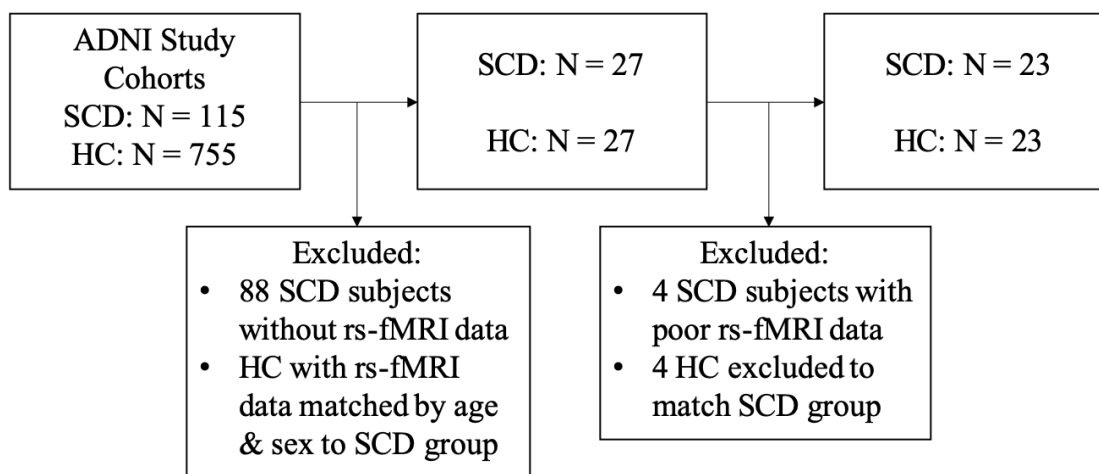


Figure 4. Flow diagram of participant selection. ADNI = Alzheimer’s Disease Neuroimaging Initiative. SMC = Significant Memory Concerns. HC = Healthy Controls.

Table 1. *Participant Demographics*

	<i>HC</i>	<i>SCD</i>	<i>HC vs. SCD</i>
Age	74.3 ± 5.0	72.9 ± 5.4	$p = 0.39$
Years of Education	16.0 ± 2.5	16.7 ± 3.0	$p = 0.35$
Females	12	12	
Males	11	11	

### Image acquisition

MRI data were retrieved from the ADNI-2 database. All images were acquired on 3 Tesla Philips MRI scanners. Whole-brain anatomical MRI scans were acquired sagittally, with a T1-weighted MPRAGE sequence, with the following parameters: a repetition time (TR) of 7 ms, an echo time of 3 ms, voxel size of 1 x 1 x 1.2 mm, and a flip angle of 9°. Functional MRI (fMRI) scans were obtained during resting state (with eyes open). Resting state fMRI scans were obtained with a T2\*-weighted echo-planar imaging sequence with the following parameters: a repetition time of 3000 ms, an echo time of 30 ms, 140 volumes, 48 slices, voxel size of 3.3 x 3.3 x 3.3 mm, and a flip angle of 80°.

## Data Analysis

**Image Preprocessing.** All data obtained from the ADNI database were in DICOM format. All structural and functional images were converted from DICOM to NIFTI format using `dcm2niix` in the MRICroGL application (Li, Morgan, Ashburner, Smith, & Rorden, 2016). All analysis steps were performed using tools within the Functional MRI of the Brain Software Library (FSL) version 6.0 (Analysis Group, FMRIB, Oxford, UK, <http://fsl.fmrib.ox.ac.uk>; Smith et al., 2004). Non-brain tissue in the raw T1 images was removed using the automated Brain Extraction Tool (Smith, 2002), followed by manual verification and optimization for each subject.

**Seed-based Resting State fMRI Functional Connectivity Analysis.** A seed-based approach was used to examine functional connectivity in the DMN. The FEAT function was used to pre-process the data (including skull removal and motion correction). No smoothing was applied. Registration of the functional data to the high resolution structural image was carried out using the boundary based registration algorithm (Greve & Fischl, 2009). Next, registration of the high resolution structural images to standard space was carried out using FLIRT (Jenkinson & Smith, 2001; Jenkinson, Bannister, Brady, & Smith, 2002) and then further refined using FNIRT nonlinear registration (Andersson 2007a, 2007b). Next, the posterior cingulate cortex region of interest (ROI or seed) was registered to individual space. This ROI/seed was created based on ROIs from previous studies (De Luca, Beckmann, De Stefano, Matthews, & Smith, 2006; Uddin, Kelly, Biswal, Castellanos, & Milham, 2008) The FEAT function was used to examine the default mode network the posterior cingulate cortex ROI/seed and to regress out the lateral ventricle signal to correct for confounding

noise. Specifically, the mean blood oxygen level-dependent signal time series was extracted from the posterior cingulate seed region and used as the model response function in a general linear model analysis. This allowed for examination of functional connectivity in the DMN through the detection of voxels with timeseries that correlate with that measured in the posterior cingulate seed. The time-series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001).

Finally, a higher-level between-group analysis was conducted to compare resting state functional connectivity in the DMN between the SCD group and controls. The higher-level analysis was carried out using a fixed effects model, by forcing the random effects variance to zero in FLAME (FMRIB's Local Analysis of Mixed Effects; Beckmann, Jenkinson, & Smith, 2003; Woolrich, Behren, Beckmann, Jenkinson & Smith, 2004; Woolrich, 2008). Z (Gaussianised T/F) statistic images were thresholded non-parametrically using clusters determined by  $Z > 2.3$  and a (corrected) cluster significance threshold of  $p = 0.05$  (Worsley, 2001).

**VBM Analysis.** A structural whole brain VBM analysis was conducted to compare grey matter densities between individuals with SCD and healthy controls. The brain extracted images were segmented into grey matter, white matter, and cerebrospinal fluid, based on voxel intensity, and a study-specific grey matter template was created. Next, the grey matter probability images were affine-registered (with FSL's FLIRT) to the GM ICBM-152 and then re-registered to the affine GM template using non-linear registration (with FSL's FNIRT) and the native grey matter images were non-linearly registered to the created study-specific template. Following this step, the images were

smoothed (3mm) and the randomize function was run (for permutation testing). Within FSL, a general linear model (GLM) approach was implemented to compare those with SCD to the healthy controls and differences were examined at the  $p < 0.05$  level with threshold free cluster enhancement (corrected for multiple comparisons).

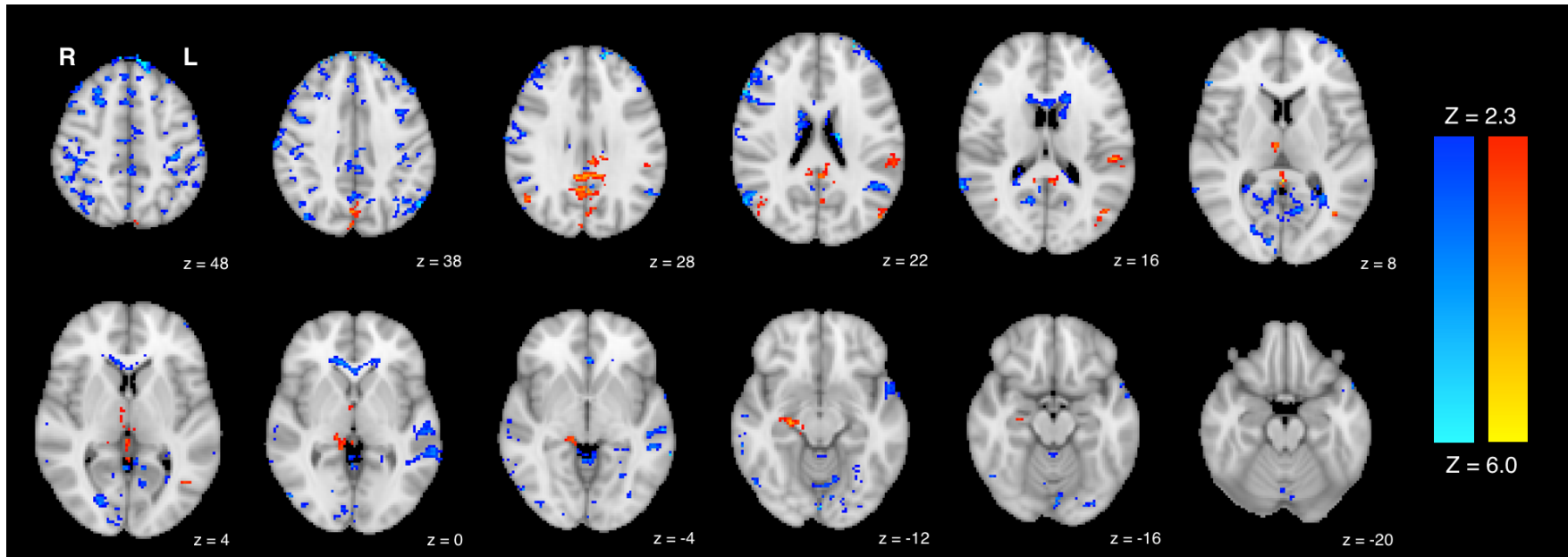
## Results

### VBM

VBM was used to examine differences in grey matter densities between the groups. This analysis did not reveal any differences between those with SCD relative to healthy controls in grey matter volume.

### Functional Connectivity.

The SCD group showed both increased and decreased functional connectivity in the DMN compared to healthy controls (Figure 5.). Specifically, cluster-level group comparisons revealed that individuals with SCD have increased functional connectivity compared to healthy controls in the right hippocampus and right posterior division of the parahippocampal gyrus, bilaterally in the thalamus and precuneus cortex (see Table 2 for peak coordinates). In contrast, those with SCD exhibited decreased functional connectivity compared to healthy controls in the right superior frontal gyrus, right occipital pole, and right superior temporal gyrus, left superior temporal gyrus in the posterior division, left precuneus cortex, left precentral gyrus, left occipital fusiform gyrus, left temporal pole, and left cerebellum. Lastly, healthy controls displayed bilateral increases in functional connectivity in the frontal pole, caudate, angular gyrus, and lingual gyrus relative to healthy controls (see Table 3 for peak coordinates of these areas).



*Figure 5.* Results of group level comparisons showing significant functional connectivity in the DMN in those with SCD relative to healthy controls. The colour red represents increased functional connectivity and blue represents decreased functional connectivity in the DMN in those with SCD compared to healthy controls.

Table 2. *Brain regions showing increased functional connectivity in participants with SCD compared to healthy controls (min Z > 2.3; cluster significance: p < 0.05, corrected for multiple comparisons). Coordinates in the MNI-152 standard space image are given.*

Brain Region	Laterality	MNI Coordinates			Z score
		X	Y	Z	
Parahippocampal Gyrus (post. div)	R	16	-32	-7	2.55
Precuneus Cortex	R	4	-60	28	3.70
Precuneus Cortex	L	-4	-74	52	2.51
Thalamus	R	4	18	6	2.41
Thalamus	L	-4	-24	6	3.15
Hippocampus	R	26	-16	-16	2.55

Table 3. *Brain regions showing decreased functional connectivity in participants with SCD relative to healthy controls (min Z > 2.3; cluster significance: p < 0.05, corrected for multiple comparisons). Coordinates in the MNI-152 standard space image are given.*

Brain Region	Laterality	MNI Coordinates			Z score
		X	Y	Z	
Frontal Pole	R	-14	62	28	2.42
Frontal Pole	L	18	56	28	3.05
Superior Frontal Gyrus	R	-2	32	52	2.82
Precentral Gyrus	L	50	6	34	3.56
Superior Temporal Gyrus	R	64	-22	-2	2.54
Superior Temporal Gyrus (post.)	L	-63	-22	-4	3.03
Caudate	R	16	-14	-22	2.74
Caudate	L	-14	-11	20	2.35
Angular Gyrus	R	54	-56	24	3.16
Angular Gyrus	L	-48	-56	22	2.31
Precuneus Cortex	L	-4	-56	22	2.54
Occipital Pole	R	16	92	0	2.45
Occipital Fusiform Gyrus	L	-32	-66	-12	2.38
Lingual Gyrus	R	4	-84	-12	2.69
Lingual Gyrus	L	-6	-84	-14	2.51
Temporal Pole	L	-52	8	-24	3.41
Cerebellum	L	-16	-68	-24	2.88

## Discussion

This present study is a valuable stepping stone to understanding individuals with SCD, as it aimed to investigate both structural and functional imaging characteristics that distinguish those with SCD from healthy controls. Our first hypothesis was that we would find decreased brain tissue density in those with SCD compared to healthy controls, however, we did not find significant differences between these groups. Our second hypothesis was that we would find increased resting state functional MRI activation in the DMN in those with SCD compared to healthy controls; our results revealed both increased and decreased activity between the groups in specific regions. These results are further discussed in the context of the existing literature below.

The structural analyses did not reveal there to be any differences in the density of grey matter in individuals with SCD compared to healthy controls. These findings are consistent with several studies that have investigated structural atrophy and have indicated that individuals with SCD often do not present with volume loss (Dong et al., 2018; Wang et al., 2013). In contrast, Saykin et al. (2006) found similar patterns of grey matter atrophy in individuals with SCD and MCI at a whole brain level compared to healthy controls. Furthermore, these findings are in contrast with several other studies that found reductions in the volume of the entorhinal cortex (Dickerson et al., 2001; Jessen et al., 2006; Killiany et al., 2000; Meiberth et al., 2015; Peter et al., 2014; Striepens et al., 2010), hippocampus (Cherbuin et al., 2015; Jessen et al., 2006; Peter et al., 2014; Saykins et al., 2006; Stewart et al., 2011; Striepens et al., 2010), left medial frontal gyrus (Saykin et al., 2006), right precentral gyrus (Saykin et al., 2006), and the amygdala (Killiany et al., 2000), specific to individuals SCD. Reasons for these mixed

reports may be due to some methodological differences across the studies, particularly with regards to sample characteristics. For instance, the work by Wang et al. (2013) and Saykin et al. (2006) found contrasting results of grey matter atrophy. Saykin et al. (2006) found there to be significant regional grey matter atrophy in SCD compared to healthy controls, but these findings may partly be attributed to the fact that the participants in this study showed there to be significant differences between groups in sex and APOE  $\epsilon$ 4 status. In comparison, Wang et al. (2013) showed no significant differences between individuals with SCD and healthy controls in grey matter structure, however, the groups were not significantly different in age, sex, education, or APOE  $\epsilon$ 4 status. The findings of significant levels of grey matter atrophy from Meiberth et al. (2015) and Striepens et al. (2010) may be attributed to the fact that individuals with SCD presented with significantly higher scores on the Beck Depression Inventory (BDI) relative to healthy controls (although no participants met criteria for a clinically significant depressive episode). Additionally, studies by Meiberth et al. (2015), Peter et al. (2014), and Striepens et al. (2010) who found significant levels of atrophy in different brain regions, may be attributed to all three of these studies having collected their SCD participants from memory clinics instead of from community samples. Perhaps individuals with SCD who are referred to or seek out memory clinics are different from those with SCD in the community who are not patients at a memory clinic. Finally, some of the studies that found significant levels of grey matter atrophy only asked one or two questions to distinguish individuals with SCD from their healthy counterparts (Cherbuin et al., 2015; Peter et al., 2014; Stewart et al., 2011), which may have contributed to differences in participant characteristics between studies.

Given that changes in brain function may precede measurable changes in brain structure, the current study also examined differences in functional connectivity in the DMN between individuals with SCD and healthy controls. Results revealed individuals with SCD to show areas of both increased and decreased resting state functional MRI activation compared to healthy controls. Specifically, areas of increased activation included the right hippocampus, right posterior division of the parahippocampal gyrus, bilateral thalamus, and bilateral precuneus cortex. These findings are consistent with those of Hafkemeijer and colleagues (2013) who found increased activation in similar areas in those with SCD compared to healthy controls. Chiesa et al. (2018) also found there to be increased resting state functional connectivity between the anterior basal forebrain and posterior cingulate cortex as well as between the posterior basal forebrain and the postcentral gyrus, dorsal cingulate cortex, temporal cortex, and anterior insulae.

Interestingly, Sperling et al. (2009) demonstrated a positive relationship between increased functional connectivity in the precuneus and posterior cingulate and beta-amyloid levels, a known neuropathological biomarker related to AD. A study by Kawagoe et al. (2019) employed a 10 item questionnaire developed by Osada et al. (1997) to calculate a “subjective memory score” where lower scores indicate higher levels of SCD severity. Kawagoe et al. (2019) found those with increased SCD severity (as measured by a questionnaire with a rating scale) to demonstrate increased functional connectivity in parietal and occipital areas. In general, these findings are congruent with a plethora of studies showing increased functional connectivity across the DMN in other cognitively normal individuals who also possess risks of developing AD, such as those with autosomal dominant AD mutation carriers (Quiroz et al., 2015), APOE  $\epsilon$ 4-carriers

(Filippini et al., 2009), and high levels of beta-amyloid deposition (Lim et al., 2014, Sperling et al., 2009). Further, researchers have posited that alterations in brain function and compensation can co-occur in those with SCD and that the alterations and compensation work together to maintain cognition within normal limits as measured by neuropsychological assessments (Li et al., 2018). Another theory for the cause of these alterations in functional connectivity may be attributed to a compensatory mechanism that is enacted when there is a failure of proper functioning within medial temporal regions (Reuter-Lorenz, 2002). Further investigations of functional connectivity using resting state fMRI are needed to evaluate its utility in early detection of AD.

Unexpectedly, the present study also revealed there to be areas of decreased functional connectivity in the DMN, specific to the right superior frontal gyrus, right occipital pole, right superior temporal gyrus, left superior temporal gyrus in the posterior division, left precuneus cortex, left precentral gyrus, left occipital fusiform gyrus, left temporal pole, and left cerebellum, as well as bilateral decreases in the frontal pole, caudate, angular gyrus, and lingual gyrus. The findings of the current study contrast those of Hafkemeijer et al. (2013), Chiesa et al. (2018), and Sperling et al. (2009) as these studies did not find the SCD group to show decreased activation at resting state compared to healthy controls. However, there are several reports in the literature of decreased connectivity in the DMN in specific regions when individuals with SCD are compared to healthy controls. In particular, Wang and colleagues (2013) found decreased connectivity in the right hippocampus and Viviano et al. (2019) described decreased connectivity across regions within the posterior memory system as well as between the lower retrosplenial cortex and precuneus in those with SCD compared to healthy controls. It has

been theorized that decreases of functional connectivity seen in later stages of AD may be preceded by past evidence of increased functional connectivity that seemed to be a compensatory mechanism at one point in time (Mormino et al., 2011). Hence, it is thought that when the threshold of neuronal damage is met an individual with SCD will transition to MCI as they are no longer able to compensate functionally and begin to show objective cognitive impairment (Jessen et al., 2014; Rabin et al., 2017). Within this theoretical context, the regions with decreased connectivity may represent areas throughout the DMN that are no longer able to compensate.

A number of studies using differing metrics have found contrasting results regarding functional connectivity in those with SCD compared to HC. For example, Hu et al. (2017) found both increased functional connectivity between the midline core network and superior medial frontal cortex and decreased functional connectivity between the dorsal medial prefrontal subnetwork and the right hippocampus. A study by Li et al. (2018) found increased levels of degree centrality in the medial temporal lobe and decreased degree centrality in the inferior parietal gyrus. Another investigation by Dong et al. (2018), found individuals with SCD to show increased relative functional connectivity strength in the left posterior cingulate cortex and precuneus, as well as increased absolute functional connectivity strength in regions associated with the DMN. In light of the mixed findings in this area, further investigation of altered functional connectivity will be an important step in characterizing these early changes in the brain related to AD.

The present study had several limitations. First, the sample size was relatively small. Although the sample size within this study is not out of the norm for neuroimaging

studies investigating SCD, it would be valuable to expand the sample size to increase the generalizability of the findings to the greater population. Second, this study was cross-sectional, in the future it would be valuable to conduct these types of analyses longitudinally to investigate which individuals with SCD are most at risk of converting to a diagnosis of MCI or AD. Third, this study did not examine differences in AD biomarkers, such as APOE  $\epsilon$ 4, beta-amyloid, and tau levels across the SCD participants. Incorporating these biomarkers of AD pathogenesis in individuals with SCD would be useful to determine if these individuals with this subjective change in cognitive abilities are in fact presenting with the hallmark biomarkers of AD.

### **Conclusion**

Individuals with SCD are thought to be the earliest along the cognitive continuum between healthy aging and AD. The current study used a multi-modal neuroimaging approach to examine differences in both brain structure and function between individuals with SCD and healthy controls. Findings revealed changes in brain function but not structure between individuals with SCD and healthy controls. Overall, this study represents a crucial step in characterizing individuals with SCD, a group recognized to be at an increased risk for developing AD. Future work incorporating both structural and functional MRI analyses should be done longitudinally to identify changes in brain structure and function prior to measurable decline on paper-and-pencil neuropsychological assessment measures.

## Chapter 3

The current study used MRI to investigate brain structure and function in individuals with SCD relative to healthy controls. Using a VBM approach, no significant differences in grey matter were revealed between the groups. In contrast, the resting state functional MRI connectivity analysis revealed significantly greater activity in the DMN including the bilateral precuneus cortex, bilateral thalamus, and right hippocampal region in individuals with SCD relative to controls, as well as significant decreases in activation in the right superior frontal gyrus, right occipital pole, right superior temporal gyrus, left superior temporal gyrus in the posterior division, left precuneus cortex, left precentral gyrus, left occipital fusiform gyrus, left temporal pole, and left cerebellum, as well as bilateral decreases in the frontal pole, caudate, angular gyrus, and lingual gyrus compared to healthy controls. The current study suggests that changes in functional connectivity within the DMN may precede structural changes in the brain, therefore representing a possible earlier biomarker for AD.

### Limitations

Despite the many strengths of the current study, such as the use of a multi-modal approach to identify changes in both brain structure and function, several limitations should be acknowledged. Notably, both the SCD and healthy control group data were obtained from the ADNI-2 database which has inherent limitations.

First, is how this database selects its participants. In order to be included in the ADNI-2 database, participants are required to be free of any evidence of infarction or focal lesions and significant neurologic comorbidities (such as Parkinson's disease, multiple sclerosis, or seizure disorder). Eligible participants must also obtain a score of

<6 on the Geriatric Depression Scale. Although these criteria are put in place to create a “pure” sample of individuals who have or at risk for AD, they also make the data less generalizable. In particular, given that many older adults show focal white matter hyperintensities on their T2-weighted MRI scans (which can provide an index of cerebrovascular health), although cerebrovascular health is a risk factor for AD. Furthermore, individuals with low mood are not eligible to participate in the ADNI study, despite the fact that many individuals experience a change in mood early on in the course of AD. Further, the ADNI dataset has not yet incorporated the SCD-plus criteria outlined by Jessen and colleagues (2014). The SCD-plus criteria outline additional elements that increase the likelihood of preclinical AD in those with SCD (Jessen et al., 2014). These elements include subjective decline in memory (rather than other domains of cognition), the onset SCD occurring within the last 5 years, being at least 60 years old at the age of onset of SCD, concerns about their SCD, and feelings of worse performance compared to same-aged peers (Jessen et al., 2014). Without including SCD-plus elements as grouping variables in the ADNI dataset, it may be possible that this SCD group is not specific to individuals with preclinical AD. Perhaps ADNI’s method of classifying individuals with SCD partly explains the null findings in the structural analysis between those with SCD and healthy controls. Taken together, the current ADNI sample is somewhat limited in terms of generalizability to the broader SCD population.

Another limitation of the ADNI sample pertains to how the groups are defined. Specifically, for the SCD group (which is called “significant memory complaint” in ADNI), individuals are only included if their subjective report for their memory concern is confirmed by scoring  $\geq 16$  on the Cognitive Change Index from the first 12 questions

(Alzheimer's Disease Neuroimaging Initiative, 2008). This is problematic as the first 12 questions on this measure pertain only to memory, where the remaining 8 questions assess executive and language functioning. Given that other studies (e.g. Ohlhauser, Parker, Smart, & Gawryluk, 2019) have found a specific relationship between SCD and executive function and that the International Working Group on SCD has advocated for broader cognitive criteria (Jessen et al., 2014), best practices in defining SCD should include concerns beyond memory.

In addition to being defined by cognitive complaints, a key characteristic of SCD is the lack of objective cognitive decline measured on neuropsychological assessment measures. Notably, within the ADNI database, both the SCD and healthy control groups were determined to have normal memory function by scoring within normal limits on the Logical Memory II subscale of the revised WMS ( $\geq 9$  for 16 years of education and above,  $\geq 5$  for 8-15 years of education, and  $\geq 3$  for 0-7 years of education), a MMSE score between 24 and 30 (inclusive), and a Clinical Dementia Rating of 0 (Alzheimer's Disease Neuroimaging Initiative, 2008). Thus, although, the ADNI-2 protocol collects data using multiple neuropsychological assessment measures at the baseline visit, only a normal score of Logical Memory II is used to determine normal memory functioning. Requiring normal performance on a battery of tests would improve the characterization of SCD.

A final limitation with the currently examined SCD group is that the duration of the cognitive complaints are unknown. Therefore, the results of the current study could be influenced by heterogeneity in the length of time individuals have experienced SCD. For example, perhaps some individuals have been stable for some time, and others are on a more progressive trajectory, which could lead to differences in neuroimaging results.

## Future Directions

In light of the limitations of this current study, there are multiple directions for future research. First, additional research is needed to better characterize *in vivo* biomarkers in SCD. These investigations should be longitudinal and focus on which individuals are most likely to convert along the continuum of AD in order to understand differences between those who convert and those who are stable over time. Differences that could be looked at between these individuals could include APOE  $\epsilon$  status, levels of beta-amyloid or tau (as measured by PET or CSF), as well as differences that may exist in individuals depending on the population they were recruited from (e.g. community vs. clinical samples).

Second, future research should use multi-modal approaches to look at differences between individuals with SCD and healthy controls. Although ADNI does not collect fMRI and diffusion tensor imaging (DTI) data on the same participants, there is evidence that differences exist between those with SCD and healthy controls using DTI (e.g., Ohlhauser et al., 2019). Studying structural and functional connectivity in the same individuals will be key for understanding the earliest changes in the brain that are related to Alzheimer's pathology.

Third, this current study only examined functional connectivity in the DMN, future work should examine other important networks in the brain such as the fronto-parietal and fronto-executive networks to see if these networks are equally or more sensitive to changes in the brain in SCD.

Fourth, it would be worthwhile to use a more in depth assessment of SCD to ensure that individuals are indeed free of objective cognitive impairment. As outlined

above, using a comprehensive battery of neuropsychological measures in combination with a thorough questionnaire of cognitive complaints (including questions on both memory and executive functions) will help to better characterize SCD.

Fifth, future research could compare additional groups along the AD continuum, including healthy controls, SCD, MCI, and AD groups using large sample sizes. Examining multiple groups along the AD continuum could help to identify subtle differences between these different stages that we would otherwise not see when only looking at a subset of groups along this continuum.

### **Conclusion**

In conclusion, this study aimed to investigate (1) if differences in grey matter density exist between individuals with SCD and healthy controls, and (2) if differences in resting state functional MRI activation exists between those with SCD and healthy controls. Findings revealed changes in brain function but not structure between individuals with SCD and healthy controls. These findings have yielded multiple avenues for continued research on MRI biomarkers for AD. The ultimate goal is to improve early detection of AD so that preventative and neuroprotective measures can be implemented at the earliest time point to reduce the devastating effects of this neurodegenerative disorder.

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