

Earlier Detection of Alzheimer's Disease: Investigating Brain-Based Changes in Older Adults with Subjective Cognitive Decline

by

Ashleigh F. Parker
M.Sc., University of Victoria, 2019
B.Sc. (Hons), University of British Columbia, 2017

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of the Requirements for the Degree of

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We acknowledge and respect the Lək̓ʷəŋən (Songhees and Esquimalt) Peoples on whose territory the university stands, and the Lək̓ʷəŋən and ƳSÁNEĆ Peoples whose historical relationships with the land continue to this day.

Supervisory Committee

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Supervisory Committee

Jodie R. Gawryluk, Department of Psychology, University of Victoria
Co-Supervisor

Cassandra Szoeka, Department of Psychology, University of Victoria
Co-Supervisor

Theone Paterson, Department of Psychology, University of Victoria
Departmental Member

Dr. Alexandre Henri-Bhargava, Island Medical Program, University of Victoria
Outside Member

Abstract

Alzheimer's disease (AD) is an incurable neurodegenerative disorder with a late clinical diagnosis, which disproportionately affects women. Research in preclinical AD has begun to focus on individuals with subjective cognitive decline (SCD), who are considered earliest on the cognitive continuum between healthy aging and AD. This dissertation is comprised of three manuscripts each focused on investigating whether neuroimaging (across modalities) can detect brain-based differences between individuals with SCD compared to their healthy counterparts. Study 1 is an in-depth systematic review of neuroimaging studies on SCD. Search results identified 62 studies that examined the use of structural and/or functional neuroimaging techniques in the detection of brain-based differences between individuals with SCD and healthy controls. While significant differences were found within and across various neuroimaging modalities, inconsistencies were observed within and between studies, suggesting the need for standardized criteria and longitudinal investigations in future research. Study 2 utilized resting-state functional MRI to explore functional connectivity differences in multiple brain networks between healthy older women and those with SCD. Results revealed increased functional connectivity in the default mode network and frontoparietal network among women with SCD independent of demographic variables, lifestyle factors, and medical comorbidities. Study 3 utilized multi-modal neuroimaging approach to examine grey and white matter differences in women with SCD compared to healthy women. No significant differences were detected in grey matter volume or white matter microstructure between the two groups. The resulting findings of studies 2 and 3, revealed the detection of differences between groups in brain function but not structure.

This finding suggests that women with SCD can be differentiated from healthy women, before any significant and irreversible brain atrophy has taken place. Together, these studies contribute to the understanding of SCD as a preclinical marker of AD. Ongoing research and advancements in the conceptualization of earlier detection of AD are expected to play an important role in the development and implementation of disease-modifying interventions at the earliest possible time point, thereby reducing the devastating effects of this neurodegenerative disorder.

Table of Contents

Supervisory Committee	ii
Abstract	iii
Table of Contents	v
List of Tables	vi
List of Figures	vii
Acknowledgments	viii
Dedication	ix
General Introduction	1
Study 1: A Systematic Review of Neuroimaging Studies Comparing Individuals with Subjective Cognitive Decline to Healthy Controls	19
Abstract	20
Introduction	22
Methods	26
Eligibility Criteria	26
Results	28
Discussion	33
Study 2: Functional Connectivity Alterations in the DMN and FPN in Women with SCD	60
Abstract	61
Introduction	63
Methods	71
Results	78
Discussion	84
Study 3: Multimodal structural MRI does not reveal differences in grey or white matter with and without subjective cognitive decline	90
Abstract	91
Introduction	92
Methods	97
Results	101
Discussion	102
Concluding Remarks	108
References	117
Appendix	147

List of Tables

Table 1.1 <i>Summary of Neuroimaging Modalities Used in the Articles Included (n = 62)</i>	44
Table 1.2 <i>Description of Brain Imaging Modalities and Summary of Results</i>	45
Table 1.3 <i>Sample Characteristics and Results of Anatomical MRI Studies (n = 11)</i>	47
Table 1.4 <i>Characteristics of DTI Studies (n = 6)</i>	48
Table 1.5 <i>Characteristics of fMRI Studies (n = 9)</i>	49
Table 1.6 <i>Characteristics of Multi-Modal MRI Studies (n = 10)</i>	50
Table 1.7 <i>Characteristics of PET Studies (n = 6)</i>	51
Table 1.8 <i>Characteristics of Multi-Modal MRI & PET Studies (n = 8)</i>	52
Table 1.9 <i>Characteristics of EEG Studies (n = 4)</i>	53
Table 1.10 <i>Characteristics of MEG Studies (n = 7)</i>	54
Table 1.11 <i>Characteristics of SPECT Studies (n = 1)</i>	55
Table 1.12 <i>Breakdown of significant and non-significant findings across neuroimaging modalities</i>	56
Table 1.13 <i>Breakdown of ratings for each item on the AXIS tool across the 62 included studies</i>	57
Table 1.14 <i>Frequency counts of each SCD-Equivalent Classifications</i>	58
Table 2.1 <i>Brain regions showing increased functional connectivity in the DMN in participants with SCD compared to healthy controls</i>	80
Table 2.2 <i>Brain regions showing increased functional connectivity in the FPN in participants with SCD compared to healthy controls</i>	82
Table 2.3 <i>Participant Demographics</i>	83
Table 3.1 <i>Participant Demographics</i>	101

List of Figures

Figure 1.1 <i>PRISMA flow diagram for the current systematic review</i>	59
Figure 2.1 <i>Flow diagram of participant selection for Study 2</i>	72
Figure 2.2 <i>Brain regions showing increased functional connectivity in the DMN in participants with SCD compared to healthy controls</i>	79
Figure 2.3 <i>Brain regions showing increased functional connectivity in the FPN in participants with SCD compared to healthy controls</i>	81
Figure 3.1 <i>Flow diagram of participant selection for Study 3</i>	98

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Finally, I am grateful to all the participants who contributed their time and insights to the WHAP.

Dedication

To the best parents I could have ever asked for, Sherry and Steve.

Introduction

Alzheimer's disease (AD) is the most common form of dementia, accounting for approximately 70% of all cases (World Health Organization, 2023, March 15). Recent research has highlighted the substantial increase in the diagnosis of dementia, revealing that the number grew from 20.2 million individuals in 1990 to 43.8 million in 2016 (Nichols et al., 2019). It is also predicted that the number of global dementia cases will triple by 2050 (Nichols et al., 2022). Given that the greatest risk factor for AD is age, and that the world's population is rapidly aging, AD and other dementias are a growing global health concern. Notably, women are disproportionately impacted by AD; approximately two-thirds of those diagnosed with AD are women (World Health Organization, 2023, March 15). As older women represent a group who are at greater risk for the development of AD, it is crucial that clinical research is conducted to advance the understanding of AD in women.

A major thrust of research on AD has focused on understanding the underlying biological mechanisms of AD. Findings suggest that the neuropathological changes associated with AD, including amyloid Beta plaques, neurofibrillary tangles, and neurodegeneration may be initiated decades before clinical symptoms are present (van Oostveen & de Lange, 2021). Despite advancements in the understanding of these biological mechanisms, clinical trials of potential disease modifying treatments for AD have yet to be successful (Tatulian, 2022). However, these unsuccessful clinical trials focused on delivering potential disease-modifying treatments to individuals who already have an established diagnosis of AD or mild cognitive impairment (MCI). Unfortunately, individuals with established diagnoses of AD or MCI have already suffered irreversible

neurodegeneration that has negatively impacted their functioning (R. A. Sperling et al., 2011). Although these clinical trials have been unsuccessful in halting or slowing the progression of AD in individuals in the mild to moderate clinical stages (Doody et al., 2014; Salloway et al., 2014), these negative results have prompted increased interest in studying the earlier pre-clinical stages of AD (Epelbaum et al., 2017).

It is hypothesized that earlier detection of AD is an essential step for successful treatment of AD. Better understanding preclinical stages of AD could lead to the development and implementation of new therapies to be delivered at earlier time points before irreversible neurodegenerative processes take place (Pais et al., 2020). Recent studies suggest that disease-modifying therapies may be most effective at these early, preclinical stages (Guzman-Martinez et al., 2021; van Oostveen & de Lange, 2021). Previous research suggests that studying individuals with subjective cognitive decline (SCD) may contribute to advancements in understanding and identifying preclinical AD (Donovan et al., 2014; Jessen et al., 2014; Mitchell et al., 2014; Reisa A. Sperling et al., 2011; Wang et al., 2021).

The concept of SCD was initially conceptualized as an early stage of dementia by Reisberg and colleagues in 1982. Those with SCD were described as individuals who report changes in their cognition but perform within normal limits based on their scores on clinical neuropsychological assessment measures (Reisberg et al., 1982). These identified characteristics of SCD are still used today, however a more comprehensive framework with additional parameters have been included in the research framework proposed by the Subjective Cognitive Decline – Initiative (SCD-I) (Jessen et al., 2014), described below.

SCD Definition and Research Criteria

The term subjective cognitive decline (SCD) was introduced in 2014 by the Subjective Cognitive Decline – Initiative (SCD-I), a working group that aimed to establish both standardized terminology and a research framework for studying SCD (Jessen et al., 2014). This working group was formed to improve research being done in this area as it has previously been described as limited due to the lack of common standards in how SCD is defined and studied. The term *Subjective Cognitive Decline* was specifically chosen as each word of this term describes the concept that the SCD-I aims to study in relation to early AD. The word *subjective* was chosen to reflect that one’s view of their cognition is self-perceived and independent of their performance on a cognitive test. The word *Cognitive* was selected to include any cognitive domain (not strictly limited to “memory” as lay people may report problems with their memory when their difficulties truly lie in a different cognitive domain). Lastly, the word *decline* was included to suggest that there has been a worsening of cognitive abilities over time, to emphasize the progressive course of AD (Jessen et al., 2014). Although the terminology was created for use in research contexts, it is believed that these same concepts are useful in clinical settings (Jessen et al., 2020).

The SCD-I also created specific research criteria for studying SCD which is made up of two specific requirements (Jessen et al., 2014). First, SCD is considered a “self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event.” Second, “Normal age-, gender-, and education-adjusted performance on standardized cognitive tests, which are used to classify MCI or prodromal AD” (Jessen et al., 2014). However, one would not be

considered to have SCD if they already have a diagnosis of MCI, prodromal AD, or dementia. They would also not be considered to have SCD if their subjective reports of cognitive decline can be better explained by a psychiatric disorder, a non-AD neurologic disease, other medical disorder, the effects of a medication, or substance use (Jessen et al., 2014).

SCD in Context of the Cognitive Continuum

SCD is conceptualized as a preclinical stage of AD (also referred to as “pre-MCI”) representing individuals at the earliest point in the cognitive continuum between healthy aging and Alzheimer’s disease (Jessen et al., 2014). In the context of the cognitive continuum, it is hypothesized that declining cognitive performance occurs in the presence of increasing AD-related pathology across clinical classifications (i.e., intact cognitive performance, SCD, MCI, and AD dementia) (Jessen et al., 2014; Rabin et al., 2017). Rabin and colleagues (2017) hypothesize that objective cognitive decline occurs after a period of time where relatively normal and stabilized cognitive functioning is observed (while AD-related pathology increases over time).

While there can be overlapping features and symptoms across SCD, MCI, and AD dementia, each classification possesses distinct components that distinguish them from one another. These distinctions are seen in presence of self-reported cognitive decline, level of objective cognitive decline as measured by standardized neuropsychological testing, and the ability to independently perform activities of daily living (ADLs). Individuals with SCD self-report declines in their cognitive abilities, demonstrate intact cognitive performance on standardized neuropsychological testing, and maintain independence in completing ADLs. In contrast, individuals with MCI may or may not

self-report a decline in their cognition (though a self-report of cognitive decline is not required for a diagnosis of MCI), will demonstrate evidence of cognitive impairment as measured by standardized neuropsychological testing, and will retain their abilities to carry out ADLs independently. As for individuals with AD, they may self-report a decline in their cognitive abilities (although at this stage, anosognosia is common, limiting accurate self-reporting of symptoms), will display more severe cognitive impairments on standardized neuropsychological testing as compared to individuals with MCI, and demonstrate significant difficulties managing ADLs independently such that they require additional supports in order to meet their care needs.

Course of SCD

As described above, individuals with SCD have been conceptualized as the earliest on the continuum towards AD between healthy aging and MCI (Jessen et al., 2014). Previous meta-analyses have found those with SCD are at twice the risk of developing MCI or dementia compared to those without SCD (Mendonça et al., 2016; Mitchell et al., 2014). More recently, a systematic review and meta-analysis found similar results reporting that those with SCD had a 2.9-fold excess risk for cognitive impairment and a 2.16-fold excess risk for developing dementia (Wang et al., 2021).

However, Jessen and colleagues (2020; 2014) have recognized that SCD is not specific to pre-clinical AD. SCD is considered to be a broad condition that may be experienced for a variety of reasons such as normal aging, psychiatric conditions, other neurological conditions, the impact of substance use, or from physician prescribed medications. Thus, not all individuals who experience symptoms of SCD will go on to develop AD or other dementias. Different trajectories have been suggested by Jessen et

al. (2020). The first is “Reversible SCD” where an individual’s perceived symptoms of SCD will remit and they will not go on to develop any objective cognitive deficits. The second trajectory is “Stable, non-reversible SCD” which refers to those who continue to experience symptoms of SCD but do not go on to develop objective cognitive impairment. The third is “SCD with subsequent progressive cognitive decline to impairments or dementia.” In this third trajectory, this cognitive decline can be caused by various neurodegenerative disorders, not only AD (Jessen et al., 2020). It is not fully understood what proportion of individuals with SCD fall into each of these three trajectories, but it is hypothesized that most of these individuals will not progress to dementia (Jessen et al., 2020).

In recognition of these different trajectories of SCD, Jessen et al. (2014) have outlined additional criteria known as SCD-plus, which represents additional features of SCD that signal a higher risk of future development of AD. These features include subjective decline in memory (rather than other domains of cognition), the onset of SCD occurring within the last 5 years, being at least 60 years old at the age of onset of SCD, having concerns about their symptoms of SCD, and feeling they perform worse than their same-aged peers (Jessen et al., 2014). If available, other SCD-plus criteria include confirmation of cognitive decline from an informant, the presence of APOE e4, and presence of AD biomarkers that define pre-clinical AD. Limited research has been conducted on SCD-plus, however longitudinal research has found those with SCD who also meet criteria for preclinical AD have a 40-62% risk of converting to MCI or dementia within three years (van Harten et al., 2013; Wolfsgruber et al., 2017).

Risk Factors for Experiencing SCD

A study by Wen et al. (2021) investigated eight risk factors associated with SCD in a large cohort of 1165 individuals without objective cognitive impairment. Specifically, Wen and colleagues (2021) examined risk factors including increasing age, female sex, anemia, thyroid diseases, minimal anxiety symptoms (scores of <7 on the Hamilton Anxiety Rating Scale), lack of exercise, daytime dysfunction, and living alone. The results of this study indicated increasing prevalence of SCD in individuals with a higher number of these risk factors (Wen et al., 2021). This study by Wen and colleagues (2021) was first of its kind to better understand the risk factors associated with experiencing SCD. Future research in this area is necessary to better understand the risk factors for experiencing SCD as well as the associated risk of SCD and its potential link to the development of subsequent dementia.

Prevalence of SCD

A US-based study reported that approximately 11% of those aged 45 years and older report SCD (Taylor et al., 2018). However, determining an accurate estimate of SCD prevalence is difficult due to issues regarding the classification of SCD across studies (Molinuevo et al., 2017). Although the criteria outlined by the SCD-I (Jessen et al., 2014) was published in 2014, there have been few research investigations that have employed their research criteria (Röhr et al., 2020). Of the studies that have followed the criteria set by the SCD-I (Jessen et al., 2014), prevalence rates of SCD have continued to vary across cohorts of cognitively unimpaired individuals, ranging from 14% to 54% (Hao et al., 2017; Roehr et al., 2019; Vlachos et al., 2019). It is hypothesized that a lack of standardized procedures for assessing SCD is responsible for these variations (Röhr et al., 2020). The need for the harmonization of existing measures in order to create a

validated SCD scale has been described as a major research priority for the SCD-I for nearly 10 years (Rabin et al., 2015). While Jessen et al. (2020) have recently provided suggestions on the additional information that should be gathered through a questionnaire evaluating SCD, no validated SCD measure has been endorsed by the SCD-I.

Despite the lack of a validated SCD measure endorsed by the SCD-I, Röhr and colleagues (2020) synthesized and harmonized self-report items across various assessments measuring self-experienced cognitive decline from 16 international population-based cohorts. The included cohorts comprised of over 39,000 participants from 15 different countries who were at least 60 years of age (Röhr et al., 2020). The estimated prevalence of SCD in cognitively healthy older adults was 25% (Röhr et al., 2020). Röhr and colleagues (2020) further analyzed whether prevalence rates varied across sociodemographic variables and regional factors. Additional demographic variables may also play a role in SCD. For example, Röhr and colleagues (2020) found individuals from lower-/middle-income countries experienced higher rates of SCD compared to those from high-income countries. Sub-group analyses found increased rates of SCD among individuals with lower levels of education, as well as in Asian and Black African individuals compared to Caucasians (Röhr et al., 2020). Interestingly, they also found that men were more likely to report SCD compared to women. However, findings across studies investigating the difference in the prevalence rates of SCD between men and women have been mixed. Specifically, while some studies have described that women report SCD at a higher rate than men (Kim et al., 2003; Müller-Gerards et al., 2019), others have found a higher prevalence of SCD in men (Wang et al., 2004) or no differences in SCD prevalence between men and women (Buckley et al., 2013). Further

research is needed to better understand the contributions of sociodemographic variables to the report and presentation of SCD.

SCD in Women: Sex-Specific Factors and Clinical Implications

It is notable that older women experience a disproportionately higher prevalence of AD (World Health Organization, 2023, March 15). Recent research discusses sex-specific differences seen between men and women as it relates to the experience of SCD and incident MCI and future development of AD. Sex-specific differences have been reported in the context of SCD and the menopausal transition, associated worries, APOE e4 status, measures of frailty, areas of cognitive strength, and rates of cognitive decline.

Menopausal Transition

It has been suggested that declines in ovarian estrogens during the menopausal transition are associated with higher rates of self-reported cognitive complaints (Grummisch et al., 2023; Hogervorst et al., 2022; Reuben et al., 2021; Weber et al., 2012). Interestingly, both the experience of SCD and the declines in ovarian estrogens are associated with an increased risk of future cognitive decline and development of AD (Reuben et al., 2021). Symptoms associated with the menopausal transition (caused by hormone fluctuations) can also contribute to self-reported cognitive decline. Specifically, menopause can disrupt temperature regulation (Maki & Thurston, 2020), blood flow (Kehmeier & Walker, 2021), inflammation (Mishra & Brinton, 2018; Straub, 2007; Y. Wang et al., 2020), glucose metabolism (Brinton, 2008; Brinton et al., 2015; Y. Wang et al., 2020), and sleep (Brown & Gervais, 2020; Schaedel et al., 2021); each of which may impact cognitive performance and brain health. The impacts of hormonal alterations

during the menopausal transition must not be overlooked in the context of increased risk for future development of AD (Reuben et al., 2021).

Worries

Heser et al. (2019) found that men were more likely to report SCD without associated worries, whereas women were more inclined to report SCD with associated concerns. Further, the results of this study also suggested that women with SCD, regardless of associated worries, were at an increased risk of developing AD and other dementias (Heser et al., 2019). In contrast, men who reported SCD with associated worries (but not in those with SCD without worries) were at an increased risk for future development of AD but not other dementias (Heser et al., 2019). These findings highlight the differences in associated risks of future development of AD and/or other dementias between men and women who report SCD with worries or without worries (Heser et al., 2019). It also underscores the importance of studying sex-specific factors relevant to the characterization of SCD and the risk it presents.

APOE e4 Status

Presence of the APOE e4 allele, a widely recognized genetic risk factor of AD, has recently been found to have sex-specific effects (Müller-Gerards et al., 2019). Specifically, findings indicate that the odds of developing MCI within 5 years were higher for women with SCD and APOE e4 +/+ status than in women with SCD and APOE e4 +/- or APOE e4 -/+, while men with SCD and APOE e4 +/- were at highest risk of incident MCI (Müller-Gerards et al., 2019). These results suggest that the combination of reported SCD and expressed APOE e4 alleles may impact future cognitive decline differently as a function of sex (Müller-Gerards et al., 2019). Notably,

another study by Liew (2022), found that SCD and APOE e4 presence independently increased the prediction of future neurocognitive disorders for both men and women. However, the co-occurrence of SCD and presence of the APOE e4 allele significantly increased the prediction of future development of neurocognitive disorders in older women specifically (Liew, 2022).

Frailty

Gifford et al. (2019) examined the association of frailty and SCD in both women and men. Interestingly, they found that frailty was not correlated with objective or subjective cognition in men. However, in women with SCD, frailty was associated with performance on multiple cognitive screening measures (Gifford et al., 2019). According to this study, manifestations of frailty in individuals with SCD differ between men and women, implying that the co-occurrence of SCD and frailty could potentially serve as a useful predictor of cognitive decline in women (Gifford et al., 2019).

Cognitive Strengths

It is well-known that women and men exhibit different cognitive strengths compared to one another in areas such as visuospatial abilities (Munro et al., 2012; Voyer et al., 2017), mental rotation (Hyde, 2016; Voyer et al., 2020), episodic memory (Asperholm et al., 2019), verbal phonemic fluency (Hirnstein et al., 2023), and verbal memory (Hirnstein et al., 2023; Munro et al., 2012; Voyer et al., 2021). Despite this knowledge, there is an absence of sex-adjusted norms in neuropsychological assessment measures used for cognitive screening, which may contribute to diagnostic inaccuracies, particularly in women (Wang et al., 2018). These discrepancies in cognitive domains could potentially lead to an underestimation of cognitive problems in women relative to

men, due to the cognitive strengths exhibited by women, such as in verbal memory (Wang et al., 2018). This study highlights the potential psychometric limitations within cognitive screening measures, which could lead to the under recognition of cognitive challenges in women, especially in preclinical stages of AD, such as SCD (Wang et al., 2018).

Rates of Cognitive Decline

Finally, a recent study by Oliver et al. (2022) found that women with SCD showed faster rates of cognitive decline, suggesting that SCD may be a more reliable predictor of future AD or other dementias in women than in men.

Interventions for SCD

Given that SCD may represent the earliest deviation on the continuum of dementia, it may also be an ideal time for intervention. However, the experience of SCD can stem from diverse etiologies, leading to challenges in determining the most effective intervention options. Regardless of the etiology underlying the experience of SCD, early intervention for cognitive symptoms could lessen symptom severity and improve quality of life. Multiple literature reviews have examined the efficacy of non-pharmacological treatments in the improvement of cognition in individuals with SCD (Mohanty & Kumar, 2022; Roheger et al., 2021; Smart et al., 2017). Smart and colleagues (2017) reported a small effect size on the improvement of cognitive variables when cognitive interventions were utilized over other behavioural, psychosocial, and alternative medicine interventions. A systematic review by Roheger et al. (2021) found participation in educational programs to be most effective in improving memory. Specifically, these educational programs comprised of psychoeducational sessions covering topics such as

healthy lifestyle factors, dementia risk, and cognitive coping strategies such as mnemonics (Cheng et al., 2018; Hong et al., 2020; Kwok et al., 2013; Lautenschlager et al., 2008; Small et al., 2006). Additionally, Roheger et al. (2021) found moderate-intensity exercise interventions to be second most effective in improving memory in those with SCD, followed by cognitive training. Another review, conducted by Mohanty and Kumar (2022), discussed the effectiveness of nonpharmacological interventions comprised of multiple components to be effective in reducing the complaints reported by individuals experiencing SCD. These multifaceted interventions included a combination of psychoeducation, cognitive training, relaxation exercises, physical exercise, and lifestyle modifications (Mohanty & Kumar, 2022). In order for targeted interventions to be most effective, it is important to understand and be able to measure changes in the brain that occur with SCD.

Neuroimaging and SCD

Neuroimaging techniques allow for observation of changes in the brain in-vivo. An in-depth systematic review of the literature of neuroimaging in those with SCD compared to healthy controls is presented in Study 1. To summarize the works completed in this review, the results demonstrated that neuroimaging methods were capable of detecting differences between healthy individuals who reported a decline in their own cognition compared to those who did not. The review covered areas of neuroimaging including MRI (both structural and functional), PET, EEG, MEG, SPECT, and multi-modal methods (Parker et al., 2022). It also highlighted various methodological differences across studies which made it challenging to synthesize the findings. Overall,

alterations in brain structure and function (as measured by various neuroimaging techniques) have been documented in those with SCD compared to healthy controls.

Neuroimaging studies have also investigated population differences between individuals with SCD and with individuals with MCI or dementia. One study found individuals with SCD from community-based samples showed a consistent pattern of atrophy in temporal/parietal cortices and hippocampus while those with SCD from clinic-based samples showed a heterogeneous pattern of atrophy in the parietal/temporal cortices (Pini & Wennberg, 2021). A study by Kuhn et al. (2021) found that those who reported greater scores of a decline in their own cognition were associated with greater levels of atrophy as seen by neuroimaging. However, for those with MCI or AD, lower severity reports of a decline in cognition were associated with a greater level of atrophy (Kuhn et al., 2021). This is thought to represent anosognosia where the individual displays a lack of insight into their condition due to the higher levels of neurodegeneration (Kuhn et al., 2021).

Magnetic Resonance Imaging in SCD

MRI is a particularly useful technique for examining pre-clinical biomarkers because MRI is non-invasive, easily repeatable, and widely available. MRI is capable of acquiring both structural and functional data. However, the only MRI biomarker that is accepted in the NIA-AA standards of AD biomarkers is the identification of brain atrophy in medial temporal lobes using voxel-based morphometry (VBM). Regardless of the acceptance of these other MRI techniques in the NIA-AA standards, other techniques such as diffusion tensor imaging (DTI) and functional MRI (fMRI) have been used in the

study of pre-clinical biomarkers for AD. The use of each of these techniques in the study of SCD are further discussed in studies 2 and 3.

Overview of Studies

This dissertation is comprised of three manuscripts, each described below. Each of these three studies focused on investigating whether neuroimaging is capable of detecting brain-based differences between individuals with SCD compared to their healthy counterparts. While the first study of this dissertation is an in-depth systematic review of determining whether neuroimaging methods are capable to find differences between these groups, the second and third studies of this dissertation specifically focus on the utility of functional and structural MRI in the detection of brain-based differences between women with SCD and healthy women.

Study 1: A Systematic Review of Neuroimaging Studies Comparing Individuals with Subjective Cognitive Decline to Healthy Controls

The goal of this systematic review sought to answer four specific questions: *1) Can differences be detected between individuals with SCD and HC using a variety of neuroimaging methods?; 2) Are the detected differences consistent within each neuroimaging technique?; 3) Are the regions (structural and functional) affected in SCD consistent with those expected in early-stage AD?; and 4) Are there methodological characteristics/differences between the studies that could impact the findings?* In this systematic review, 62 neuroimaging studies were critically examined and the findings from each were described. The results from the included studies were synthesized and each of the above questions were answered narratively based on the findings.

Study 2: Resting State Functional Connectivity Analyses between Healthy Older Women with or without Subjective Cognitive Decline

The goal of this second study was to investigate whether differences in brain function exist between healthy older women who report SCD compared to those who do not. This study examined resting state functional connectivity in the default mode network, frontoparietal network, and salience network. Comparisons were also made between groups to examine whether differences between women with SCD and controls existed on various demographic variables, modifiable health risk factors previously published by the *Lancet* Commission on dementia prevention (Livingston et al., 2020). Seed-based resting state fMRI connectivity analyses were used to examine difference between groups in each network of interest. All participants were part of the Women's Healthy Ageing Project (WHAP). Neuroimaging data were collected on a 3T MRI scanner. Non-imaging data were retrieved from BioGrid, the data repository holding all data information for the WHAP (including demographic information, neuropsychological test scores, self-report measures, and information on biological data, etc.). It was hypothesized that (1) women with SCD would show differences in resting-state functional connectivity compared to healthy women, and (2) there would be minimal differences between women with SCD and healthy women across various demographic variables, lifestyle factors, and medical comorbidities as the participants of this study were community-dwelling women experiencing healthy aging.

Study 3: Multi-Modal MRI Study Investigating Grey Matter and White Matter in Older Women with or without Subjective Cognitive Decline

The goal of this third study was to investigate whether healthy older women who report SCD show differences in brain structure compared to healthy older women who do not report SCD. This study examined both grey matter volume (using VBM) and white matter integrity (using diffusion tensor imaging metrics to measure fractional anisotropy and mean diffusivity). All participants were drawn from the WHAP and were a subset of the participants from Study 2 (including those from the previous study who had also undergone resting state fMRI). Neuroimaging data were collected on a 3T MRI scanner. Again, the non-imaging data were retrieved from BioGrid (including demographic information, neuropsychological test scores, self-report measures, and information on biological data, etc.). It was hypothesized that (1) there would be no significant differences in grey matter volume between women with SCD and healthy women, and (2) that women with SCD would demonstrate lower fractional anisotropy (FA) and higher mean diffusivity (MD) in widespread brain regions compared to healthy women.

Study 1: A Systematic Review of Neuroimaging Studies Comparing Individuals with Subjective Cognitive Decline to Healthy Controls

This chapter includes published work:

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Abstract

Background: Individuals with subjective cognitive decline (SCD) are hypothesized to be the earliest along the cognitive continuum between healthy aging and Alzheimer's disease (AD), although more research is needed on this topic. Given that treatment approaches may be most effective pre-clinically, a primary objective of emerging research is to identify biological markers of SCD using neuroimaging methods.

Objective: The current review aimed to comprehensively present the neuroimaging studies on SCD to date.

Methods: PubMed and PsycINFO databases were searched for neuroimaging studies of individuals with SCD. Quality assessments were completed using the Appraisal tool for Cross-Sectional Studies.

Results: In total, 62 neuroimaging studies investigating differences between participants with SCD and healthy controls were identified. Specifically, the number of studies were as follows: 36 MRI, 6 PET, 8 MRI/PET, 4 EEG, 7 MEG, and 1 SPECT. Across neuroimaging modalities, 48 of the 62 included studies revealed significant differences in brain structure and/or function between groups.

Conclusion: Neuroimaging methods can identify differences between healthy controls and individuals with SCD. However, inconsistent results were found within and between neuroimaging modalities. Discrepancies across studies may be best accounted for by methodological differences, notably variable criteria for SCD, and differences in participant characteristics and risk factors for AD. Clinic based recruitment and cross-sectional study design were common and may bias the literature. Future neuroimaging investigations of SCD should consistently incorporate the standardized research criteria

for SCD (as recommended by the SCD-Initiative), include more details of their SCD sample and their symptoms, and examine groups longitudinally.

Introduction

Globally, dementia affects roughly 43.8 million older adults (Nichols et al., 2019). One of the most common forms of dementia includes Alzheimer's disease (AD), an incurable neurodegenerative disorder that accounts for 60-70% of all dementia cases (World Health Organization, 2020, September 21). Currently, the disease-modifying treatments for AD aim to prevent symptom progression. However, much of this research has been focused on treating patients with amnesic mild cognitive impairment (aMCI) or AD itself who have already experienced significant neurodegeneration that has impacted their cognition and ability to carry out instrumental activities of daily living. In light of this, one objective of emerging research in AD has shifted towards identifying pre-clinical biomarkers in individuals at risk for developing AD. Broadly, the goal of the emerging research is to find a way of identifying individuals who will later develop AD before significant neurocognitive symptoms develop; a time point which is believed to be the period during which disease-modifying treatments are most effective (Berti et al., 2016; Imtiaz et al., 2014; Reisa A. Sperling et al., 2011).

More recently, some studies in pre-clinical AD have begun to examine individuals with subjective cognitive decline (SCD). Individuals with SCD have been conceptualized as the group showing the earliest signs of decline on the cognitive continuum towards AD (i.e., between healthy aging and MCI) (Jessen et al., 2014). In 2014, an international working group on SCD was formed to propose a framework for research on SCD (Jessen et al., 2014). Specifically, Jessen et al. (2014) describe individuals with SCD to self-report a decline in their own cognitive abilities, but these self-reports are not corroborated by impaired performance on neuropsychological assessment measures. Instead, these

individuals perform within normal limits on these measures (Jessen et al., 2014). Within the literature, healthy controls (HC) are essentially the same as those with SCD, in terms of demographics and normal performance on neuropsychological assessment; the main difference between these two groups is the subjective report of cognitive decline.

In 2017, Molinuevo and colleagues of the SCD-I (2017) published a research article providing recommendations for operationalizing SCD and implementing the SCD criteria in research studies as outlined by Jessen et al. (2014). Notably, Jessen and colleagues (2014) recognize that the experience of SCD is not specific to preclinical AD. In fact, SCD may be experienced for a variety of reasons such as normal aging, psychiatric conditions, other neurological conditions, the impact of substance use, or from medications. In recognition of these different causes of SCD, Jessen et al. (2020; 2014) have outlined additional criteria known as SCD-plus, which represents additional features of SCD that signal a higher risk of future development of AD. Such risk factors include but are not limited to concern of experiencing SCD, onset of SCD at age 60 years or older, persistence of SCD over time, and seeking medical attention for these symptoms (Jessen et al., 2020). Despite the creation of the research framework for SCD, advancement in SCD research has not progressed as rapidly as other areas of dementia research. This stalled progression may be attributed to a lack of common terminology and research standards across studies (Rabin et al., 2017).

Being able to differentiate between those with SCD relative to HC is important but inherently difficult, given that individuals with SCD demonstrate normal levels of cognitive functioning as measured on neuropsychological assessment measures. As paper-and-pencil neuropsychological assessment measures are unable to differentiate

between those with SCD and healthy individuals, there is a distinct need for brain-based biomarkers within the SCD group that could signal future risk of developing AD.

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 three different categories of biomarkers, including 1) accumulation of beta-amyloid plaques or associated pathologic state (as measured by amyloid positron emission tomography (PET) imaging, low cerebrospinal fluid (CSF) $A\beta_{42}$, or CSF $A\beta_{40}/A\beta_{42}$ ratio), 2) accumulation of tau tangles or associated pathologic state (measured by tau PET or CSF phosphorylated tau (P-tau), and 3) neuronal injury or neurodegeneration (measured by structural magnetic resonance imaging (MRI), fluorodeoxyglucose (FDG) PET, or CSF total tau (T-tau)) (Jack et al., 2018). Although not included in this research framework of AD, a multitude of different neuroimaging techniques have been used to study disease progression of AD. These methods include other MRI metrics (i.e., functional MRI (fMRI), diffusion-tensor imaging (DTI), etc.), electroencephalography (EEG), magnetoencephalography (MEG), and multi-modal methods incorporating a combination of neuroimaging techniques. Although these techniques are not included in the NIA-AA criteria, they may be especially relevant moving forward because MRI and EEG are widely available and thus ecologically relevant to clinicians and researchers compared to techniques such as PET which are often only available at major medical centres.

Importantly, a main thrust of biomarker research has focused on applying neuroimaging techniques to better understand brain-based changes in individuals with

SCD relative to HC. Therefore, the major objectives of the current systematic review are: to comprehensively present the neuroimaging studies on SCD to date, to synthesize findings across studies and imaging modalities, and to identify steps for future research that will move this field forward. In the context of these aims, the current review sought to address four specific questions based on the current literature: *1) Can differences be detected between individuals with SCD and HC using a variety of neuroimaging methods?; 2) Are the detected differences consistent within each neuroimaging technique?; 3) Are the regions (structural and functional) affected in SCD consistent with those expected in early-stage AD?; and 4) Are there methodological characteristics/differences between the studies that could impact the findings?*

Methods

Eligibility Criteria

English-language, peer-reviewed, human studies, that reported original research with full-text availability were considered eligible for inclusion. Additional inclusion criteria based on the research topic included the necessity of an SCD group (or equivalent condition group). It should be noted that given the variability in nomenclature prior to the recommendations of the International Working Group of the SCD-Initiative (Jessen et al., 2014), the applied definition of SCD included individuals who were identified within an article to have cognitive complaints of any type (e.g. specific to memory, or more general cognitive complaints) in combination with neuropsychological testing sufficient to confirm that participants were functioning within normal limits. Studies were included when participants were aged 55 years and above, to account for the approximate 15-year timeframe to AD conversion that has been proposed (Reisberg & Gauthier, 2008). Studies with a lower minimum age were included if they provided age-stratified data with a distinct 55+ age group. Finally, included studies must have included the use of a neuroimaging method, as well as an observational study design (no intervention studies were included). The review protocol for this study was registered with PROSPERO (CRD 42021235940).

Search Strategy

PubMed and PsycINFO databases were searched using a combination of relevant keywords agreed upon by the authors (see appendix A for search terms in full). Following an initial screen to exclude ineligible articles and duplicates, the suitability of each article was independently adjudicated by two of the authors (two of AP, LO, VS,

JRG). Where there was disagreement between the initial raters, the third author's rating determined whether a given study was included.

Data Analysis and Synthesis

Studies were organized according to the neuroimaging methods employed: MRI (including anatomical MRI, DTI, fMRI and multi-modal MRI), PET, SPECT, EEG, MEG, and multi-modal neuroimaging combining MRI and PET. For each study, the term/construct of interest (e.g., SCD, subjective memory impairment, subjective cognitive complaints, etc.), number of participants, mean sample age, mean sample education, number of males and females, prevalence of APOE $\epsilon 4$, recruitment source, and results relevant to SCD are tabulated.

Study Quality Ratings

Each study was also rated (by one of AP, LO, VS, CMS, JRG) for quality using the Appraisal Tool for Cross Sectional Studies (AXIS) tool (Downes et al., 2016), to evaluate risk of bias, study design quality, and quality of reporting. The AXIS tool is comprised of 20 questions and was not designed to yield a total quality score out of 20 as each item cannot be weighted equally (Downes et al., 2016). We assessed and interpreted items individually to evaluate each study's overall quality (Downes et al., 2016). Although the AXIS tool (Downes et al., 2016) is designed to be used with cross-sectional studies, to maintain consistency we also used this scale when rating the quality of longitudinal studies.

Results

Systematic Review

The search was conducted on February 14, 2021. Initial search results yielded 619 studies, with 395 articles from PubMed and 224 articles from PsycINFO. Following manual removal of duplicates and evident irrelevant entries (e.g., meta-analyses, intervention studies), 505 abstracts were reviewed for inclusion and exclusion criteria. Following this initial review and manual retrieval of known articles that fit inclusion criteria, 296 full text articles were identified for more in-depth review. After the review of each article by two authors, discrepancies between authors were found for 82 articles. The nature of these 82 discrepancies pertained to correlational studies investigating severity of SCD symptoms in relation to neuroimaging, studies lacking a distinct HC group apart from those with SCD, and studies where the outcomes were focused on creation of novel methods. All discrepancies were successfully reconciled by a third reviewer who was not involved in the initial rating of that article. The exclusions primarily resulted from an undefined SCD group (e.g., lack of discrimination between those with SCD and MCI) or lack of reporting on neuroimaging biomarkers (e.g., reporting of cerebrospinal fluid biomarkers). Results of this process are summarized in Figure 1 using the PRISMA Flow Diagram (Moher et al., 2009). A list of the articles excluded from this review is provided in the supplementary materials. A final sample of 62 articles published between 2010 and 2021 were included in the final review.

Table 1.1 shows the number of studies included in each neuroimaging modality. Table 1.2 provides brief descriptions of each neuroimaging technique as well as an overarching summary of the results. Grouped by neuroimaging modality, Tables 1.3-1.11

present more detailed information on each study including details on the participant sample and relevant SCD results for each included article. Table 1.12 shows a count of the significant and non-significant findings separated by neuroimaging modality considering the studies that incorporated multiple neuroimaging modalities.

Anatomical MRI Results

16 of 28 studies (eight from Table 1.3, five from Table 1.6, and three from Table 1.8) found significant differences between those with SCD compared to healthy controls using anatomical MRI neuroimaging analyses. Across studies that examined brain atrophy in SCD, reductions in grey matter volume were commonly found in the amygdala (Hafkemeijer et al., 2013; Kim et al., 2013; Striepens et al., 2010), hippocampus (Archer et al., 2010; Hafkemeijer et al., 2013; Kim et al., 2013; Lindberg et al., 2017; Marcotte et al., 2019; Meiberth et al., 2015; Ryu et al., 2017; Scheef et al., 2012; Striepens et al., 2010), entorhinal cortex (Marcotte et al., 2019; Meiberth et al., 2015; Ryu et al., 2017; Striepens et al., 2010), precuneus (Hafkemeijer et al., 2013; Hong et al., 2015), and various frontal areas (Hafkemeijer et al., 2013; Hong et al., 2015; Kuhn et al., 2019; Toledo et al., 2015). Cortical thickness analyses revealed significantly reduced parenchymal tissue in the left entorhinal cortex (Fan et al., 2018; Marcotte et al., 2019; Meiberth et al., 2015).

DTI Results

In investigations of the microstructural characteristics of white matter, using DTI, 10 of 13 studies (five from Table 1.4, four from Table 1.6, and one from Table 1.8) found widespread differences between SCD and HC groups in various metrics (such as fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), or axial

diffusivity (AxD)). Although loss of white matter integrity was widespread, common regions of decreased FA in those with SCD included the corpus callosum (Hong et al., 2015; X.-Y. Li et al., 2016; Luo et al., 2020; Ohlhauser et al., 2019), superior longitudinal fasciculi (X.-Y. Li et al., 2016; Ohlhauser et al., 2019), hippocampus (Hong et al., 2015; Ohlhauser et al., 2019; Ryu et al., 2017), and uncinate fasciculus (Fan et al., 2018; X.-Y. Li et al., 2016). Increased MD in those with SCD were also widespread across studies, with common regions including the corpus callosum (Hong et al., 2015; X.-Y. Li et al., 2016; Luo et al., 2020; Ohlhauser et al., 2019), superior longitudinal fasciculus (X.-Y. Li et al., 2016; Ohlhauser et al., 2019), hippocampus (Hong et al., 2015; Luo et al., 2020; Ryu et al., 2017; Shao et al., 2019), and cingulum (Hong et al., 2015; X.-Y. Li et al., 2016; Luo et al., 2020).

fMRI Results

When investigating differences between HC and SCD using fMRI techniques, 11 of 15 studies (six from Table 1.5, four from Table 1.6, and one from Table 1.8) found significant results. Considering resting-state fMRI studies, individuals with SCD exhibited differences in functional connectivity in areas associated with the default mode network (DMN) compared to HC (Hafkemeijer et al., 2013; Parker et al., 2020). In studies using task-based fMRI, increased functional activity was found in the precuneus during a divided attention task (Dumas et al., 2013), as well as in the posterior cingulate and thalamus during a working memory task (Rodda et al., 2011). Interestingly, increased functional connectivity was also seen in the precuneus and thalamus in the studies conducted by Hafkemeijer et al. (2013) and Parker et al. (2020) using resting-state fMRI.

PET Results

Ten of 14 studies (four from Table 1.7 and six from Table 1.8) looking at PET yielded significant findings. Six of nine studies that examined beta-amyloid found that individuals with SCD had significantly higher beta-amyloid deposition relative to HC (Jiménez-Bonilla et al., 2016; Perrotin et al., 2017; Risacher et al., 2015; Rowe et al., 2010; Snitz et al., 2015; Voevodskaya et al., 2016). All three studies that investigated tau levels in SCD vs. HC found significantly higher tau values in those with SCD relative to HC (Risacher et al., 2015; Toledo et al., 2015; Voevodskaya et al., 2016). Finally, three of four studies found significant glucose hypometabolism in those with SCD compared to their healthy counterparts (Brugnolo et al., 2014; Scheef et al., 2012; Song et al., 2016).

EEG Results

There were four studies that used various EEG techniques (e.g. EEG rhythms, amplitudes and microstate maps) to examine differences between HC and SCD groups (see Table 1.9). All four studies found significant differences; however, little commonality was found between studies due to the disparate nature of their research questions of interest. See Table 1.8 for a summary of research findings from EEG studies.

MEG Results

Five of the seven studies that used MEG to investigate differences between SCD and HC found significant results. Interestingly, all seven of these studies were comprised of participants from the same recruitment sources, however their sample size increased over time. As each of these studies focused on evaluating unique research questions, the findings from each study yielded unique results which are described in Table 1.10.

SPECT Results

Only one study used SPECT to study differences between HC and those with SCD (see Table 1.11). This study by Niwa et al. (Niwa et al., 2016) found that individuals with SCD showed hypoperfusion in the caudate, thalamus, and bilateral temporal regions compared to HC.

Study Quality Ratings

The AXIS tool was used to assess study quality in cross-sectional and longitudinal studies. The AXIS tool does not yield a total numerical score, as a total score would not meaningfully communicate the level of quality across studies as study quality is assessed over 20 components (Downes et al., 2016). Table 1.13 shows a breakdown of the quality ratings for the 62 included studies for each of the 20 items on the AXIS tool. Information on the quality assessment for each individual study can be found in the supplemental materials.

Discussion

With the goal of synthesizing the existing neuroimaging studies on SCD and identifying steps for future research that will move this field forward, the current study sought to address four specific questions that will be discussed herein.

1. Can differences be detected between individuals with SCD compared to HC using neuroimaging methods?

A major purpose of this review was to synthesize the neuroimaging literature comparing individuals with SCD to HC. Of the 62 included articles, there were significant findings across each imaging modality. In total, 48 articles identified significant differences between SCD and HC groups (with the findings for each neuroimaging modality reviewed below). Notably, significant differences were not detected between HC and individuals with SCD in every study. For instance, some studies found significant differences between SCD and other patient groups, such as MCI or AD, while there were no significant differences between the HC and SCD groups. Further, some studies only found differences between HC and SCD when controlling for other variables such as high PiB, or APOE4, etc. Notably, methodological considerations were very important to the outcomes of each study. Nonetheless, it is clear that significant differences between HC and individuals with SCD have been found using each of the neuroimaging techniques included in the current review. This evidence suggests that there are detectable structural and functional differences in the brains of cognitively normal individuals who report symptoms of SCD compared to those who do not.

2. Are the detected differences consistent within each neuroimaging technique?

Taken together, 26 of 41 studies that incorporated structural neuroimaging analyses and 31 of 41 studies that incorporated functional neuroimaging analyses found significant differences between HCs and those with SCD (Note: The number of incorporated analyses is greater than the total number of studies included in this review as many studies incorporated more than one neuroimaging technique). Overall, there were some common findings within neuroimaging techniques, particularly for the structural imaging approaches. Functional studies that took similar approaches seemed to have consistent results, although the small number of studies and wide variety of analysis techniques employed led to unique findings across studies. Replication of these findings and applying multimodal approaches for the same participants represent important steps for future research.

3. Are the regions affected in SCD consistent with those expected in early-stage AD?

Across structural MRI studies, we saw areas of atrophy in regions that are consistent with early AD, such as the hippocampus (Cherbuin et al., 2015; Saykin et al., 2006) and entorhinal cortex (Dickerson et al., 2001; Jessen et al., 2006; Killany et al., 2000). Although atrophy was detected in brain regions associated with AD, studies also reported structural atrophy beyond the hippocampus and entorhinal cortex, including frontal regions and widespread white matter tracts. It is possible that the additional regions of atrophy identified in these SCD studies relates to the aforementioned variability in etiology of SCD; not all individuals with SCD will convert to AD.

Functional MRI studies of preclinical AD represent a relatively new and emerging area of research. Currently, fMRI biomarkers are not included in the AT(N) biomarker grouping outlined by Jack et al. (Jack et al., 2018). Although there are no guidelines for

AD specific biomarkers such as altered functional connectivity through analysis of fMRI, previous research has noted the usefulness of resting-state fMRI in its ability to distinguish between groups of HC, MCI, and AD (Damoiseaux, 2012; Rombouts et al., 2005; Vemuri et al., 2012). A recent review examining the potential of functional imaging biomarkers for neurodegenerative disorders examined 95 papers focused on functional connectivity in AD and reported that evidence for reduced connectivity in the DMN (including the precuneus, posterior cingulate and prefrontal cortex) in AD has been well established (Hohenfeld et al., 2018). In the current systematic review, the findings for individuals with SCD showed decreases in functional connectivity in the DMN consistent with AD. Remarkably, increases in functional connectivity were also detected, mostly in frontal regions, setting the findings for individuals with SCD apart from those with AD. It is possible that at earlier stages of the continuum of cognitive decline, individuals with SCD are able to compensate for cognitive challenges, as demonstrated by increased functional connectivity (prior to observable structural atrophy). These findings are congruent with the Posterior-Anterior-Shift with Aging (PASA) model, which characterizes a shift in functional activity from posterior regions of the brain to frontal regions of the brain, reflective of executive based compensation (Davis et al., 2007). However, at later stages such as AD, these compensatory mechanisms may no longer subsist. To investigate these possibilities, more research is needed to capture individuals with SCD, MCI and AD using the same methods longitudinally.

Similar to fMRI, EEG and MEG are not included in the current AT(N) biomarker grouping (Jack et al., 2018). Recently, Horvath et al. (Horvath et al., 2018) published a critical review of EEG/ERP biomarkers for AD that included more than 300 citations

focused on a wide variety of methodologies and types of dementia. They concluded that a majority of studies detected alterations in AD, with variations in latency, amplitude, and source localization. They noted that “outcome variability is a serious issue” that may primarily relate to sample size. The current review included four EEG studies focused on individuals with SCD that had a wide variety of methods and sample sizes; therefore, it is not yet possible to compare findings across EEG/ERP studies on SCD to findings in AD. Similarly, with all the MEG studies on SCD coming from one sample and only one published report using SPECT, the outcomes of these studies cannot yet be thoroughly compared to findings from studies focused on AD. Overall, techniques such as EEG and MEG offer complementary information to MRI methods. In future dementia research, it will be important for techniques such as these to be anchored to other methods that we have a greater knowledge base in (such as MRI or PET).

Within the PET literature, it has been well established that markers of amyloid and tau are measurable hallmarks of AD. The current review revealed mixed findings within the SCD PET literature, with some studies revealing greater tau and amyloid values in SCD relative to HC groups, but other studies finding no significant differences. These mixed findings are almost certainly attributable to the methodological differences between studies, discussed next.

4. Are there methodological characteristics/differences between the studies that could impact the findings?

In synthesizing neuroimaging studies on SCD vs. HC, several methodological differences that could lead to discrepant findings became apparent. Below we discuss several methodological differences including differences in definitions and

characterization of SCD (i.e., lack of standardized terms and criteria for SCD), APOE e4 status, participant recruitment location, study design, and inclusion/exclusion criteria which may have led to inconsistent findings and may be exerting a broader impact on the SCD neuroimaging literature.

Definitions and characterization of SCD

Across the studies in this systematic review, there was a lack of consistency in the terminology and criteria characterizing individuals with subjective reports of cognitive decline. Across the 62 studies, eight different terms were used to describe those with subjective cognitive decline or SCD-equivalent classifications. Overall, the term SCD was used in just over half of the included studies (see Table 1.14 for the frequency counts of each of these eight terms). Almost all of the studies that used the term SCD were published after 2014, which may suggest these studies are following the guidance of Jessen and colleagues of the SCD Initiative, an international working group focused on the advancement of knowledge in the realm of SCD. However, some of the studies that used other terms to refer to SCD such as SMI or SCI were also published after 2014, and do not follow the recommendations set out by the SCD-Initiative (Jessen et al., 2014). As a result, some studies may have only included individuals with subjective complaints in the domain of memory, while others may have included individuals with subjective decline in other domains, such as executive function (which SCD is intended to capture).

Studies often lacked detailed descriptions of SCD reports such as severity of cognitive concerns, which cognitive domains are affected, onset and length of SCD, the persistence of SCD symptoms, and corroboration of decline from an informant report. For example, in documenting and determining inclusion criteria for SCD, some studies

only asked one or two questions about whether the person experiences SCD. Meanwhile other studies included completion of questionnaires with specific cut-off scores (e.g., Cognitive Change Index and SCD-Q), however the rationale for the specified cut-off scores is not typically provided. Furthermore, some studies used comprehensive assessments with several cognitive measures to ensure objective cognitive performance of the participants fell within the normal range, while others only administered cognitive screeners or select subtests from different cognitive measures.

APOE e4 Status

In the literature, it is widely accepted that the presence of the APOE e4 allele is associated with an increased risk of developing late-onset AD (Altmann et al., 2014; Corder et al., 1993; Hohman et al., 2018; Liu et al., 2013). However, in this review, there was variability across studies in reporting APOE e4 status in their groups. Out of the 62 included articles, only 20 articles included information on APOE e4 status. These were seen across anatomical MRI, DTI, fMRI, multi-modal MRI, PET, and MRI & PET studies. No articles reported APOE e4 status who utilized EEG, MEG, or SPECT.

Participant Recruitment Location

Most of the articles included in the current review recruited their samples from memory clinics. Of the 62 articles included in this systematic review, only 11 articles investigated differences between HC and individuals with SCD in community samples, rather than memory clinics. In many studies, it appeared that recruitment from a memory clinic was part of the inclusion criteria for their SCD group. The results of the 11 studies that utilized community recruitment (or both clinic and community recruitment) for their SCD groups were mixed. Eight of these 11 studies found significant differences between

HC and individuals with SCD (Chételat, Villemagne, Pike, et al., 2010; Dumas et al., 2013; Marcotte et al., 2019; Perrotin et al., 2017; Shao et al., 2019; Smart et al., 2014; Viviano et al., 2019; Xue et al., 2019). Community recruitment was not utilized in stand-alone PET, MEG, or SPECT studies. Studies that recruited individuals with SCD from memory clinics may yield participant samples with greater levels of concern about their SCD compared to studies that recruited individuals with SCD from the community who were not actively seeking medical care (Molinuevo et al., 2017). Furthermore, as most SCD participants were recruited from memory clinics, most located within larger cities, studies tended to include participants with higher levels of education (e.g. a mean of 16 years of education was not uncommon). It is unclear if this represents a sampling bias or whether individuals with higher levels of education are more likely to report and seek care for their SCD. It is also possible that individuals with SCD and lower levels of education may yield different findings.

Study Design

Nearly all the studies included in this review were cross-sectional. It is possible that different results would be revealed if within-subject longitudinal study designs were utilized. Investigating SCD longitudinally will be important in understanding who is more likely to progress from SCD to AD-related or non-AD related dementia in the future.

There was also a wide range in sample size observed in the literature. In the current systematic review, sample sizes for the SCD groups ranged from 5 to 210, which may also have impacted the statistical power to detect differences from HC groups.

Inclusion/Exclusion Criteria

Many of the studies included in this review listed exclusion criteria regarding their sample such as history of a mental disorder, depression, prescription of psychotropic or psychoactive medications, history of stroke, history of addiction, history of traumatic brain injury that could cause cognitive impairment, or structural brain abnormalities such as white matter hyperintensities or vascular problems. Molinuevo and colleagues (2017) recommended three areas of information that should be included in research on SCD including information on the measurement approach, defined cut-off scores for subjective report measures of SCD, and defined cut-off scores for measures evaluating objective cognition. In the current review, a large majority of studies adequately described the measurement approach such that they included information on the research environment and recruitment source, the names of the measures used, who completed the measures, how the measures were administered, the comparison group (i.e., HC), and the domains of cognition that were assessed. Although a large majority of the studies reviewed provided detailed information on their measurement approach, several of these studies did not provide well-described defined cut-off scores on the subjective and objective report measures. While some studies provided defined cut-off scores for the objective measures, many simply stated that performance by the SCD and HC group were within normal limits.

Limitations

The search strategy in the current review was limited to published studies written in English available on the PubMed and PSYCINFO databases and systematic searches were not conducted outside of these databases nor were unpublished studies solicited. It is possible that studies included in this review are skewed towards those with significant

findings due to the “file drawer problem” (Rosenthal, 1979). Although the current systematic review provides a comprehensive synthesis of neuroimaging findings in individuals with SCD, there were several types of studies that were not included. Specifically, this review sought to detail group differences between individuals with SCD compared to HC. This specific criterion led to the exclusion of studies that did not include a separate SCD group from HC (i.e., control groups were comprised of healthy individuals with or without reports of SCD). This criterion also excluded studies without a distinct control group (i.e., healthy individuals without SCD) but investigated differences between individuals with SCD relative to a cognitively impaired group, such as MCI or AD. Similarly, studies that only investigated relationships or associations between the severity of SCD symptoms and neuroimaging metrics were also excluded if they did not report group differences in neuroimaging metrics between individuals with SCD and HC.

Future Directions

There are several specific recommendations for future research that can be made based on the extant literature. In particular, studies investigating SCD should engage in standardized research practices outlined by the SCD-Initiative, using both the proposed standardized terminology and group classification of individuals with SCD. Further, SCD-plus criteria should be applied to specifically examine individuals with SCD that have an increased risk of future cognitive decline. Notably, the criteria for SCD-plus has been recently updated by Jessen et al. (2020) and recommendations for operationalizing SCD have been well described by Molinuevo et al (2017). Relatedly, the inclusion of more details on the SCD groups being studied will be useful in contextualizing the

findings of each study. Specifically, including data on the nature of the self-experienced cognitive decline such as persistence of symptoms, length of time experiencing SCD, and the cognitive domain(s) affected, will help contextualize results based on participant characteristics. It will also be important for future studies to include information on the diversity of the samples as well as consider whether cultural differences impact the presentation and/or identification of SCD. Collecting information on APOE e4 from participants should be continued in order to investigate the relationship between APOE, SCD, and AD. Additionally, longitudinal study designs should be used to provide valuable information regarding conversion rates and distinguishing between individuals with SCD who progress from subjective to objective cognitive decline based on neuropsychological measures and those who remain cognitively stable. Longitudinal designs would also help determine whether SCD is indicative of early AD or if it is related to other forms of dementia. Furthermore, multiple measurements could help to model the progression of change over time (e.g., Ashford & Schmitt (2001)). Finally, along with consistency, multimodal methods and replications with large sample sizes will be crucial for translating research findings on individuals with SCD into practice.

Conclusions

Biomarker research has focused on the identification of pre-clinical indicators of AD. We have completed the most comprehensive overview of published neuroimaging studies comparing individuals with SCD to HC to date. The current review found that differences can be detected between individuals with SCD and HC across all included neuroimaging modalities, anatomical MRI, DTI, fMRI, PET, EEG, MEG, SPECT, and multi-modal neuroimaging. These findings suggest that neuroimaging is capable of

detecting differences between individuals experiencing both normal and non-normal aging, even during SCD where no objective impairments in cognition have yet taken place. Although significant differences were found between individuals with SCD and HC across the neuroimaging modalities included in this review, results were inconsistent both within and across neuroimaging modalities likely due to methodological variations. Due to the inconsistencies in methodology, the level of generalizability of the findings across studies is unknown. Since SCD may arise from other etiologies apart from preclinical AD, it is important that future research in this area is designed and conducted purposefully, recognizing the impact of methodology on the study outcome. Implementation of recommendations for future neuroimaging studies on SCD are imperative to understanding the earliest changes in the brain related to cognitive decline, including AD.

Table 1.1

Summary of Neuroimaging Modalities Used in the Articles Included (n = 62)

Neuroimaging Modality	Table Number	Number of Studies
MRI		
Anatomical MRI	1.3	11
DTI	1.4	6
fMRI	1.5	9
Multi-Modal MRI	1.6	10
PET	1.7	6
MRI & PET	1.8	8
EEG	1.9	4
MEG	1.10	7
SPECT	1.11	1

DTI: Diffusion Tensor Imaging; EEG: Electroencephalography; fMRI: Functional Magnetic Resonance Imaging; MEG: Magnetoencephalography; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; SPECT: Single-Photon Emission Computed Tomography

Table 1.2*Description of Brain Imaging Modalities and Summary of Results*

Modality	Description	Brain regions with detectable difference in SCD-equivalent group vs. HC
Anatomical MRI	Anatomical MRI detects atrophy or volume loss as well as changes in tissue characteristics through measuring the nuclear magnetic resonance of protons (i.e., hydrogen atoms in water) to create a computerized 3D image of tissues. Common techniques include voxel-based morphometry and cortical thickness analysis.	Hippocampus (Archer et al., 2010; Hafkemeijer et al., 2013; Kim et al., 2013; Perrotin et al., 2015; Scheef et al., 2012; Striepens et al., 2010); amygdala (Kim et al., 2013); dorsal frontal cortex (Kuhn et al., 2019); entorhinal cortex (Fan et al., 2018; Marcotte et al., 2019; Meiberth et al., 2015; Ryu et al., 2017); cholinergic basal forebrain (Scheef et al., 2019); medial frontal cortex (Hafkemeijer et al., 2013); orbitofrontal gyrus (Hong et al., 2015); inferior frontal gyrus (Hong et al., 2015); right calcarine gyrus (Hong et al., 2015); inferior temporal gyrus (Hong et al., 2015); lingual gyrus (Hong et al., 2015); precentral gyrus (Hafkemeijer et al., 2013); precuneus (Hafkemeijer et al., 2013; Hong et al., 2015); cuneus (Hafkemeijer et al., 2013); anterior cingulate cortex (Hafkemeijer et al., 2013); mid-cingulate areas (Hong et al., 2015); temporal-parietal regions (Chételat, Villemagne, Pike, et al., 2010); frontal regions (Toledo et al., 2015)
DTI	DTI uses diffusion weighted imaging to detect directionality and magnitude of diffusion which reflects underlying tissue boundaries as well as the microstructural integrity of white matter inferred from the diffusion properties (i.e., Brownian motion) of water molecules. Common metrics include apparent diffusion coefficient, fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AxD), radial diffusivity (RD).	Corpus callosum (Hong et al., 2015; X.-Y. Li et al., 2016; Ohlhauser et al., 2019); retrosplenial cortices (Selnes et al., 2012); forceps major and minor (Luo et al., 2020; Ohlhauser et al., 2019); corticospinal tract (X.-Y. Li et al., 2016; Luo et al., 2020; Ohlhauser et al., 2019); superior and inferior longitudinal fasciculi (X.-Y. Li et al., 2016; Ohlhauser et al., 2019); uncinate fasciculi (Fan et al., 2018; Yasuno et al., 2015); internal capsule (X.-Y. Li et al., 2016); corona radiata (X.-Y. Li et al., 2016; Ohlhauser et al., 2019); thalamic radiation (X.-Y. Li et al., 2016; Luo et al., 2020; Ohlhauser et al., 2019; Shu et al., 2018); inferior fronto-occipital fasciculus (Luo et al., 2020); left cingulum (Luo et al., 2020; Shao et al., 2019); cerebellum (Ohlhauser et al., 2019); entorhinal white matter (Ryu et al., 2017); hippocampus (Hong et al., 2015; Ohlhauser et al., 2019; Ryu et al., 2017); cingulum (Hong et al., 2015; Yasuno et al., 2015); posterior cingulate (Selnes et al., 2012); middle temporal (Selnes et al., 2012)
fMRI	fMRI measures differences in the magnetic properties of oxygenated vs. deoxygenated hemoglobin as an indirect measure of brain activity (i.e., blood oxygen level dependent (BOLD) signal). Common methods include resting state functional connectivity (FC) analyses as well as task-based analyses (i.e., correlation between the time course of the BOLD signal between brain regions or with a given task).	<i>Increases in SCD relative to HC:</i> frontal medial cortex with retrosplenial cortex (Dillen et al., 2016); left thalamus (Dong et al., 2020); left inferior temporal lobe (Dong et al., 2020); bilateral superior frontal gyrus (Xue et al., 2019); right superior temporal gyrus (Sun et al., 2016); occipital gyrus (Sun et al., 2016); cerebellum posterior lobe (Sun et al., 2016); inferior parietal lobe (Sun et al., 2016); default mode network (Hafkemeijer et al., 2013; Parker et al., 2020); medial visual network (Hafkemeijer et al., 2013). <i>Decreases in SCD relative to HC:</i> left orbital frontal gyrus (Dong et al., 2020); precuneus (Xue et al., 2019); retrosplenial cortex and the dorsal medial prefrontal cortex and anterior cingulate cortex (Yasuno et al., 2015); retrosplenial cortex and precuneus (Viviano et al., 2019); default mode network (Viviano et al., 2019); medial visual network (Hafkemeijer et al., 2013) <i>Task-based fMRI differences:</i> Increased activation in the cingulate cortex, precuneus, and middle frontal gyrus during the N-back task (Dumas et al., 2013); increased activation in the right dorsolateral prefrontal cortex and decreased activation in the right hippocampus during an episodic memory task (Erk et al., 2011); increased activation in the bilateral caudate, posterior cingulate, thalamus, and left medial temporal lobe during a divided attention task (Rodda et al., 2011)
PET	PET can detect changes in cellular metabolism or the presence of particular proteins through measuring the spatial localization of a given radiotracer (neuroanatomical location is determined through combination with CT or MRI). Common radiotracers include 18-fluorodeoxyglucose (FDG), Pittsburgh compound B (PiB) and 18-flutemetamol.	Higher mean global SUVR values (Jiménez-Bonilla et al., 2016); higher SUVR values in the frontal-, parietal-, and lateral-temporal cortex (Snitz et al., 2015); higher SUVR values in the precuneus and posterior cingulate cortex (Voevodskaya et al., 2016); beta-amyloid in various regions (Risacher et al., 2015; Rowe et al., 2010); glucose hypometabolism in periventricular regions (Song et al., 2016); glucose hypometabolism in the right precuneus (Scheef et al., 2012); glucose hypermetabolism in the right medial temporal lobe (Scheef et al., 2012); higher phosphorylated-tau values (Risacher et al., 2015; Toledo et al., 2015; Voevodskaya et al., 2016); higher total-tau values (Voevodskaya et al., 2016)
EEG	EEG measures the electrical activity of neurons (primarily the pyramidal neurons of the cortex). Common metrics include waveforms (i.e., alpha, beta, theta, delta, gamma) as well as task-based components associated with specific information processing (e.g. N170, P300).	Abnormal EEG rhythms in alpha, theta, delta cortical sources (Babiloni et al., 2010); topographical differences in regions associated with attention networks on microstate maps (Smailovic et al., 2019); <i>Task-based EEG:</i> Differences in N170 amplitudes when presented with fear stimuli (Lazarou et al., 2018); Differences in P300 amplitudes during an attentional control task (Smart et al., 2014)

MEG	MEG measures the magnetic field signature of cortical neuronal activity and can detect the temporal sequence of neuronal activation within a neural system as well as the location of activation, when paired with structural imaging techniques (e.g. anatomical MRI).	Lower synchronization values (Bajo et al., 2012); decreased alpha relative power bilaterally in prefrontal areas and in middle and superior temporal lobes (López-Sanz et al., 2016); increased functional connectivity in the anterior network (López-Sanz, Bruña, et al., 2017); decreased functional connectivity in the posterior network (López-Sanz, Bruña, et al., 2017); decreased network clustering in beta and theta bands (López-Sanz, Garcés, et al., 2017); decreased modularity in the alpha band (López-Sanz, Garcés, et al., 2017); increased nodal degree in left postcentral node (López-Sanz, Garcés, et al., 2017); <i>Task-based MEG</i> : Greater activity in parietal, temporal, occipital-temporal, and prefrontal regions during a memory task (Maestu et al., 2011)
SPECT	SPECT can measure regional cerebral blood flow using radioactive tracers and can detect different variables based on the specific tracer used (e.g., can be used to infer specific neurotransmitters)	Caudate, thalamus, and bilateral temporal regions (Niwa et al., 2016)

DTI: Diffusion Tensor Imaging; EEG: Electroencephalography; fMRI: Functional Magnetic Resonance Imaging; MEG: Magnetoencephalography; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; SPECT: Single-Photon Emission Computed Tomography

Table 1.3*Sample Characteristics and Results of Anatomical MRI Studies (n = 11)*

Study	Study Characteristics							Neuroimaging results in context of SCD vs. HC
	SCD Label	N	Mean Age (SD)	Mean Edu. (SD)	Sex: M/F	APOE e4	Recruitment Source	
Archer et al. (2010)	SNCI	28 ¹ ; 4 ²	61.9 (8.7) ¹ ; 70.8 (4.8) ²	14.3 (2.8) ¹ ; 15.8 (2.5) ²	13/15 ¹ ; 2/2 ²	11 ¹ ; 2 ²	Clinic	Compared with HC, those with SNCI (both progressors and non-progressors) did not show significantly greater rates of whole brain atrophy, ventricular change, or hippocampal atrophy. When analyzed separately, SNCI progressors had greater hippocampal atrophy compared to HC, while SNCI non-progressors showed significantly less whole brain atrophy compared to HC.
Kim et al. (2013)	SMI	90	65.8 (8.5)	10.4 (5.1)	28/62	-	Clinic	Those in the SCD group had smaller hippocampal and amygdalar volumes compared to HC.
Kuhn et al. (2019)	SCD	23 ³ ; 27 ⁴	71.7 (6.6) ³ ; 68.3 (8.0) ⁴	12.65 (4.1) ³ ; 12.85 (3.6) ⁴	9/14 ³ ; 16/11 ⁴	6 ³ ; 4 ⁴	Clinic & Community (IMAP+)	Compared to HC, the SCD-clinic group had greater atrophy progression over time in the dorsal frontal cortex. No significant differences were found between the SCD-community group and HC in atrophy progression.
Lauriola et al. (2017)	SCD	32	64.8 (6.3)	11.6 (4.2)	11/21	-	Community	No significant differences between SCD and HC groups.
Lindberg et al. (2017)	SCD	183	70.5 (5.7)	-	83/100	73	Clinic (BioFINDER)	No significant differences in brain volume were found between SCD and HC groups.
Marcotte et al. (2019)	SCD	66	71 (6.4)	-	29/37	-	Clinic & Community	Only the left entorhinal cortex showed greater cortical thickness and volume in HC relative to the SCD group, but effect sizes were limited. No other significant differences were found between SCD and HC.
Meiberth et al. (2015)	SMI	41	68.9 (7.2)	14.8 (3.5)	29/12	-	Clinic	Those with SMI showed significant decreases in the left entorhinal cortex compared with HC.
Perrotin et al. (2015)	SCD	17	69.1 (8.5)	12.8 (3.9)	12/5	-	Clinic	Compared with HC, those with SCD had significant TIV-normalized volume decreases in global hippocampal volume. Those with SCD also showed significantly greater hippocampal atrophy in the CA1 subfield as well as slight involvement in the subiculum.
Platero et al. (2019)	SCD	87	71.7 (5.1)	12.9 (5.5)	19/68	-	Clinic	No significant differences between SCD and HC groups.
Scheef et al. (2019)	SCD	24	67 (6.1)	15.0 (3.6)	18/6	7	Clinic	Relative to HC, those with group showed a significant volume reduction in the cholinergic basal forebrain, with greatest effects seen in the medial septal nucleus (Ch1), the vertical nucleus of the diagonal band of Broca (Ch2), and the cholinergic component of the nucleus basalis Meynert (Ch4).
Striepens et al. (2010)	SMI	21	66.3 (6.2)	14.6 (3.6)	15/6	5 (e4+); 16 (e4-)	Clinic	Compared with HC, those with SCD showed significant volume reductions in the right amygdala, bilateral hippocampus, and bilateral entorhinal cortex. No significant differences were found in total brain volume between HC and SCD groups.

Bold text denotes statistical significance found between SCD and HC groups; ¹: SCD non-progressors; ²: SCD progressors; ³: Recruited from the community; ⁴: Recruited from a clinic; - : Not Reported; APOE e4: Apolipoprotein E-4; CA1: Cornu Ammonis 1; Edu: Education; F: Female; HC: Healthy Controls; M: Male; MRI: Magnetic Resonance Imaging; SCD: Subjective Cognitive Decline; SD: Standard Deviation; SNCI: Symptoms of memory loss but No objective Cognitive Impairment; SMI: Subjective Memory Impairment; TIV: Total Intracranial Volume

Table 1.4*Characteristics of DTI Studies (n = 6)*

Study	Study Characteristics							Neuroimaging results in context of SCD vs. HC
	SCD Label	N	Mean Age (SD)	Mean Edu. (SD)	Sex: M/F	APOE e4	Recruitment Source	
X.-Y. Li et al. (2016)	SCD	27	65.3 (8.0)	11.4 (3.9)	9/18	-	Clinic	Those with SCD showed decreased FA and increased MD in widespread regions, including but not limited to the corpus callosum, corticospinal tracts, superior and inferior longitudinal fasciculi. Those with SCD also showed increased AxD in areas including but not limited to the internal capsule, corona radiata, and posterior thalamic radiation.
Luo et al. (2020)	SCD	38	66.42 (6.69)	12.24 (3.412)	17/21	-	Clinic	Compared to HC, those with SCD had significantly decreased FA values in the forceps major and forceps minor, and increased MD in the bilateral anterior thalamic radiation, forceps minor, left corticospinal tract, and inferior fronto-occipital fasciculus, and left cingulum (cingulate gyrus and hippocampus).
Ohlhauser et al. (2019)	SCD	30	72.9 (4.8)	16.4 (2.6)	10/20	10	Clinic (ADNI)	Compared to HC, those with SCD showed significantly decreased FA values in the bilateral anterior thalamic radiations, cerebellum, corpus callosum, corticospinal tracts, forceps major and minor, superior and inferior longitudinal fasciculi, and hippocampus. Further, those with SCD showed significantly increased MD values in the bilateral corpus callosum, corticospinal tracts, superior corona radiata, and superior and inferior longitudinal fasciculi relative to HC.
Shao et al. (2019)	SMI	20	62.4 (5.3)	10.5 (2.9)	10:10	-	Community (BABRI)	Individuals with SCD had lower white matter integrity (e.g., lower FA and higher MD) compared to HC in the left cingulum of the hippocampus.
Shu et al. (2018)	SCD	36	63.5 (8.7)	11.5 (4.6)	15/21	11 ¹	Clinic	Those with SCD demonstrated lower global and local efficiency compared to HC, especially linked to bilateral prefrontal regions and the left thalamus.
Wang et al. (2016)	SCD	21	62.9 (9.2)	10.7 (4.1)	6/15	-	Clinic	No significant differences were found between SCD and HC groups. Though not significant, those with SCD fell between HC and those with aMCI on most metrics.

Bold text denotes statistical significance found between SCD and HC groups; ¹: Only 22 participants (of 36) had information on APOE status; - : Not Reported

aMCI: Amnesic Mild Cognitive Impairment; APOE e4: Apolipoprotein E-4; AxD: Axial Diffusivity; BABRI: Beijing Aging Brain Rejuvenation Initiative; Edu: Education; F: Female; FA: Fractional Anisotropy; HC: Healthy Controls; M: Male; MD: Mean Diffusivity; SCD: Subjective Cognitive Decline; SD: Standard Deviation; SMI: Subjective Memory Impairment

Table 1.5*Characteristics of fMRI Studies (n =9)*

Study	Study Characteristics							Results
	SCD Label	N	Mean Age (SD)	Mean Edu. (SD)	Sex: M/F	APOE e4	Recruitment Source	
Contreras et al. (2019)	SCD	27 ¹ ; 16 ²	70.11 (9.92) ¹ ; 73.38 (7.95) ²	17.11 (2.36) ¹ ; 17.37 (1.93) ²	9/18 ¹ ; 8/8 ²	-	Clinic	No significant FC pattern differences were found in SCD compared to HC.
Dillen et al. (2016)	SCI	27	65.7 (7.9)	13.6 (4.2)	12/15	8	Clinic	Compared with HC, those with SCD showed greater levels of FC in the frontal medial cortex using the retrosplenial cortex as the seed region. No differences in FC were seen between SCD and HC groups when using the posterior cingulate cortex as the seed region.
Dillen et al. (2017)	SCD	28	65.8 (7.8)	13.6 (4.2)	13/15	8	Clinic	No significant differences were found between HC and SCD group in frontoparietal coupling.
Dong et al. (2020)	SCD	63	65.8 (5.0)	11.9 (2.8)	43/20	18	Clinic	Compared with HC, those with SCD showed significant differences in temporal flexibility and spatiotemporal diversity. Specifically, those with SCD showed decreases in the left orbital frontal gyrus and increases multiple areas including but not limited to the left thalamus and left inferior temporal lobe.
Dumas et al. (2013)	CC	12	57.1 (2.3)	16.0 (2.4)	0/12	-	Community	During a visual-verbal version of the N-back task, those with SCD showed increased activation in the cingulate gyrus, precuneus, and middle frontal gyrus relative to HC. Compared to HC, those with SCD would also recruit additional areas part of the working memory network on the N-back task when it increased in difficulty.
Erk et al. (2011)	SMI	19	68.4 (5.7)	14.5 (3.5)	14/5	-	Clinic	Compared with HC, those with SCD showed reduced activation in the right hippocampus and increased activation in the right dorsolateral prefrontal cortex during a task of episodic memory recall. No differences in activation were found between SCD and HC groups on a task of working memory.
Rodda et al. (2011)	SCI	11	64.0 (59.0-66.0) ³	11.0 (10.0-13.0) ³	6/5	-	Clinic	Compared with HC, those with SCD showed increased functional activation in the bilateral caudate, posterior cingulate, thalamus, and left medial temporal lobe during a divided attention task.
van Rooden et al. (2016)	SCI	18	66.5 (11.2)	3.5 ⁴ (3) ⁵	13/5	-	Clinic	No significant differences were found between HC and SCD groups in cortical phase shift.
Xue et al. (2019)	SCD	10	63.10 (8.77)	13.85 (1.83)	4/10	-	Clinic & Community	Compared with HC, those with SCD showed increased FC in the bilateral superior frontal gyrus and decreased FC in the precuneus.

Bold text denotes statistical significance found between SCD and HC groups; ¹: Recruited from the Indiana Alzheimer's Disease Center; ²: Recruited from the Indiana Memory and Aging Study; ³: Range; ⁴: Median; ⁵: Verhage Scale; - : Not Reported; APOE e4: Apolipoprotein E-4; CC: Cognitive Complaints; Edu: Education; F: Female; FC: Functional Connectivity; HC: Healthy Controls; M: Male; SCD: Subjective Cognitive Decline; SCI: Subjective Cognitive Impairment; SD: Standard Deviation; SMI: Subjective Memory Impairment

Table 1.6*Characteristics of Multi-Modal MRI Studies (n = 10)*

Study	Study Characteristics								Results
	Imaging Modality	SCD Label	N	Mean Age (SD)	Mean Edu. (SD)	Sex: M/F	APOE e4	Recruitment Source	
Fan et al. (2018)	MRI DTI	SCD	43	66.1 (7.0)	13.6 (2.9)	21/22	-	Clinic	Compared to HC, SCD had decreased cortical thickness in medial temporal cortical areas including the bilateral perirhinal cortex, bilateral parahippocampal cortex, and left entorhinal cortex. Further, those with SCD had significantly decreased FA in the right and left uncinate fasciculi compared to HC.
Hafkemeijer et al. (2013)	MRI fMRI	SMC	25	71.4 (9.2)	15.3 (2.5)	14/11	-	Clinic	Compared with HC, those SCD showed atrophy in various areas including the hippocampus, medial prefrontal cortex, precentral gyrus, precuneus, cuneus, and the anterior cingulate cortex. Further, those with SCD showed increased functional connectivity in areas of the default mode network and medial visual network.
Hong et al. (2015)	MRI DTI	SMI	28	70.9 (6.23)	9.2 (5.7)	7/19 ¹	-	Clinic	Compared with HC, those with SCD showed decreased FA and increased MD the hippocampal body, anterior cingulum, posterior cingulum, anterior corpus callosum, and posterior corpus callosum. Further, those with SCD showed gray matter atrophy in the left orbito-frontal gyrus, inferior frontal gyrus, right calcarine gyrus, precuneus, lingual gyrus, inferior temporal gyrus, and both mid-cingulate areas, compared with HC.
Kiuchi et al. (2014)	MRI DTI	SCI	28	70.5 (7.3)	12.36 (2.23)	9/19	-	Clinic	No significant differences between HC and SCD groups.
Parker et al. (2020)	MRI fMRI	SCD	23	72.9 (5.4)	16.7 (3.0)	11/12	7	Clinic (ADNI)	No significant structural differences in grey matter density between SCD and HC as assessed by VBM. Individuals with SCD showed increased and decreased functional connectivity in various regions relative to HC in the default mode network.
Ryu et al. (2017)	MRI DTI	SMI	18	69.89 (6.26)	10.08 (5.59)	5/13	5	Clinic	Compared with HC, those with SCD showed significantly decreased volume in the entorhinal cortex (but not in the hippocampus). Further, those with SMI showed lower FA and higher MD in entorhinal white matter and in the hippocampal body relative to HC.
Scarapicchia et al. (2019)	MRI fMRI	SCD	19	72.2 (5.2)	16.3 (3.16)	9/10	-	Clinic (ADNI)	No significant differences between individual with SCD and HC in WMH burden or in whole brain resting state BOLD variability in white or grey matter.
Selnes et al. (2012)	MRI DTI	SCI	16	59.2 (45-71) ²	-	5/11	-	Clinic	Compared with HC, those with SCD had significantly higher MD and radial diffusivity values in the middle temporal, posterior cingulate, and retrosplenial cortices. No significant differences were found between HC and SCD groups for cortical thickness.
Sun et al. (2016)	MRI fMRI	SCD	25	65.52 (6.12)	10.64 (4.10)	14/11	-	Clinic	Compared with HC, those with SCD showed increased ALFF values in the right superior temporal gyrus, inferior and middle occipital gyrus, cerebellum posterior lobe, and bilateral inferior parietal lobe. Further, no significant differences in grey matter volume were found between SCD and HC groups.
Viviano et al. (2019)	MRI fMRI DTI	SCD	35	68.51 (7.66)	-	13/22	-	Clinic & Community	Relative to HC, those with SCD showed lower FC in posterior memory systems, whose structures largely overlap with the default mode network. The SCD group also demonstrated lower FC between the retrosplenial cortex and the precuneus, relative to HC. Further, SCD and HC groups did not differ on DTI metrics.

Bold text denotes statistical significance found between SCD and HC groups; ¹: This study reported 28 participants in the SMI group, but only 19/26 of the participants being female; ²: Range; - : Not Reported; ALFF: Amplitude of Low-Frequency Fluctuations; APOE e4: Apolipoprotein E-4; BOLD: Blood-Oxygen-Level-Dependent; Edu: Education; F: Female; FA: Fractional Anisotropy; FC: Functional Connectivity; HC: Healthy Controls; M: Male; MD: Mean Diffusivity; SCD: Subjective Cognitive Decline; SCI: Subjective Cognitive Impairment; SD: Standard Deviation; SMC: Subjective Memory Complaints; SMI: Subjective Memory Impairment

Table 1.7*Characteristics of PET Studies (n = 6)*

Study	Study Characteristics							Results
	SCD Label	N	Mean Age (SD)	Mean Edu. (SD)	Sex: M/F	APOE e4	Recruitment Source	
Brugnolo et al. (2014)	SMC	32	70.47 (7.68)	10.06 (4.27)	15/17	-	Clinic	No significant differences between HC and SCD groups in glucose metabolism.
Jiménez-Bonilla et al. (2016)	SMC	8	65 (11) ¹	-	-	-	Clinic	Compared to HC, those with SCD showed significantly higher mean global SUVR.
Rodda et al. (2010)	SCI	5	64.2 (3.53)	-	-	-	Clinic	No significant differences were found between HC and SCD groups in PiB uptake ratio.
Snitz et al. (2015)	SCD	14	68.1 (4.0)	17.6 (2.07)	5/9	4	Clinic	Compared to HC, those with SCD showed significantly higher SUVR values in the frontal, parietal, and lateral temporal cortex.
Song et al. (2016)	SMI	68	69.94 (6.44)	11.72 (3.65)	25/43	-	Clinic	Compared to HC, those with SCD showed glucose hypometabolism in periventricular regions.
Voevodskaya et al. (2016)	SCD	49	70.7 (5.7)	12.1 (3.8)	22/27	35	Clinic	Relative to HC (both with and without abnormal levels of CSF Aβ42 levels), those with SCD possessed significant higher tau values. Relative to HC (without abnormal CSF Aβ42 levels), those with SCD possessed significantly higher SUVR of the precuneus and posterior cingulate cortex using [¹⁸ F]-flutemetamol PET.

Bold text denotes statistical significance found between SCD and HC groups; ¹: Value for the entire study (not just the SCD group); - : Not Reported; APOE e4: Apolipoprotein E-4; CSF: Cerebrospinal Fluid; Edu: Education; HC: Healthy Controls; F: Female; M: Male; PET: Positron Emission Tomography; PiB: Pittsburgh Compound B; SCD: Subjective Cognitive Decline; SCI: Subjective Cognitive Impairment; SD: Standard Deviation; SMC: Subjective Memory Complaints; SUVR: Standardized Uptake Value Ratio;

Table 1.8*Characteristics of Multi-Modal MRI & PET Studies (n = 8)*

Study	Study Characteristics								Results
	Imaging Modality	SCD Label	N	Mean Age (SD)	Mean Edu. (SD)	Sex: M/F	APOE e4	Recruitment Source	
Chételat, Villemagne, Pike, et al. (2010)	MRI PET	SCI	30 ¹ ; 19 ²	72.1 (7.1) ¹ ; 76.7 (6.5) ²	13.7 (3.5) ¹ ; 12.7 (3.4) ²	17/13 ¹ ; 7/12 ²	1 ¹ ; 12 ²	Community (AIBL)	In those with SCD, there was increased atrophy in temporoparietal regions and in the anterior and posterior cingulate cortex in the high ¹¹ C-PiB group compared to the low ¹¹ C-PiB group. They also found significant differences in grey matter atrophy in the temporal lobes of SCD individuals with high beta-amyloid deposition compared to HC with high beta-amyloid
Chételat, Villemagne, Bourgeat, et al. (2010)	MRI PET	SCI	49	73.9 (7.2)	13.3 (3.5)	24/25	-	Community (AIBL)	No significant differences were found in global neocortical PiB-SUVR or grey matter volume in SCI compared with HC.
Perrotin et al. (2017)	MRI PET	SCD	35 ³ ; 28 ⁴	70.8 (7.5) ³ ; 67.6 (7.7) ⁴	12.6 (4.2) ³ ; 13.3 (3.4) ⁴	14/21 ³ ; 17/11 ⁴	8 ³ ; 4 ⁴	Clinic & Community	Both SCD groups had higher beta-amyloid deposition compared to HC but did not show significant differences between each other. No differences in brain structure were found between HC and SCD from the community. No reported results on brain structure between HC and SCD from clinic sample.
Risacher et al. (2015)	MRI PET	SMC on	71 ⁵ ; 33 ⁶	72.5 (5.7) ⁵ ; 70.3 (5.2) ⁶	16.6 (2.7) ⁵ ; 17.2 (2.0) ⁶	31/40 ⁵ ; 12/21 ⁶	0 ⁵ ; 33 ⁶	Clinic (ADNI)	No significant differences in glucose metabolism or medial temporal lobe atrophy were found in SCD (e4+ or e4-) compared to HC. However, those with SCD e4+ had greater amyloid deposition across multiple brain regions and higher p-tau levels compared to HC (both with e4+ and e4-).
Rowe et al. (2010)	MRI PET	SCD	96	71.2 (7.4)	-	47/49	36	Clinic	At the group level, no significant differences were found between SCD and HC in hippocampal volumes and beta-amyloid burden. However, those with SCD e4+ showed significantly higher beta-amyloid burden compared to those with SCD e4- and HC (both with e4+ and e4-). No differences in hippocampal volumes were found when groups were stratified by APOE e4 carrier status.
Scheef et al. (2012)	MRI PET	SMI	31 ⁷ ; 27 ⁸	67.6 (6.2) ⁷ ; 67.4 (6.5) ⁸	14.4 (3.4) ⁷ ; 14.7 (2.9) ⁸	22/9 ⁷ ; 19/8 ⁸	9 ⁷ ; 9 ⁸	Clinic	SCD group showed hypometabolism in the right precuneus and hypermetabolism in the right medial temporal lobe as well as increased grey matter atrophy in the right hippocampus compared to HC.
Toledo et al. (2015)	MRI PET	SMC	71 ⁹ ; 65 ¹⁰	71.6 (5.2) ⁹ ; 71.3 (5.2) ¹⁰	- ⁹ ; - ¹⁰	25/46 ⁹ ; 22/43 ¹⁰	24 ⁹ ; 21 ¹⁰	Clinic (ADNI)	Results found those with SCD had greater levels of brain atrophy with a frontal pattern of atrophy compared to HC. Those with SCD had higher levels of phosphorylated tau ₁₈₁ compared to HC
Yasuno et al. (2015)	DTI fMRI PET	SCI	23	69.6 (8.0)	13.7 (2.1)	13/10	-	Clinic	Compared with HC, those with SCD had decreased functional connectivity between the retrosplenial cortex and the dorsal medial prefrontal cortex and anterior cingulate cortex. SCD subjects also had lower fractional anisotropy in the superior longitudinal fasciculus and higher FA in the left cingulum relative to HC. No significant differences in global cortical mean PiB binding potential were found between HC vs. SCD.

Bold text denotes statistical significance found between SCD and HC groups; ¹: Low-PiB subjective cognitive impairment group; ²: High-PiB subjective cognitive impairment group; ³: SCD recruited from community; ⁴: SCD recruited from clinic; ⁵: APOE e4- group; ⁶: APOE e4+ group; ⁷: at baseline; ⁸: at follow-up; ⁹: 5th percentile; ¹⁰: 10th percentile; - : Not Reported; APOE e4: Apolipoprotein E-4; Edu: Education; F: Female; FA: Fractional Anisotropy; HC: Healthy Controls; M: Male; MD: Mean Diffusivity; PiB: Pittsburgh Compound B; SCD: Subjective Cognitive Decline; SCI: Subjective Cognitive Impairment; SD: Standard Deviation; SMC: Subjective Memory Complaints; SMCon: Subjective Memory Concerns; SMI: Subjective Memory Impairment; SUVr: Standardized Uptake Value Ratio

Table 1.9*Characteristics of EEG Studies (n = 4)*

Study	Study Characteristics							Results
	SCD Label	N	Mean Age (SD)	Mean Edu. (SD)	Sex: M/F	APOE e4	Recruitment Source	
Babiloni et al. (2010)	SMC	53	69 (0.99 ¹)	12 (0.49 ¹)	30/23	-	Clinic (DESCRIPA)	Compared to HC, those with SCD showed abnormal EEG rhythms in alpha, delta, and theta cortical sources.
Lazarou et al. (2018)	SMI	14	69.9 (6.83)	11.7 (2.58)	7/7	-	Clinic	Compared to HC, those with SCD showed significantly larger N170 amplitudes when viewing facial stimuli of “fear,” no difference in N170 amplitude was seen between these groups when viewing facial stimuli of “anger.” Further, no significant differences between HC and SCD were seen in N170 latencies when viewing facial stimuli of either “anger” or “fear.”
Smailovic et al. (2019)	SCD	210	60.0 (6.1)	13.3 (3.6)	79/131	-	Clinic	Topographical between group comparison of microstate maps revealed significant differences between SCD and HC (in regions associated with attention networks).
Smart et al. (2014)	SCD	17	69.47 (2.38)	16.53 (2.55)	5/12	-	Community	Compared to HC, those with SCD had weaker P300 amplitudes for rare NoGo and frequent Go stimuli during an attention control task.

Bold text denotes statistical significance found between SCD and HC groups; ¹: Standard Error; ²: Median; - : Not Reported; APOE e4:

Apolipoprotein E-4; Edu: Education; EEG: Electroencephalography; F: Female; HC: Healthy Controls; M: Male; SCD: Subjective Cognitive Decline; SD: Standard Deviation; SMC: Subjective Memory Complaints; SMI: Subjective Memory Impairment

Table 1.10*Characteristics of MEG Studies (n = 7)*

Study	Study Characteristics							Results
	SCD Label	N	Mean Age (SD)	Mean Edu. (SD)	Sex: M/F	APOE e4	Recruitment Source	
Bajo et al. (2012)	SCD	12	72.5 (6)	8.3 (-)	3/9	-	Clinic	Compared with HC, those with SCD had a similar pattern of connectivity, but a lower synchronization value.
López-Sanz et al. (2016)	SCD	41	71.6 (4.5)	14.2 (5.8)	9/32	-	Clinic	Compared with HC, those with SCD showed decreased alpha relative power bilaterally in prefrontal areas and in the middle and superior temporal lobes. No significant differences in hippocampal volumes or alpha peak frequency were found between those with SCD and HC.
López-Sanz, Bruña, et al. (2017)	SCD	41	71.6 (4.5)	-	-	-	Clinic	Compared to HC, those with SCD showed increased FC in the anterior network and decreased FC in the posterior network.
López-Sanz, Garcés, et al. (2017)	SCD	55	71 (5.0)	3.95 (1)	13/42	-	Clinic	Compared to HC, those with SCD showed a decrease in global network clustering in beta and theta bands as well as a decreased in modularity in the alpha band. Further, in the left postcentral node, those with SCD showed a nodal degree increase relative to HC. No differences were found between those with SCD and HC in small-world topology or in hippocampal volumes.
Maestu et al. (2011)	SCD	12	72.5 (6)	8.3 (-)	3/9	-	Clinic	Compared to HC, those with SCD showed greater activity during a memory task in the parietal, temporal, occipital-temporal and prefrontal regions.
Serrano et al. (2020)	SCD	49	72.0 (4.4)	14.1 (5.5)	11/38	-	Clinic	No significant differences were found between HC and SCD groups.
Shumbayawonda et al. (2020)	SCD	33	71.88 (4.29)	-	12/21	-	Clinic	Compared to HC, those with SCD showed greater mean global complexity in MEG signal source space, although this finding was not statistically significant.

Bold text denotes statistical significance found between SCD and HC groups; - : Not reported; APOE e4: Apolipoprotein E-4; Edu: Education; F: Female; FC: Functional Connectivity; HC: Healthy Controls; M: Male; MEG: Magnetoencephalography; SCD: Subjective Cognitive Decline; SD: Standard Deviation

Table 1.11*Characteristics of SPECT Studies (n = 1)*

Study	Study Characteristics							Results
	SCD Label	N	Mean Age (SD)	Mean Edu. (SD)	Sex: M/F	APOE e4	Recruitment Source	
Niwa et al. (2016)	SCC	32	68.4 (59-75 ¹)	12.7 (9-16 ¹)	17/15	-	Clinic	Compared with HC, those with SCD showed hypoperfusion in the caudate, thalamus, and bilateral temporal regions.

Bold text denotes statistical significance found between SCD and HC groups; ¹: Range; - : Not Reported; APOE e4: Apolipoprotein E-4; Edu: Education; F: Female; HC: Healthy Controls; M: Male; SCC: Subjective Cognitive Concerns; SCD: Subjective Cognitive Decline; SD: Standard Deviation; SPECT: Single-Photon Emission Computed Tomography

Table 1.12*Breakdown of significant and non-significant findings across neuroimaging modalities*

Neuroimaging Type	Total number of incorporated analyses	Number of Sig. Findings	Number of Non-Sig. Findings
Anatomical MRI	28	16	12
DTI	13	10	3
fMRI	15	11	4
PET	14	10	4
EEG	4	4	0
MEG	7	5	2
SPECT	1	1	0

Note: The total number of analyses exceeds the number of studies included in this review because this table accounts for studies that incorporated multiple neuroimaging analyses.

DTI: Diffusion Tensor Imaging; EEG: Electroencephalography; fMRI: Functional Magnetic Resonance Imaging; MEG: Magnetoencephalography; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; SPECT: Single-Photon Emission Computed Tomography

Table 1.13*Breakdown of ratings for each item on the AXIS tool across the 62 included studies*

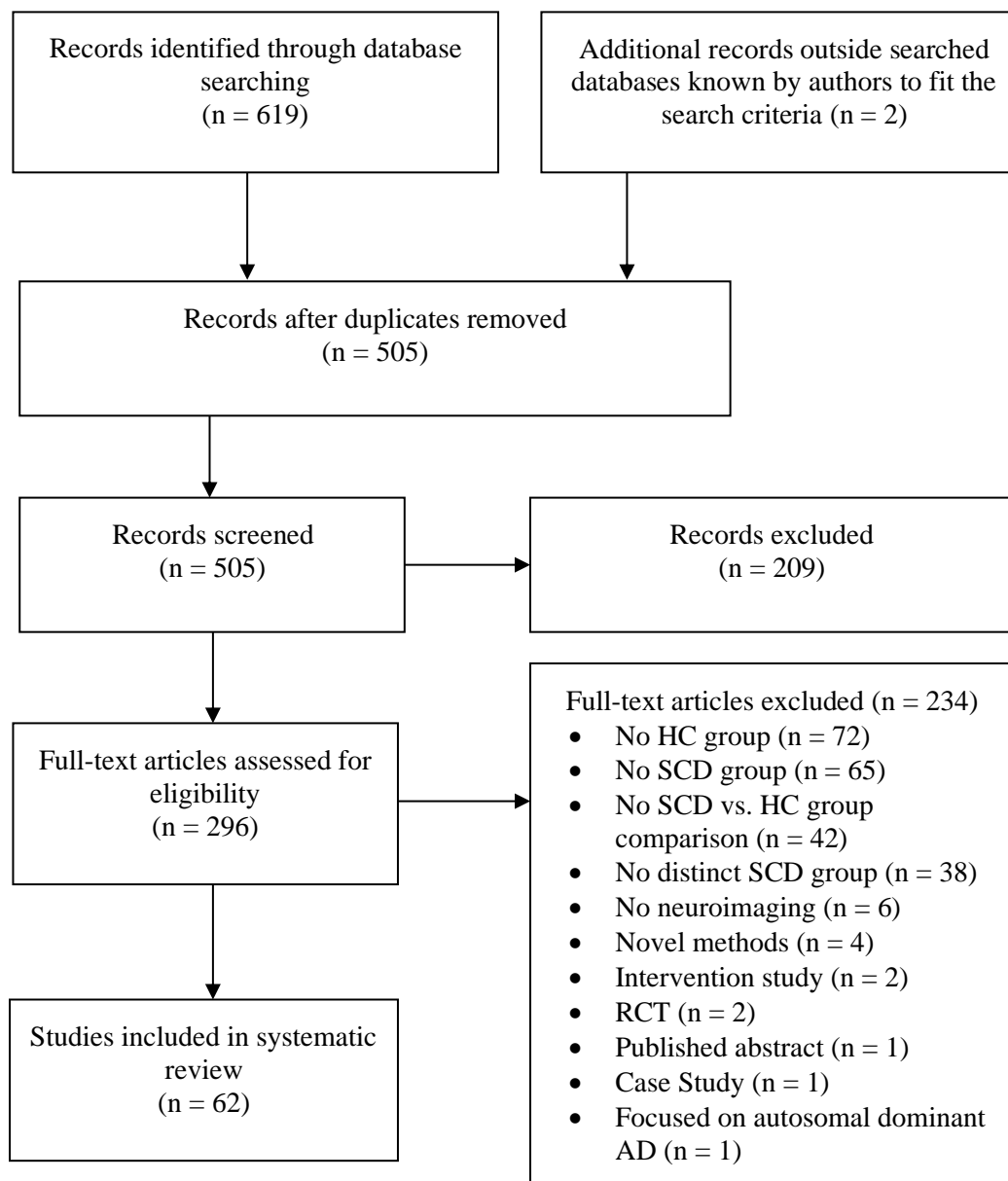
AXIS Tool Items:	Y	N	U	N/A
1. Were the aims/objectives of the study clear?	62	0	0	0
2. Was the study design appropriate for the stated aim(s)?	62	0	0	0
3. Was the sample size justified?	26	36	0	0
4. Was the target/reference population clearly defined? (Is it clear who the research was about?)	60	1	0	1
5. Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?	49	8	4	1
6. Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?	52	6	4	0
7. Were measures undertaken to address and categorize non-responders?	3	13	10	36
8. Were the risk factor and outcome variables measured appropriate to the aims of the study?	60	0	1	1
9. Were the risk factor and outcome variables measured correctly using instruments/measurements that have been trialed, piloted, or published previously?	59	2	1	0
10. Is it clear what was used to determine statistical significance and/or precision estimates? (E.g., p values, CIs)	61	1	0	0
11. Were the methods (including statistical methods) sufficiently described to enable them to be repeated?	57	4	1	0
12. Were the basic data adequately described?	58	4	0	0
13. Does the response rate raise concerns about non-response bias?*	2	21	13	26
14. If appropriate, was information about non-responders described?	2	19	4	37
15. Were the results internally consistent?	54	4	2	2
16. Were the results for the analyses described in the methods presented?	61	0	1	0
17. Were the authors discussions and conclusions justified by the results?	60	1	1	0
18. Were the limitations of the study discussed?	50	12	0	0
19. Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?*	8	52	2	0
20. Was ethical approval or consent of participants attained?	61	0	1	0

AXIS tool: Appraisal Tool for Cross-Sectional Studies; Y: Yes; N: No; U: Unclear; N/A: Not applicable; *: Item is reverse scored (i.e., N rating is positive)

Table 1.14*Frequency counts of each SCD-Equivalent Classifications*

SCD-Equivalent Classification	Abbreviation	Frequency
Subjective Cognitive Decline	SCD	34
Subjective Memory Impairment	SMI	10
Subjective Cognitive Impairment	SCI	9
Subjective Memory Complaints	SMC	5
Cognitive Complaints	CC	1
Subjective Cognitive Concerns	SCC	1
Subjective Memory Concerns	SMCon	1
Symptoms of memory loss but No Cognitive Impairment	SNCI	1
	Total	62

Figure 1.1 PRISMA flow diagram for the current systematic review



**Study 2: Functional Connectivity Alterations in the DMN and FPN in Women with
SCD**

Parker, A. F., Szoek, C., Kwan, H., Henri-Bhargava, A. & Gawryluk, J. R.

Abstract

Background: Alzheimer's disease (AD) is an incurable neurodegenerative disorder, which disproportionately affects women. Along the continuum of dementia, those who experience subjective cognitive decline (SCD) are thought to be the earliest group at risk for the future development of AD.

Objective: The current study investigated differences in functional connectivity between healthy older women and older women with SCD in multiple resting-state functional connectivity networks. This study also examined whether additional differences existed between women with and without SCD, in various demographic variables, lifestyle factors, and medical comorbidities.

Methods: 3T high-resolution resting-state functional MRI (fMRI) scans were retrieved for 25 healthy older women and 25 older women who self-report SCD from the Women's Healthy Ageing Program (WHAP). A seed-based approach was executed in FMRIB's Software Library (FSL) to examine significant differences in functional connectivity within the default mode network (DMN), frontoparietal network (FPN), and salience network (SN) between groups. Group comparisons were conducted between women with SCD and healthy women on various demographic variables, lifestyle factors, and medical comorbidities.

Results: fMRI results revealed significantly greater functional connectivity in the DMN in women with SCD relative to healthy women in regions the right inferior frontal gyrus (pars triangularis), frontal pole, insular cortex, and frontal orbital cortex. fMRI results also revealed significantly greater functional connectivity in the FPN in women with SCD in the left amygdala, right frontal pole, lingual gyrus, lateral occipital cortex

(superior), parahippocampal gyrus, precuneus cortex, and bilateral cingulate gyrus (posterior), lateral occipital gyrus (inferior), and thalamus. No significant differences in functional connectivity were seen between groups in the SN. Further, no significant differences were seen between demographic variables, lifestyle factors, and medical comorbidities between groups.

Conclusion: Findings revealed significant increases in functional connectivity in the DMN and FPN in older women with SCD compared to healthy older women. These increases were seen between groups that differed solely on the self-report of SCD, with no significant differences were detected between groups on comparisons of various demographic variables, lifestyle factors, and medical comorbidities.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that affects 43.1 million older adults worldwide (Nichols et al., 2019). The socioeconomic burden of caring for individuals with AD and related dementias is a costly endeavor and given that the prevalence of AD is expected to triple by 2050, it is crucial that methods for earlier detection and intervention to be developed to better manage care for these individuals (Alzheimer's Association, 2023).

One potential avenue for research on pre-clinical AD involves a focus on subjective cognitive decline (SCD). People with SCD self-report declines in their cognition despite normal performance on traditional neuropsychological assessment measures and may be earliest in the continuum of dementia (Jessen et al., 2014). However, it is important to note that not all individuals who experience symptoms of SCD will go on to develop AD or other dementias. Different trajectories have been suggested for individuals with SCD, including those with reversible SCD, stable non-reversible SCD, and SCD with subsequent cognitive decline to levels of mild cognitive impairment or dementia (Jessen et al., 2014; Mitchell et al., 2014). The SCD-Initiative has also codified criteria labeled as "SCD-plus" which describes additional criteria that may represent individuals at a greater risk for developing AD in the future (Jessen et al., 2014). Deriving biomarkers that can identify individuals likely to progress along the continuum to MCI and AD is an imperative focus of current research.

The NIA-AA has proposed a research framework for the study of *in vivo* biomarkers of AD which incorporates brain atrophy as measured by structural MRI (Jack et al., 2018). Although biomarkers that measure the AD hallmarks of amyloid, tau and

neurodegeneration have been focused upon, there are additional neuroimaging techniques that have been employed to explore AD and its progression, which are not presently encompassed by the NIA-AA framework. Notably, previous research has suggested that changes in brain function may precede changes in structure (Parker et al., 2020). It has been suggested that those with SCD may be experiencing functional dysconnectivity and not yet displaying cell loss that can be seen at later points on the cognitive continuum (when objective cognitive abilities and ability to carry out IADLs are impacted). Among functional neuroimaging techniques, functional magnetic resonance imaging (fMRI) has demonstrated promise as a valuable research tool resting-state to examine functional connectivity and network alterations in the brains of individuals with MCI or AD compared to healthy controls (Hohenfeld et al., 2018). Currently, fewer studies have been conducted examining differences in functional connectivity between individuals with SCD and healthy controls, and more research is needed to better understand how changes in brain function may reflect a potential biomarker for future development of AD (Viviano & Damoiseaux, 2020).

Resting-state fMRI measures spontaneous fluctuations in blood oxygen level-dependent (BOLD) signals in different brain regions at the voxel level (Heeger & Ress, 2002). When an individual is undergoing a resting-state fMRI scan, they are instructed to rest with their eyes open or closed and not to think about anything in particular, allowing for the examination of functional connectivity between brain networks. Although several analysis approaches exist, seed-analyses have been commonly used to examine differences in functional connectivity patterns in the brain.

The default mode network (DMN) is the most studied resting-state network in the literature for detecting disruptions in functioning in relation to the development of AD and other dementias. The DMN is 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 anatomical regions involved in the DMN include the posterior cingulate cortex, precuneus, medial temporal lobes, and medial prefrontal areas (Raichle, 2015).

In addition to the DMN, other functional connectivity networks such as the frontoparietal network (FPN) and salience network (SN) (Badhwar et al., 2017; Song et al., 2021) have demonstrated differences between healthy older adults and those with MCI or AD. The FPN is implicated in attention, decision making, working memory, and cognitive control (Marek & Dosenbach, 2018; Vincent et al., 2008) and includes the involvement of the inferior parietal cortex, insula, superior lateral occipital cortex, supramarginal gyrus, supplementary motor areas, and ventral visual cortex (Dosenbach et al., 2006; Fox et al., 2005). The SN is involved in social functioning, communication, and self-awareness through detection and integration of salient cognitive, emotional, and sensory stimuli in one's environment (Menon, 2015; Menon & Uddin, 2010; Seeley et al., 2007). The brain regions associated with the anterior insula and dorsal anterior cingulate cortex (Menon, 2015). Depending on the importance of the stimuli presented, the SN will either direct more or less attentional processing towards the stimuli presented (Menon, 2015). During cognitive tasks, the SN will engage the FPN and disengage the DMN in order to focus on the task at hand. In contrast, during rest or passive states, the

SN tends to exhibit the opposite pattern, with disengagement from the FPN and re-engagement with the DMN (Chand et al., 2017).

A review by Viviano and Damoiseaux (2020) highlight how alterations in functional connectivity between those with SCD and healthy controls may be a sensitive method to detect future development of AD or other dementias when other indicators of dementia risk are not present during this preclinical phase. In fact, previous studies have reported differences in functional connectivity between those with SCD and healthy controls while these groups did not differ on measures of amyloid or tau deposition (Li et al., 2018; Yasuno et al., 2015). However, the findings across studies have been mixed, where those with SCD have either no difference (Contreras et al., 2019; Scarapicchia et al., 2019), increased functional connectivity (Dillen et al., 2016; Hafkemeijer et al., 2013), decreased functional connectivity (Viviano et al., 2019; Wang et al., 2013; Yasuno et al., 2015), or both increased and decreased functional connectivity (Parker et al., 2020; Vega et al., 2016; Xue et al., 2019) when compared with healthy controls. Although there seems to be conflicting results when it comes to functional connectivity in those with SCD compared to healthy controls, it is hypothesized that these results may be influenced by the amount of time individuals have been living with SCD (Viviano & Damoiseaux, 2020). It has been suggested that those who show increased functional connectivity reflect individuals who are in an early stage of SCD whereas lower functional connectivity reflects those who have experienced SCD for a longer time period (Sperling et al., 2010), although longitudinal studies are needed to verify this theory.

Consideration of risk factors for cognitive decline alongside neuroimaging results may provide additional understanding of individuals with SCD. Although advanced age

is the largest risk factor for future development of dementia, several potentially modifiable risk factors for dementia have been outlined (Livingston et al., 2020). These potentially modifiable risk factors include less education, hearing loss, traumatic brain injury, hypertension, excessive alcohol consumption (>21 units/week), obesity (BMI ≥ 30), smoking, depression, social isolation, physical inactivity, diabetes, and exposure to air pollution (Livingston et al., 2020). With the elimination of these 12 risk factors, it is estimated that up to 40% of dementias may be delayed or prevented (Livingston et al., 2020). A study by Omura et al. (2022) found that individuals with SCD were more likely to report a higher number of risk factors associated with dementia compared to those without SCD. Although it is difficult to understand the amount of risk reduced by addressing these modifiable risk factors, it is possible that early identification of SCD and dementia-related risk factors may allow health care professionals to intervene promptly through monitoring of cognitive symptoms moving forward and addressal of presenting risk factors.

In fact, studies outside of the neuroimaging literature have found demographic variables, lifestyle factors, and health related concerns differ between those with SCD and healthy controls. Recent studies have investigated patterns of multimorbidity in SCD samples to examine whether these variables are associated with difficulties related to SCD (Liu & Jiang, 2022). A systematic review by Li, Tan, Tan, & Xu (2023) discuss a number of different predictors of further cognitive deterioration in those who report SCD. Some of these predictors include factors outlined in SCD-plus criteria, lower education, presence of APOE e4, older age, depression, anxiety, and current smoking (Li et al., 2023). For instance, studies have reported that current but not former smokers with SCD

have a higher risk of developing AD in the future compared to those who have never smoked (Ahn et al., 2020; Liu & Jiang, 2022). SCD has also been associated with depression and lower quality of life scores and experiencing symptoms of depression has also been associated with increased risk of conversion from SCD to aMCI or dementia (Ahn et al., 2020; Lee & Ho Chung, 2022; Liew, 2019). The prevalence of reporting SCD was highest in those with depression (28.5%) and hearing loss (24.7%) (Omura et al., 2022).

Mixed findings have been reported regarding BMI and risk of AD conversion in those with SCD. Higher BMI has been associated with both lower risk (Ahn et al., 2020; Barnes et al., 2009; Fitzpatrick et al., 2009; Gustafson & Luchsinger, 2013; Qizilbash et al., 2015; Xu et al., 2011) and higher risk (Beydoun et al., 2008; Loeff & Walach, 2013; Profenno et al., 2010; Sellbom & Gunstad, 2012) of converting from SCD to MCI or AD. It is hypothesized that lower BMI may be attributed to metabolic changes that take place in latent or preclinical AD, however, this mechanism is not fully understood (Hao et al., 2019).

Increased physical activity has long been recognized for its benefits on brain health (Sun et al., 2021; Zheng et al., 2016). In those with SCD, physical activity has also been reported to potentially slow conversion to MCI or dementia (Bessi et al., 2018; Muñoz et al., 2020). Additionally, engagement in leisure activities and mentally stimulating tasks have been reported as protective factors for delaying cognitive decline and AB deposition (Bessi et al., 2018).

Limited research has been conducted on differences in functional connectivity across multiple networks in those with SCD compared to healthy controls. Although

these studies have included cognitive scores and neuroimaging data, there has been a lack of available information on these participants apart from sex, education, and age. This limited availability of participant characteristics impeded researchers' ability to confidently determine whether differences in brain metrics between these two groups are solely attributed to the experience of SCD.

To gain a better understanding of functional biomarkers in SCD and associated risks of developing AD in the future, more comprehensive research is needed. Such research should investigate multiple rs-fMRI functional connectivity networks and thoroughly examine participant characteristics in individuals who report SCD. In addition, previous research has emphasized the importance of including additional information such as demographics, potentially modifiable lifestyle factors, and medical comorbidities to provide a more comprehensive description of the individuals included in the SCD group. Incorporating such information may improve our understanding of SCD and who is most at risk of developing AD in the future.

The current study examined resting-state functional connectivity across three different networks as well as demographic and lifestyle variables between women with SCD and healthy women. Specifically, we examined resting-state functional connectivity of the DMN, FPN, and SN between groups. Based on previous research, it was hypothesized that women with SCD would show differences in resting-state functional connectivity compared to healthy women. Given that studies of SCD often do not provide much information on their SCD cohort, we also examine demographic variables, lifestyle factors, and medical comorbidities consistent with those outlined by Livingston and colleagues (2020). We hypothesized that there would be minimal differences between

women with SCD and healthy women, as participants recruited for this study were community-dwelling women experiencing healthy aging.

Methods

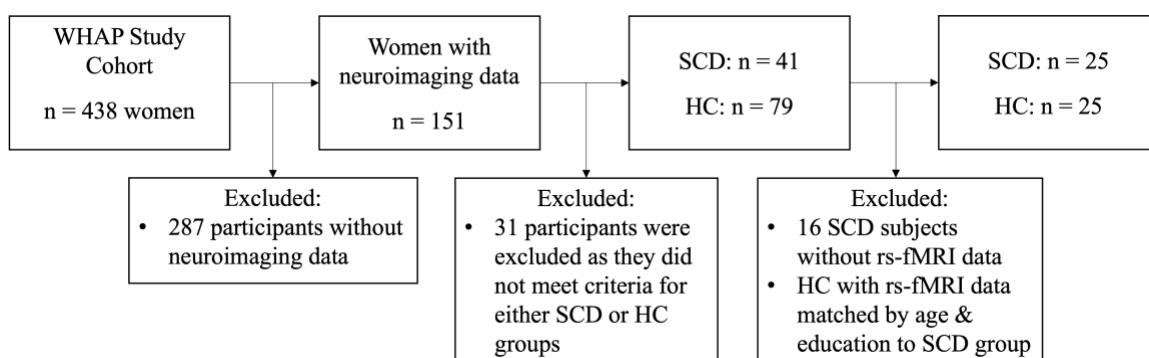
Sample

Data were obtained from the Women's Healthy Ageing Project (WHAP). The WHAP, initially named the Melbourne Women's Midlife Health Project is an ongoing longitudinal population-based study that began in 1991. The WHAP is an Australian-based project initiated in the early 1990s to examine factors influencing women's health during and after menopause (Szoeki et al., 2016; Szoeki et al., 2013). All participants were Australian Caucasian women. Initially, over 1,897 women aged 45-55 were included to participate in the baseline cross-sectional study. To be deemed eligible for the longitudinal study, participants needed to have determinable menopausal status, defined as having had menses in the previous three months, an intact uterus with at least one ovary, and not taking oral contraceptives or hormone therapy. Of the 1,897 women who participated in the baseline study, 779 women were deemed eligible, and 438 consented to participate in the longitudinal study. The WHAP research spans various areas, including quality of life, mental and cognitive health, cardiovascular health, musculoskeletal health, lifestyle, women's health, and hormonal transitions. To date, this longitudinal study cohort has maintained nearly 50% retention over 30 years of follow-up assessments. Additional information regarding the recruitment and development of this research program have been previously published (Szoeki et al., 2016; Szoeki et al., 2013).

The data utilized in the present study was collected between 2012-2015 and includes MRI data as well as neuropsychological, psychosocial, and lifestyle data. The participants from the WHAP were then sorted into one of two groups, SCD or healthy controls. A

flow chart of participant selection is shown in Figure 2.1. Both the SCD and healthy control groups were closely modeled after those in the cohorts described in ADNI-2 (Alzheimer’s Disease Neuroimaging Initiative, 2008b). All SCD participants self-reported a significant memory concern and achieved 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 SCD groups exhibited normal memory function on the Logical Memory II subscale of the revised WMS (≥ 9 for 16 years of education and above, ≥ 5 for 8-15 years of education, and ≥ 3 for 0-7 years of education), a MMSE score between 24 and 30 (inclusive), and a Clinical Dementia Rating of 0.

Figure 2.1 Flow diagram of participant selection for Study 2



Note. WHAP = Women’s Healthy Ageing Project. SCD = Subjective Cognitive Decline.

HC = Healthy Controls.

Image Acquisition

MRI data were retrieved from the WHAP. 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 $1 \times 1 \times 1.2$ mm, and a flip angle of 9° . fMRI scans were obtained during resting state (with eyes open). T2*-weighted, gradient EPI data were acquired continuously with an 8-channel birdcage radio frequency head coil. Each scan generated 180 volumes of whole-brain, 41-slice acquisition (TR = 3000 ms, TE = 30 ms, flip angle = 90° , voxel size = 3.0 mm^3) for a 6 min duration acquisition. Participants were asked to keep eyes open and fixed on a projected cross hair.

Data Analyses

Image Preprocessing. All MRI data obtained from the WHAP were in DICOM format. All structural images were converted from DICOM to NIFTI format using `dcm2niix` in the MRICroGL application (X. Li et al., 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. 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 et al., 2002; Jenkinson

& Smith, 2001) and then further refined using FNIRT nonlinear registration (Andersson et al., 2007a, 2007b).

Seed-based Resting State fMRI Functional Connectivity Analysis. A seed-based approach was used to examine functional connectivity in the DMN, FPN, and SN. Three separate regions of interest (ROIs or seed-regions) were created in order to examine each of these functional networks. These regions were modeled after previously used ROIs as documented in the literature, including the left posterior cingulate for the DMN (De Luca et al., 2006), the right inferior parietal sulcus for the FPN (Voss et al., 2010), and the right dorsal anterior cingulate cortex for the SN (He et al., 2014). For each of these brain structures, a spherical ROI with a 5 voxel (5 mm) radius was generated, with the centre point anchored to the corresponding MNI coordinates of each brain region as reported in the literature. Each of the created ROIs were generated using the MNI-152 T1 1mm brain as the template.

Each of these created ROIs were then registered to individual space. Next, the FEAT function was used to examine each of the networks using the corresponding ROIs as well as regress out the lateral ventricle signal to correct for confounding noise (Oschmann & Gawryluk, 2020; Parker et al., 2020; Scarapicchia et al., 2019).

Specifically, the mean blood oxygen level-dependent signal time series was extracted from each of the seed regions and used as the model response function in a general linear model. This allowed for examination of functional connectivity in the DMN, FPN, and SN respectively, through the detection of voxels with timeseries that correlated with that measured in each of the seed regions. The time-series statistical

analysis was then carried out using FILM with local autocorrelation correction (Woolrich et al., 2001).

Finally, a higher-level between-group analysis was conducted to compare resting state functional connectivity in each of the networks (DMN, FPN, and SN) 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 et al., 2003; Woolrich, 2008; Woolrich et al., 2004). Z (Gaussianised T/F) statistic images were thresholded non-parametrically using clusters determined by $Z > 3.0$ and a (corrected) cluster significance threshold of $p = 0.05$ (Worsley, 2001). The regional anatomy showing significant alterations in functional connectivity were identified using the Harvard-Oxford Cortical Structural Atlas.

Demographics Analysis

Education. Education was further categorized into five distinct groups, those with 16 or more years of education, those with 13-15 years of education, those with 9-12 years of education, those with 7-8 years of education, and those with 6 or less years of education.

Smoking. Participants were asked whether they are currently smoking. Participants were categorized into two groups, those who currently smoke and those who do not.

Obesity (Body-Mass Index (BMI) ≥ 30). The WHAP collected physical data to determine the BMI of their participants. This data was recorded numerically.

Alcohol Use. Participants were asked to rate their alcohol use during follow up visits for the WHAP. Specifically, participants were asked "In the last 7 days, about how

many alcoholic drinks have you consumed?”. The data from this question was categorized into seven categories, ≥ 15 drinks, 8-14 drinks, 7 drinks, 3-6 drinks, 2 drinks, 1 drink, or none.

Physical Activity. Participants were asked to rate how often they engage in physical activity. Specifically, participants were asked “How often if at all do you participate in energetic physical activities which make you breathe harder, puff, or pant?”. Participants could choose between seven different options: everyday, 4-6 times per week, 2-3 times per week, once per week, a few times a month, less than once a month, or never.

Hypertension. Blood pressure data was collected from participants for both systolic blood pressure and diastolic blood pressure (both measured in mm Hg). Participants were classified as having hypertension if they self-reported taking anti-hypertensive medications or measured ≥ 140 mm Hg for systolic blood pressure or ≥ 90 mm Hg for diastolic blood pressure. Participants were categorized as being hypertensive or not based on the above criteria.

Diabetes. Participants were asked to self-report whether they have a diagnosis of diabetes. Data on fasting plasma glucose or HbA_{1c} was not collected.

Social Isolation. Social isolation was measured through analyzing self-reported loneliness. Participants were asked “During the last week, how often have you been feeling lonely?”. This question is an item from the Affectometer 2 (Kammann & Flett, 1983). Participants were provided with five response options: most of the time, often, sometimes, hardly ever, or can’t say.

Traumatic Brain Injury. Participants were asked to self-report whether they have ever experienced a traumatic brain injury. Specifically, participants were asked “Have you suffered a serious head injury?”. If participants were to endorse a previous head injury, no data was collected on whether loss of consciousness was experienced.

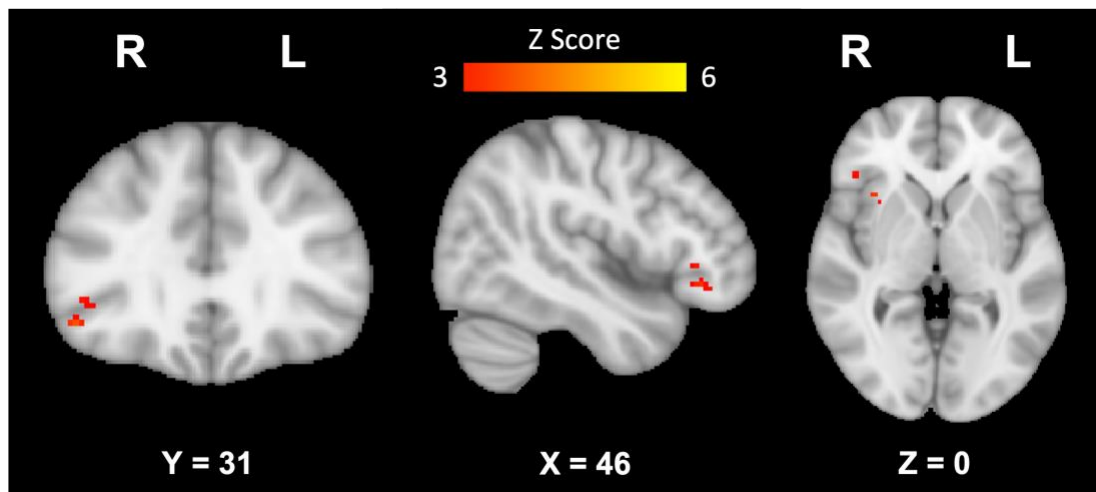
Results

Resting state seed-based fMRI analyses revealed significant differences in functional connectivity between groups for the DMN and FPN where women with SCD showed increased functional connectivity in various regions of the brain compared to healthy women. In the DMN, women with SCD showed increased functional connectivity in the right frontal orbital cortex, frontal pole, inferior frontal gyrus (pars triangularis), and insular cortex. In the FPN, women with SCD showed increased functional connectivity in the left amygdala, right frontal pole, lingual gyrus, lateral occipital cortex (superior), parahippocampal gyrus, precuneus cortex, and bilateral cingulate gyrus (posterior), lateral occipital gyrus (inferior), and thalamus. No differences in functional connectivity in the SN were found between women with SCD compared to healthy women.

Demographic Analyses

No significant differences were found between women with SCD and healthy women among variables of obesity, diabetes, hypertension, physical activity, social isolation, alcohol use, previous brain injury, and current smoking.

Figure 2.2 Brain regions showing increased functional connectivity in the DMN in participants with SCD compared to healthy controls



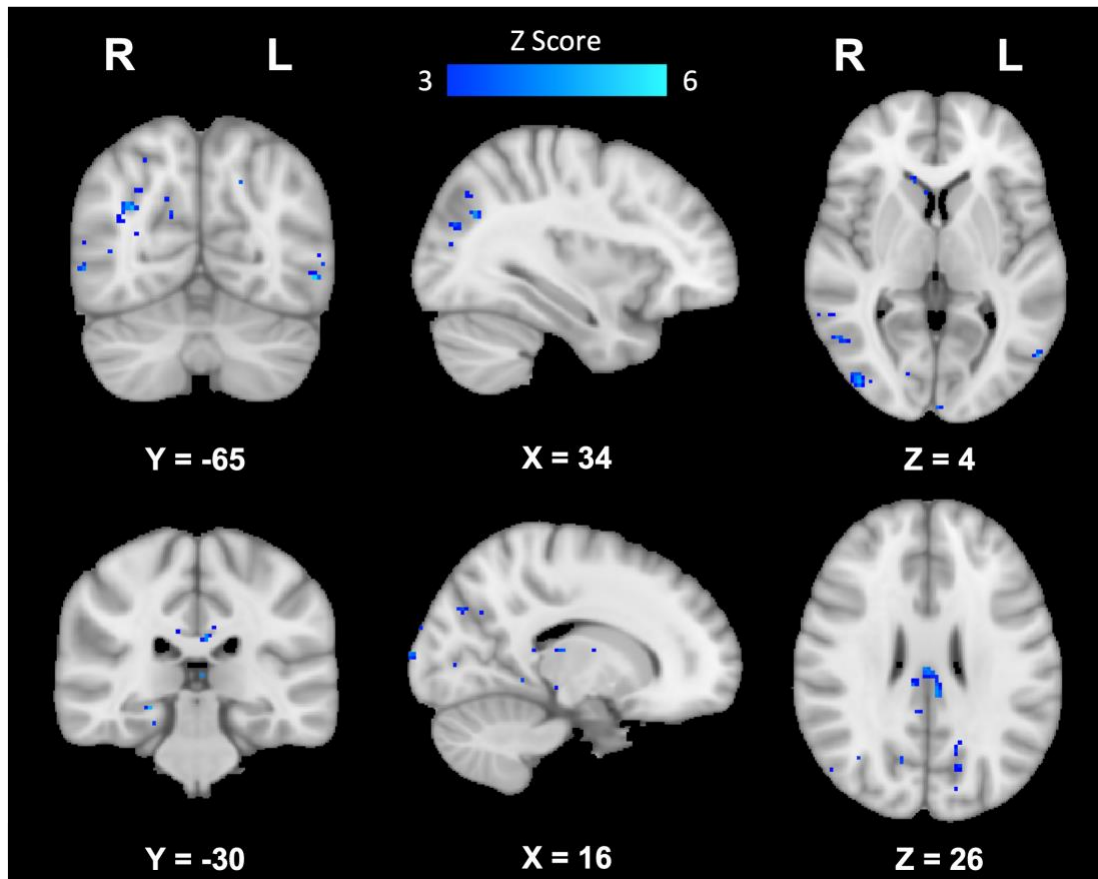
Note. From left to right: sagittal, coronal, and axial slices of the brain displaying results of group level comparisons showing significantly increased functional connectivity in the DMN in women with SCD compared to healthy women; corrected for multiple comparisons, $p < 0.05$.

Table 2.1 *Brain regions showing increased functional connectivity in the DMN in participants with SCD compared to healthy controls*

Brain Region	Laterality	MNI Coordinates			Z score
		X	Y	Z	
Inferior Frontal Gyrus, pars triangularis	R	46	29	0	3.25
Frontal Pole	R	46	35	-10	3.11
Insular Cortex	R	36	18	0	3.59
Frontal Orbital Cortex	R	48	29	-8	3.99

Note. Brain regions showing increased functional connectivity in the DMN in participants with SCD compared to healthy controls (min $Z > 3.0$; cluster significance: $p < 0.05$, corrected for multiple comparisons). Coordinates in the MNI-152 standard space image are given.

Figure 2.3 Brain regions showing increased functional connectivity in the FPN in participants with SCD compared to healthy controls



Note. From left to right: sagittal, coronal, and axial slices of the brain displaying results of group level comparisons showing significantly increased functional connectivity in the FPN in women with SCD compared to healthy women; corrected for multiple comparisons, $p < 0.05$.

Table 2.2 Brain regions showing increased functional connectivity in the FPN in participants with SCD compared to healthy controls

Brain Region	Laterality	MNI Coordinates			Z score
		X	Y	Z	
Parahippocampal Gyrus	R	22	-35	-16	3.30
Cingulate Gyrus (Posterior)	L	-4	-36	23	4.38
Cingulate Gyrus (Posterior)	R	2	-23	25	3.54
Thalamus	R	18	-23	12	3.08
Thalamus	L	-4	-18	13	4.04
Lateral Occipital Cortex (Superior)	R	35	-65	28	3.79
Lateral Occipital Cortex (Inferior)	R	42	-84	4	3.96
Lateral Occipital Cortex (Inferior)	L	-54	-65	-5	3.54
Lingual Gyrus	R	12	-44	-4	3.15
Frontal Pole	R	28	48	16	3.96
Amygdala	L	-22	-8	-10	3.21
Precuneus Cortex	R	19	-68	33	3.14
Insular Cortex	L	-38	-11	9	3.24
Caudate	L	-8	0	9	3.08
Hippocampus	R	25	-30	-9	4.01

Note. Brain regions showing increased functional connectivity in the FPN in participants with SCD compared to healthy controls (min $Z > 3.0$; cluster significance: $p < 0.05$, corrected for multiple comparisons). Coordinates in the MNI-152 standard space image are given.

Table 2.3 Participant Demographics

	<i>HC</i>	<i>SCD</i>	<i>HC vs. SCD</i>
Age	69.80 ± 2.55	69.48 ± 2.87	$p = 0.68^a$
Years of Education	14.24 ± 3.22	13.28 ± 3.61	$p = 0.33^a$
Sex (M/F)	0/25	0/25	
Number of Pregnancies	3.52 ± 1.53	2.76 ± 1.36	$p = 0.07^a$
Age at Final Menstrual Period	52.83 ± 2.32 ^b	53.54 ± 1.40 ^c	$p = 0.44^a$
HRT Use Ever Count	0	1	
APOE e4	7 ^d	1 ^e	
BMI	26.42 ± 3.59	27.35 ± 5.23	$p = 0.46^a$
Diabetic Count	1	1	
Hypertension Count	18	17	
Current Smoker Count	2	1	
TBI Count	2	2	
Alcohol Use		f	
≥15 drinks/week	1	3	
8-14 drinks/week	0	2	
7 drinks/week	6	6	
3-6 drinks/week	5	2	$p = 0.61^g$
2 drinks/week	3	3	
1 drink/week	1	1	
None	9	7	
Physical Activity			
Everyday	1	0	
4-6/week	2	0	
2-3/week	0	2	$p = 0.16^g$
1/week	5	7	
Few times/month	11	6	
<1/month	3	8	
Never	3	2	
Social Isolation			
Most of the time	0	0	
Often	0	0	
Sometimes	2	1	$p = 0.55^g$
Hardly Ever	23	24	
Can't Say	0	0	

^a p-value of t-test; ^b n = 14; ^c n = 8; ^d n = 23; ^e n = 22; ^f n = 24; ^g p-value of chi-square test

Discussion

The current study represents an important step in characterizing functional connectivity and sociodemographic differences between older women who report SCD compared to healthy older women. The first aim of the present study was to determine whether there are functional connectivity differences between women with SCD and healthy women. Based on our previous work and review of literature, we hypothesized that functional connectivity would differ between these groups in all three of the networks investigated, including the DMN, FPN, and SN. Upon completion of the analyses, we found that older women who reported SCD showed increased functional connectivity in the DMN and FPN, while no decreases in functional connectivity were observed between these groups within these networks. Finally, our findings indicated no significant difference in functional connectivity between these groups in the SN. The second aim of this study was to examine whether these two groups differed on demographic variables, lifestyle factors, and medical comorbidities outlined by Livingston and colleagues (2020) as many studies of SCD do not provide detailed information on these variables in their study cohorts. As our participants were drawn from a healthy aging study cohort, we hypothesized that there would be minimal differences between women with SCD and healthy women, which was in line with our findings.

Our results are consistent with several studies that found increased functional connectivity in the DMN in individuals with SCD compared to healthy controls where those with SCD (Chiesa et al., 2019; Dillen et al., 2016; Hafkemeijer et al., 2013; Sperling et al., 2009; Verfaillie et al., 2018). While we did not find significant differences

between those with SCD and healthy controls in the SN, a previous study has found increased functional connectivity in this network in those with SCD compared to healthy controls (Xue et al., 2021). We were challenged to find any previous study that examined functional connectivity differences in the FPN using resting-state fMRI in individuals with SCD. However, studies have found functional connectivity alterations between individuals with SCD and healthy controls in the FPN while using task-based fMRI. A review by Viviano and Damoiseaux (2020), hypothesized that alterations in the FPN or SN may occur before differences are seen in the DMN. Our current results contrast this hypothesis as we saw increased functional connectivity in the DMN and FPN, while no differences were seen in the SN between groups. However, our results were based on resting-state fMRI protocols where as previous studies have seen alterations in the SN between those with SCD compared to healthy controls on task-based fMRI analyses (Hu et al., 2017)

Broadly, in terms of cognitive theories of aging, the current findings align with the Scaffolding Theory of Aging and Cognition – Revised (STAC-R) which describes functional compensation mechanisms (i.e., increased functional connectivity) as a means of over-recruiting additional cortical areas to support neural circuitry that is underperforming (Reuter-Lorenz & Park, 2014). Our findings of increased functional connectivity in frontal regions, specifically within the DMN also corresponds with the Posterior-Anterior Shift in Aging (PASA) model. The PASA model describes a shift in functional activity from the posterior to frontal regions of the brain (Davis et al., 2007). However, the study of these cognitive theories are mainly done in groups comparing older adults to younger adults. Further research is necessary to better understand the

relevance of these cognitive theories when evaluating brain-based differences between older adults who report SCD and those without cognitive complaints.

Previous studies comparing those with SCD to healthy controls have primarily focused on age and education as differentiating factors, without thoroughly examining other demographic or lifestyle variables. In the current study, we sought to investigate whether additional differences existed between these two groups other than the experience of SCD by including comparisons on potentially modifiable risk factors outlined by Livingston et al. (2020). We specifically examined variables including obesity, diabetes, hypertension, physical activity, social isolation, alcohol use, previous brain injury, and current smoking. In line with our hypothesis, we did not observe any significant differences between women with SCD and healthy women across these variables. This finding is intriguing since we observed differences in functional connectivity between these two groups based solely on the self-reporting of SCD, while no other significant differences were identified on these demographic variables, lifestyle factors, and medical comorbidities.

This current study possesses several notable strengths. A fundamental strength of this study was the comprehensive examination of resting-state functional connectivity differences across three distinct networks – the DMN, FPN, and SN – between women with SCD in comparison to healthy women across. To our knowledge, this is the first study to examine differences in multiple networks between individuals with SCD and healthy controls in a sample comprising of women. By specifically examining functional connectivity differences in older women with SCD, the findings of this study enhance the current understanding of cognitive health in women. Using resting-state fMRI was

another strength of this study and can ensure inclusivity in data collection. This approach is well-suited for the study of individuals with compromised cognitive abilities. While task-based fMRI remains a valuable tool for investigating alterations in functional connectivity, it is important to acknowledge that individuals with advanced dementia often encounter challenges when attempting to complete complex tasks, rendering the resting-state approach as a more viable and informative alternative. Another strength of this study was the incorporation of demographic variables, lifestyle factors, and medical comorbidities. The inclusion of these variables allowed for a comprehensive characterization of the sample and confirmed that among these variables considered, the only discernible distinction between these two groups was the self-reported experience of SCD.

There were also several limitations of this current study that may help inform the direction of future research in this area. First, there was a limited statistical power due to the sample size of the study, however, we included the maximum number of participants available in the WHAP as participants were required to have undergone both structural and functional MRI. Second, this study employed a cross-sectional design. Future research would benefit from using longitudinal designs that could elucidate the functional connectivity changes between these groups over time. Third, the current study only included healthy women and women with SCD. Future studies would benefit from including a broader range of groups across the cognitive continuum, such as healthy controls, individuals with SCD, MCI, and AD. By incorporating each of these groups, researchers may gain a more comprehensive understanding of the differences in functional connectivity across the cognitive continuum. A fourth limitation was the

absence of specific information regarding participants' experience of SCD. Despite participants completing a multitude of cognitive tests and lifestyle questionnaires, this dataset lacked detailed information outlined by the SCD-I. Future research should consider incorporating specific information to gain a better understanding of the relationship between SCD and functional connectivity alterations. Recent research has suggests that the experience of persistent SCD over several years should be included in the SCD-plus criteria (Liew, 2020). Liew (2020) conducted a study investigating differing trajectories of SCD and their impact on conversion rates to MCI or dementia. The findings revealed that older individuals who reported persistent SCD had a probability greater than 75% of developing MCI or dementia in 10 years (Liew, 2020).

Conclusion

This study aimed to investigate the differences in functional connectivity networks, specifically the DMN, FPN, and SN, between healthy older women and older women with SCD. The results revealed increased functional connectivity in older women with SCD in the DMN and FPN compared to healthy older women. Notably, no decreases in functional connectivity were found between the two groups across networks, and no significant differences in functional connectivity were detected in the SN. The observed findings of increased functional connectivity (rather than decreased functional connectivity) between groups may be attributed to characteristics of the participant sample which comprised of community-dwelling women who are likely in the earlier stages of experiencing SCD. Further, no differences emerged between groups in various demographic variables, lifestyle factors, and medical comorbidities. The absence of differences between groups on these variables highlights how the only distinction

between the two groups was the self-report of SCD. To gain a more comprehensive understanding of functional connectivity analyses within the same cohort of participants. Additionally, it would be valuable to incorporate demographic variables, lifestyle factors, and medical comorbidities, as well as capture specific information regarding SCD-plus criteria as well as the duration of time that individuals have been experiencing SCD. The inclusion of this information would contribute to a more fulsome description of the individuals included in the SCD group and provide further insights into the relationship between functional connectivity and the experience of SCD. Overall, the findings of this study provide valuable insights into the neural mechanisms underlying SCD and highlights the importance of considering functional connectivity alterations in understanding preclinical manifestations of AD.

Study 3: Multimodal structural MRI does not reveal differences in grey or white matter with and without subjective cognitive decline

Brief Report

Parker, A. F., Szoek, C., Kwan, H., Henri-Bhargava, A. & Gawryluk, J. R.

Abstract

Background: Subjective cognitive decline (SCD) is considered the earliest stage on the cognitive continuum of Alzheimer's disease.

Objective: To use a multi-modal neuroimaging approach to examine differences in grey and white matter in women with SCD compared to women without SCD.

Methods: 3T T1 and diffusion weighted images were retrieved from the Women's Healthy Ageing Project for 41 women with SCD and 41 healthy women.

Results: There were no differences in grey matter volume (measured by VBM) or white matter microstructure (measured by DTI) between women with and without SCD.

Conclusions: Structural imaging may not detect differences in brain structure in community-dwelling women with SCD.

Introduction

Dementia is a growing health issue worldwide (Nichols et al., 2019). In 1990, approximately 20.2 million older adults were living with dementia; by 2016 the number more than doubled to 43.8 million (Nichols et al., 2019), and by 2050, it's predicted that 153 million people will be experiencing dementia (Nichols et al., 2022). The most common form of dementia, making up approximately 70% of cases, is Alzheimer's disease, a progressive, incurable neurodegenerative disorder, characterized by primary memory impairment and challenges with activities of daily living (World Health Organization, 2020, September 21). The greatest risk factor for Alzheimer's disease is age and the prevalence is higher in women, emphasizing the need for research on aging women (World Health Organization, 2023, March 15).

Alzheimer's disease has a late clinical diagnosis, which typically occurs after significant clinical symptoms such as memory impairment and substantial neurodegeneration has already taken place. However, it is thought that these neurodegenerative processes begin 20 years or more before clinical symptoms present (Braak et al., 2011; Gordon et al., 2018). Although it has been a major focus of ongoing research, identification of healthy individuals who are at a greater risk of developing AD is notoriously challenging. In the last decade, there has been more attention placed on studying individuals who report subjective cognitive decline (SCD); individuals who self-report a decline in their cognitive abilities but perform within normal limits on neuropsychological assessment (Jessen et al., 2014). Previous research has found that up to 60% of individuals who report SCD will convert to diagnoses of MCI or AD within a 15-year time period (Reisberg & Gauthier, 2008; Si et al., 2020). Previous research has

also suggested that females who report SCD exhibit a faster decline in cognition compared to males who report SCD (Oliver et al., 2022). Given that SCD may shed new light on early changes in an individual's cognitive functioning, research groups including the Subjective Cognitive Decline-Initiative (SCD-I), International Working Group (IWG), and US National Institute of Aging – Alzheimer's Association (NIA-AA) are in agreement that SCD represents a preclinical stage of AD and that detectable biomarkers likely exist in this group (Jack et al., 2011; Jack et al., 2018; Reisa A. Sperling et al., 2011).

According to the NIA-AA, structural magnetic resonance imaging (MRI) showing atrophy of the medial temporal lobes is a gold standard measure for identifying AD pathology (Jack et al., 2018). Structural neuroimaging using MRI has also been used to study brain-based differences between individuals with SCD and healthy controls, however, studies employing structural MRI techniques such as voxel-based morphometry have found mixed results. Consistent with findings in AD, some studies detected reduced grey matter volume in the hippocampus (Hafkemeijer et al., 2013; Kim et al., 2013; Perrotin et al., 2015; Scheef et al., 2012), amygdala (Hafkemeijer et al., 2013; Kim et al., 2013; Striepens et al., 2010), entorhinal cortex (Fan et al., 2018; Marcotte et al., 2019; Meiberth et al., 2015; Ryu et al., 2017), and precuneus (Hafkemeijer et al., 2013; Hong et al., 2015) in those with SCD. In contrast, several other studies found no differences between those with SCD compared to healthy controls (Kiuchi et al., 2014; Lauriola et al., 2017; Lindberg et al., 2017; Parker et al., 2020; Platero et al., 2019; Sun et al., 2016).

Although not included in the research framework set out by the NIA-AA (Jack et al., 2018), other MRI techniques such as diffusion tensor imaging (DTI) have been used

to study AD pathology in preclinical samples. Similar to the results seen in VBM analyses, DTI studies have yielded mixed results in comparisons of individuals with and without SCD. For instance, some studies have found decreased fractional anisotropy (FA) and increased mean diffusivity (MD) in the corpus callosum (Hong et al., 2015; X.-Y. Li et al., 2016; Luo et al., 2020; Ohlhauser et al., 2019), superior longitudinal fasciculus (X.-Y. Li et al., 2016; Ohlhauser et al., 2019), and hippocampus (Hong et al., 2015; Ryu et al., 2017), whereas other studies have found no differences in FA and MD between these groups (Kiuchi et al., 2014; Viviano et al., 2019; Wang et al., 2016).

A challenge with ongoing research examining differences between individuals with and without SCD has been the ability to apply a multimodal approach within the same set of participants. For example, our group has previously examined data from the ADNI, looking specifically at difference between healthy controls and those categorized as having “significant memory complaints”, which essentially represents people with SCD. An initial study focused on white matter microstructure and found widespread differences in DTI metrics between individuals with and without SCD (Ohlhauser et al., 2019). To follow up, we examined grey matter volume, and did not find between group differences (Parker et al., 2020). Unfortunately, these studies did not have overlapping participants and it remains important to examine both grey matter and white matter differences between individuals with SCD compared to healthy controls in the same participant groups. To date, two studies have investigated both grey matter volume and white matter microstructure in individuals with SCD (Cedres et al., 2021; Liang et al., 2021). Cedres et al. (2021) reported significant correlations between the number of subjective complaints and both white matter integrity and cortical thickness. Liang et al.

(2021) used structural MRI and DTI to examine whether covariant grey matter and white matter abnormalities could differentiate individuals with SCD from healthy controls.

Abnormalities were seen in the grey matter of the precentral gyrus, post central gyrus, middle frontal gyrus, and middle temporal gyrus, while white matter abnormalities were seen in regions of the anterior thalamic radiations and superior longitudinal fasciculus.

The emerging literature highlights the need for a better understanding of preclinical AD in women and the importance of multi-modal neuroimaging investigations within the same participant sample. This study used a whole-brain approach to examine structural brain differences in those with SCD compared to healthy controls. This method allowed for an unbiased examination of potential differences across the entire brain, rather than limiting the investigation to memory-associated areas such as the hippocampus and medial temporal lobe. The decision to use this approach was based on previous findings from our research group, which showed a widespread relationship between DTI metrics and executive function in individuals with SCD, but not in healthy controls, with no observed relationship with memory in either group.

Therefore, the current study examined group differences in grey matter volume and white matter integrity between women with SCD compared to healthy women. Although previous studies yield mixed findings on whether differences in brain structure can be detected between individuals with SCD and healthy controls, our hypotheses were guided by the our previous work using voxel-based morphometry (Parker et al., 2020) and DTI (Ohlhauser et al., 2019) approaches. First, we hypothesized that there would not be significant differences in grey matter volume between women with SCD and healthy

women. Second, we hypothesized that women with SCD would have lower FA and higher MD compared to healthy women in widespread regions.

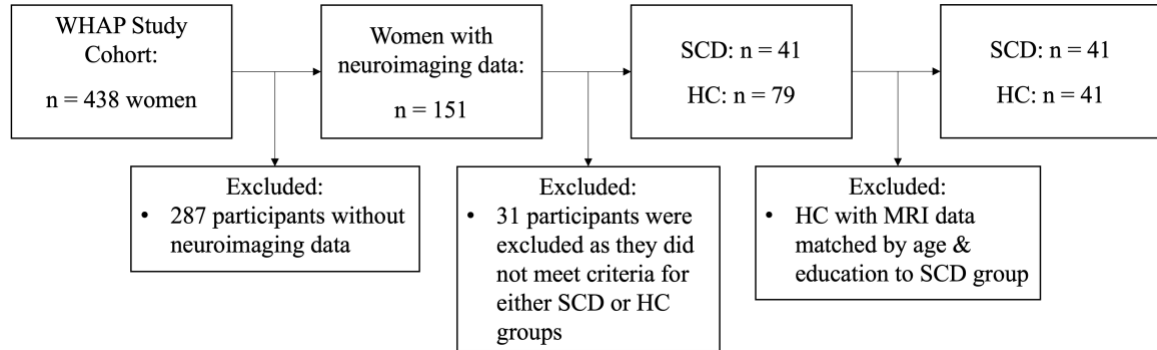
Methods

Data Collection

The data used in the present study were obtained from the Women's Healthy Ageing Project (WHAP). The WHAP, initially named the Melbourne Women's Midlife Health Project is an ongoing longitudinal population-based study that began in 1991. A detailed description of the WHAP can be found in previous publications (Szoek et al., 2016; Szoek et al., 2013). The data utilized in this study was collected in 2012-2015 and includes MRI data as well as neuropsychological, psychosocial, and lifestyle data.

Participant Selection

All participants were selected from the WHAP database and were stratified into one of two groups, SCD or healthy controls (HC). Classification of these groups were closely modeled after the cohorts described in ADNI-2 (Alzheimer's Disease Neuroimaging Initiative, 2008a). All SCD participants self-reported a significant memory concern and achieved 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 HC and SCD groups exhibited normal memory function on the Logical Memory II subscale of the revised WMS (≥ 9 for 16 years of education and above, ≥ 5 for 8-15 years of education, and ≥ 3 for 0-7 years of education), a MMSE score between 24 and 30 (inclusive), and a Clinical Dementia Rating of 0.

Figure 3.1 Flow diagram of participant selection for Study 3

Note. WHAP = Women’s Healthy Ageing Project. SCD = Subjective Cognitive Decline.
HC = Healthy Controls.

Image Acquisition

All images were acquired on a Siemens 3 T Tim Trio Scanner. Whole-brain anatomical MRI scans were acquired sagittally, with a T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) MRI with the following parameters: repetition time (TR) of 2300 ms, and echo time (TE) of 2.98 ms, voxel size of 1 mm³, and a flip angle of 9°. Diffusion-weighted images were acquired using an echo planar imaging (EPI) sequence, with the following parameters: TR of 8500 ms, TE of 90 ms, voxel size of 2.5 mm³, Field of View of 240 mm, b value = 0 or 1000 s/mm², total slices = 55, and 30 diffusion directions.

Neuroimaging Data Analysis

Image Preprocessing. All MRI data obtained from the WHAP were in DICOM format. Structural images were converted from DICOM to NIFTI format using `dcm2niix` in the MRICroGL application (X. Li et al., 2016). 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).

VBM Analysis. A structural whole brain VBM analysis was conducted to compare grey matter densities between women with SCD and healthy women. 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. 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 24 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 (TFCE; corrected for multiple comparisons). TFCE utilizes an algorithm which was designed to better discriminate between signal and noise yielding results with better sensitivity compared to other methods such as cluster-based or voxel-based thresholding (Smith & Nichols, 2009). Between-group comparisons were then made between women with SCD and healthy women subjects.

DTI Analysis. Diffusion-weighted images were corrected for eddy current distortions and head movement using Eddy correct tool and nonbrain tissue was removed using Brain Extraction tool (Smith, 2002). FA and MD maps were created using DTIfit

and input into TBSS (Smith et al., 2006). All data were nonlinearly aligned to FMRIB58_FA space. Then, the mean FA image was created and thresholded ($FA > 0.2$) to create the mean FA skeleton. Voxelwise statistical analyses were performed using Randomise with TFCE was also used to correct for multiple comparisons ($p < 0.05$). Between-group comparisons were made between women with SCD and healthy women subjects.

Results

Participant Characteristics

A total of 41 women with SCD (mean age = 70.00; SD = 2.66) and 41 healthy women (mean age = 70.02, SD = 2.53) were included. There were no significant differences between groups in terms of age, education level, and sex (see Table 1).

Table 3.1 *Participant Demographics*

	<i>HC</i>	<i>SCD</i>	<i>HC vs. SCD</i>
Age	70.02 ± 2.53	70.00 ± 2.66	$p = 0.96$
Years of Education	13.78 ± 3.49	14.00 ± 3.75	$p = 0.78$
Sex (M/F)	0/41	0/41	
APOE e4 presence	10 ^a	7 ^b	

^a n = 38; ^b n = 35

VBM

VBM was used to examine whole brain differences in grey matter volume between the groups. This analysis did not reveal any significant differences between individuals with SCD relative to healthy women in grey matter volume.

DTI

There were no significant differences in white matter microstructure as measured by FA or MD between women with SCD compared to healthy women.

Discussion

SCD is considered the earliest stage on the continuum of Alzheimer's disease, and using multi-modal neuroimaging approaches in the same individuals has been recommended to characterize brain-based biomarkers in SCD (e.g., Parker et al., 2022). There is also a need to better understand trajectories for women, given that women have a higher prevalence of Alzheimer's disease (World Health Organization, 2023, March 15) and that women with SCD have been shown to experience faster cognitive decline (Oliver et al., 2022). Therefore, the aim of the current study was to investigate differences between women with and without SCD using VBM and DTI to examine both grey matter volume and white matter microstructure.

Based on previous studies, we first hypothesized that there would not be significant differences between groups in grey matter volume, which was in line with the current findings. While null hypotheses are typically assumed to be true until evidence suggests otherwise, confirming a null hypothesis contradicts its foundational principle which is to serve as a default position to be tested against an alternative hypothesis. However, these current results are consistent with our previous research (Parker et al., 2020), and several other studies that also observed no significant differences in grey matter volume between individuals with SCD and healthy controls (Chételat, Villemagne, Bourgeat, et al., 2010; Kiuchi et al., 2014; Perrotin et al., 2017; Platero et al., 2019; Sun et al., 2016). However, our findings are also in contrast with other studies that reported significantly lower grey matter volume in medial temporal and frontal regions in those with SCD compared to healthy controls (Hafkemeijer et al., 2013; Ryu et al., 2017; Toledo et al., 2015).

Secondly, we hypothesized that women with SCD would have lower white matter integrity (i.e., decreased FA and increased MD) compared to healthy controls; however, no significant differences were detected between groups. These results are consistent with other studies that did not find significant differences between individuals with SCD and healthy controls (Kiuchi et al., 2014; Viviano et al., 2019; Wang et al., 2016). However, the DTI results in this study are also in contrast with other research that found significant differences between those with SCD compared to healthy controls in white matter integrity. Specifically, these studies reported individuals with SCD showing decreased FA and increased MD in widespread regions compared to healthy controls (Hong et al., 2015; X.-Y. Li et al., 2016; Luo et al., 2020; Ohlhauser et al., 2019; Ryu et al., 2017; Shao et al., 2019).

The existing literature examining structural brain differences between individuals with and without SCD in grey matter volume and white matter microstructure has yielded mixed findings (Arrondo et al., 2022; Parker et al., 2022; Viviano & Damoiseaux, 2020). The discrepancy in results across studies can likely be attributed to methodological differences between studies such as variations in the operational definition of SCD used and the neuroimaging analysis approaches taken for each study (Hill et al., 2017; Molinuevo et al., 2017; Parker et al., 2022; X. Wang et al., 2020). Other differences in methodology that could impact findings include differences in APOE e4 status (Saykin et al., 2006), symptoms of anxiety (Kuhn et al., 2019), symptoms of depression (Kuhn et al., 2019; Meiberth et al., 2015; Scheef et al., 2019; Striepens et al., 2010) and recruitment source (Meiberth et al., 2015; Peter et al., 2014).

It is possible that the participants in the current study, community-dwelling women recruited for a study on healthy aging, represent individuals at the earliest stages of the cognitive continuum between normal cognition and dementia. Thus, differences in brain structure may not yet be detectable in these groups of women (Viviano & Damoiseaux, 2020). For instance, previous studies that recruited participants from memory clinics found significant differences between people with SCD and healthy controls in grey matter volume (Hafkemeijer et al., 2013; Kuhn et al., 2019; Liang et al., 2021; Ryu et al., 2017; Toledo et al., 2015) and white matter microstructure (Hong et al., 2015; X.-Y. Li et al., 2016; Liang et al., 2021; Luo et al., 2020; Ohlhauser et al., 2019; Ryu et al., 2017; Yasuno et al., 2015). It is possible that individuals with SCD who are recruited from memory clinics may experience greater levels of concern regarding their own cognition related to individuals with SCD who have not presented for medical follow-up for SCD. In order to better understand the reasons for these disparate findings, future studies should include detailed information on their participant sample and follow the research criteria outlined by the SCD-I (Jessen et al., 2014). Another strength of this study was the focus of SCD in women. Women have been reported to be at a greater risk for being diagnosed with AD, as approximately two-thirds of those diagnosed with AD are women (Alzheimer's Association, 2023). A study by Oliver et al. (2022) suggests that SCD may be a better predictor of future cognitive decline in women than men, as the results suggested that women with SCD experienced a steeper decline in cognition over a 15-year time period than their male counterparts with SCD and both men and women without SCD (Oliver et al., 2022). More research is needed to understand sex- and

gender-based differences in cognitive decline and progression of neurodegenerative diseases such as AD.

Interestingly, our group recently examined a subset of the current sample of women from the WHAP who had resting state fMRI data available, to investigate differences in functional connectivity between women with and without SCD. The results demonstrated significantly greater functional connectivity in the default mode network and frontoparietal network in women with SCD compared to healthy women (Parker et al., submitted). These findings of significant differences in brain function but not structure between women with SCD and healthy controls from the same sample highlights the importance of investigating functional connectivity alterations as a potential marker of future cognitive decline in individuals with SCD.

The current study had several limitations worth noting. First, the cross-sectional design limited our ability to track changes over time. A longitudinal analysis would provide valuable insights into whether changes in grey matter volume and/or white matter integrity manifest over time as participants progress further along the cognitive continuum (from healthy cognition to increasing cognitive impairment). A second limitation of this study was the small sample size. Although it is possible that the small sample size limited power to detect differences between groups in the current study, it is noteworthy that our sample size is in line with other recent studies on SCD (Parker et al., 2022). Third, our dataset lacked specific details about the nature of SCD symptoms experienced by participants. Having more detailed information on the specific symptoms, such as the duration of symptoms, would be of benefit to understanding the relationship between SCD symptomology and brain structure.

Future research should also continue to investigate other neuroimaging modalities that may be capable of differentiating healthy controls from individuals with SCD. In particular, changes in brain function may precede changes in brain structure, especially in individuals who are very early on the cognitive continuum between healthy cognition and severe cognitive impairments (Sun et al., 2016; Verfaillie et al., 2018; Viviano & Damoiseaux, 2020).

Conclusion

This current study adds to the existing body of literature that examines differences in brain structure between individuals with SCD and healthy controls. Following VBM and DTI analyses, our findings revealed no significant differences in either grey matter volume or white matter integrity between women with SCD and healthy women, all of whom were community-dwelling participants. While these results were not fully aligned with our hypotheses, our results may be explained by the composition of our sample. Our sample was comprised of women who are likely in very early stages on the cognitive continuum between healthy cognition and increasing cognitive impairments, where differences in brain structure are not yet observable. However, differences were found between groups when a subset of these participants were analyzed on resting-state functional connectivity through fMRI (Parker et al., submitted). These results highlight the importance of studying different neuroimaging modalities in the same participant sample as differences in brain structure may not be readily detectable at initial stages of cognitive decline whereas differences in brain function may be able to provide valuable insights in distinguishing individuals with SCD from healthy controls. Overall, early identification of changes in brain-based biomarkers that may indicate an increased risk of

developing AD in the future may allow for the implementation of preventative measures that will lead to improved quality of life for aging individuals.

Concluding Remarks

Each of the three studies presented in this manuscript-based dissertation sought to investigate whether neuroimaging is capable of detecting brain-based differences between individuals who report SCD and healthy individuals who do not. This program of research was developed in the context of the late clinical diagnosis that is associated with neurodegenerative disorders such as AD and other dementias. In this dissertation, I evaluated the recent literature pertaining to SCD and neuroimaging as well as conducted multi-modal MRI investigations to evaluate the use of structural and functional MRI in the detection of brain-based differences between women with SCD and women without. Given that older women are at an increased risk for developing AD, our primary research focused on women.

Study 1 was a systematic review focused on neuroimaging studies comparing individuals with SCD and healthy controls. The neuroimaging modalities included in this study were anatomical MRI, DTI, fMRI, multi-modal MRI, PET, MRI & PET, EEG, MEG, and SPECT. This study sought to answer a series of research questions related to the use of neuroimaging in the differentiation of these groups. The results of this systematic review indicated that each of the neuroimaging modalities could differentiate those with SCD from healthy controls. Common findings were seen within neuroimaging approaches, particularly for structural imaging. Across structural MRI studies, atrophy was seen in regions that are consistent with early AD, however, atrophy was seen in additional areas including frontal regions and widespread white matter tracts. For functional studies, similar findings were seen for studies that utilized similar methods, however, findings were unique for studies with differing analysis techniques. Although

the use of fMRI biomarkers is not currently incorporated in the framework set out by the NIA-AA (Jack et al., 2018), the study of preclinical AD using fMRI is an emerging area of research. In this systematic review, those with SCD showed decreases in functional connectivity in the DMN which is consistent with what is seen in those with AD. In contrast with results from previous fMRI studies focused on individuals with AD, increases in functional connectivity in frontal regions were detected in those with SCD. After the synthesis of the 62 neuroimaging studies focused on the comparison of SCD and healthy controls, it was apparent that there were several methodological differences across studies that could explain the discrepant findings within imaging modalities. These methodological differences included variations in the definition and characterization of SCD, participant recruitment location, consideration of participant's APOE e4 status, study design, and inclusion/exclusion criteria. Following standardized research practices outlined by the SCD-Initiative (Jessen et al., 2020; Jessen et al., 2014) such as the use of standardized terminology and group classification of individuals with SCD will be important in contextualizing the composition of SCD cohorts across research studies moving forward.

Study 2 investigated whether resting state functional connectivity differed between women with SCD and women without SCD, across the default mode network (DMN), frontoparietal network (FPN), and the salience network (SN). We also explored whether these groups differed across various demographic variables, lifestyle factors, and medical comorbidities. It was hypothesized that 1) women with SCD would show differences in resting-state functional connectivity compared to healthy women and 2) that minimal differences would be observed between groups across the various

demographic variables, lifestyle factors, and medical comorbidities examined. The results of this study found increased functional connectivity in women with SCD relative to healthy women in the DMN and FPN. No decreases in functional connectivity were seen in women with SCD compared to healthy women. There were no significant differences in functional connectivity seen between groups in the SN. Further, no differences were seen between the two groups for any of the demographic variables, lifestyle factors, and medical factors evaluated. Notably, these groups only differed on their self-report of SCD. Thus, women with SCD displayed increased functional connectivity in the DMN and FPN relative to healthy women. These findings of increased functional activity, in the context of functional compensation mechanisms, are consistent with the STAC-R (Reuter-Lorenz & Park, 2014) and PASA (Davis et al., 2007) models of cognition. These results provide valuable insights into the neural mechanisms underlying SCD and highlights the utility of resting-state fMRI for the advancement of understanding preclinical manifestations of AD such as SCD.

Study 3 was a multi-modal investigation examining differences in grey matter volume (measured by VBM) and white matter microstructure (measured by DTI) between women with SCD and women without. Notably, there was an overlap of 50 participants between Study 2 and the total 82 participants in Study 3. First, it was hypothesized that no significant differences in grey matter volume would be detected between women with SCD and healthy women. Second, it was hypothesized that women with SCD would demonstrate lower FA and higher MD in white matter microstructure compared to healthy women. Neither of these structural analyses yielded significant findings between groups. The results from this study demonstrate that structural

neuroimaging techniques such as VBM and DTI may not be able to differentiate women with SCD from healthy women, particularly in participants who are community-dwelling. It is possible that community-dwelling participants who report SCD, such as the women in this study, represent those who are in the very early stages of cognitive decline where differences in brain structure are not yet discernable from healthy controls.

Strengths

There are notable strengths throughout this dissertation. In terms of study 1, the literature review that I presented was comprehensive, including not only magnetic resonance imaging but all available neuroimaging techniques that have been used to compare those with SCD to healthy controls. Another key strength of this work was the incorporation of the various terminologies that have been used to describe SCD. This approach ensured that relevant results were not overlooked due to the methodological differences across studies.

With regards to studies 2 and 3, a major strength and novel contribution was the application of multimodal neuroimaging analyses of the same subset of participants from the WHAP. This approach allowed for the identification of which MRI technique was effective in differentiating women with SCD from healthy women. Notably, this type of examination is not possible in many other large databases, such as the Alzheimer's Disease Neuroimaging Initiative database, because each participant has only undergone one type of imaging acquisition (e.g. DTI or fMRI, but not both). Within these studies, the analyses also underwent a high level of quality control. For example, the preprocessing step of brain extraction used in studies 2 and 3 were conducted individually for each participant. This tailored approach allowed for optimization of the

neuroimaging data that was used in each analysis. It is not uncommon for standardized automated preprocessing pipelines to be used in preparing neuroimaging data for analysis, however, the use of standardized brain extraction parameters for all participants can yield suboptimal preprocessed data due to the lack of consideration of individual variability seen across participants. Despite being time-intensive, optimizing the brain extractions ensured that our analyses utilized accurate and complete neuroimaging data for each participant which leads to increased confidence in the resulting findings.

Another noteworthy strength of studies 2 and 3 is that women participants were drawn from the WHAP database. The WHAP database collected multimodal neuroimaging data as well as detailed information on various demographic variables, lifestyle factors, and medical comorbidities. The availability of this data allowed for studies 2 and 3 to conduct additional analyses to determine whether women with SCD differed from healthy women based on these factors. This represents a significant strength of the WHAP database as such detailed participant information is often unavailable in other datasets. As it was confirmed that there were no significant differences between the groups based on the included demographic variables, lifestyle factors, and medical comorbidities in both studies 2 and 3, the findings of increased functional connectivity in women with SCD compared to healthy women suggests that the findings are attributed to the presence of SCD rather than the impacts of another variable.

Finally, studies 2 and 3 focused specifically on women. Given that women have historically been underrepresented in medical research, the focus on women in this dissertation addresses a significant research gap. By studying women, these papers

contribute to a more comprehensive, inclusive, and equitable understanding of the global health challenges posed by AD, particularly considering the disproportionate impact of this condition on women.

Limitations

Although there were multiple strengths to the research studies presented in this dissertation, several limitations to the present work must be acknowledged.

In terms of the systematic review, the comprehensive capture of neuroimaging techniques was a strength, but also created challenges. In particular, synthesizing the literature and determining generalizable findings was difficult due to the multitude of methodological differences between studies. Nevertheless, the review highlighted the importance of operationalizing SCD and how varied methodological approaches can contribute to variance in the results within neuroimaging techniques.

A limitation of both studies 2 and 3 was the relatively small sample size; however, the maximum number of participants from the WHAP dataset who met the criteria were included. The sample sizes in these studies were also comparable to the sample sizes of other neuroimaging studies.

Both studies 2 and 3 used a cross-sectional research design. The use of a cross-sectional design limits the ability to understand which women with SCD progress to MCI or AD. Future studies may benefit from utilizing longitudinal designs that could allow for the evaluation of changes in brain function or structure over time. This, in turn, could aid in the identification of those with SCD who subsequently develop MCI or AD.

Although studies 2 and 3 included detailed information regarding demographic variables, lifestyle factors, and medical comorbidities, the dataset did not collect specific

information regarding participants' experience of SCD, such as SCD-plus variables that have been outlined by the SCD-Initiative (Jessen et al., 2020; Jessen et al., 2014). Access to such information could provide researchers with deeper insights into their study groups and advance the understanding of SCD-plus criteria and its potential implications for future cognitive decline.

Lastly, studies 2 and 3 focused on the study of SCD in women from a western, educated, industrialized, rich, and democratic (WEIRD) population (community-dwelling women in Australia). Although individuals from WEIRD populations are often those who make up the participants of medical, psychological, and behavioural research, the experiences of individuals from WEIRD populations are not readily generalizable to other global populations (Henrich et al., 2010). Future research would benefit from continued study in SCD outside of WEIRD populations to better understand the prevalence of SCD and risk of future dementia in populations with lower socioeconomic resources. By focusing on the study of individuals outside of WEIRD populations, it is hypothesized that such efforts will enhance the quality and generalizability of research findings while simultaneously promoting equity, inclusivity, and global relevance.

Future Directions

Replication of neuroimaging findings across modalities is necessary. In order to replicate findings, it will be important for researchers to explore the demographic variables, lifestyle factors, and medical comorbidities that may be present in their participants. Many studies have reported demographic variables such as age, sex, and education, however, very few studies have reported on other participant characteristics, characteristics that may otherwise explain the observed differences or absence thereof

between those with SCD compared to healthy controls in neuroimaging analyses. More information is also needed about participants and their experience of SCD and symptoms. This includes length of time with SCD, age of onset, concerns related to experience of SCD, and specifically self-reporting a worsening in their memory skills (Jessen et al., 2020; Jessen et al., 2014). Including information on the presence of APOE e4 will also be an important variable to include moving forward. Future studies should also employ multi-modal neuroimaging in the same participants; this approach will help advance the understanding of which neuroimaging modalities are most effective at detecting differences between those with SCD and those without. Conducting different neuroimaging modalities on the same participants will be imperative. Without this level of comparability, it will remain unclear whether observed group differences are attributed to the neuroimaging modality used or to other factors, such as demographic variables, lifestyle factors, or medical comorbidities. As seen in studies 2 and 3, findings revealed significant differences between groups solely based on reports of SCD from in healthy community-dwelling women. There was overlap in the participants who underwent structural and functional neuroimaging in Studies 2 and 3. Women with SCD showed alterations in functional connectivity while no differences were observed in structural analysis of grey matter and white matter. Moving forward, longitudinal analyses will provide valuable insights into SCD and its associated course. Currently, there is limited knowledge about who is most at risk for the future development of AD. Longitudinal studies may assist researchers in identifying individuals at higher and lower risk of future development of AD, potentially informing the timing of interventions before significant and irreversible neurodegeneration has occurred.

Conclusion

As the world's population continues to rapidly age, it is crucial to identify those who are most at risk of developing age-related disorders such as AD. The studies conducted in this dissertation were designed to contribute to our understanding of earlier detection of AD, particularly in individuals with SCD compared to their healthy counterparts, using multimodal MRI. Study 1 demonstrated that various neuroimaging modalities are capable of distinguishing individuals with SCD from healthy controls. The results of studies 2 and 3 revealed changes in brain function but not structure in women with SCD compared to healthy women. Notably, no other differences were found between these groups on various demographic variables, lifestyle factors, and medical comorbidities – these groups only differed by the participant's report of SCD (suggestive of a preclinical manifestation of AD). The finding of differences in brain function prior to brain structure in women with SCD compared to their healthy counterparts is an important realization. This finding suggests that women with SCD can be differentiated from healthy women, before any significant and irreversible brain atrophy has taken place. Ultimately, ongoing research and advancements in the conceptualization of earlier detection of AD are expected to play an important role in the development and implementation of disease-modifying interventions at the earliest possible time point, thereby reducing the devastating effects of this neurodegenerative disorder.

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Appendix

Appendix 1

Search Terms

S1

("subjective cognitive decline" OR "subjective memory complain*" OR "subjective memory impairment" OR "subjective cognitive complain*" OR "subjective cognitive impairment" OR "prodromal Alzheimer's disease" OR "preclinical Alzheimer's disease" OR "preclinical dementia" OR "memory complain*" OR "subjective memory loss" OR "subjective cognitive concern*")

S2

("MRI" or "magnetic resonance imaging" OR "fMRI" OR "functional magnetic resonance imaging" OR "DTI" OR "diffusion tensor imaging" OR "DSI" OR "diffusion spectrum imaging" OR "EEG" OR "electroencephalography" OR "ERP" OR "event related potential" OR "electrophysiological imaging" OR "MEG" OR "magnetoencephalography" OR "fNIRS" OR "function near-infrared spectroscopy" OR "PET" OR "positron emission tomography" OR "SPECT" OR "single photon emission computed tomography" OR "CT" OR "computed tomography" OR "BOLD" OR "blood oxygen level dependent" OR "amyloid PET")

S3

((((DE "Magnetic Resonance Imaging" OR DE "Diffusion Tensor Imaging" OR DE "Functional Magnetic Resonance Imaging") OR (DE "Electroencephalography" OR DE "Alpha Rhythm" OR DE "Beta Rhythm" OR DE "Delta Rhythm" OR DE "Gamma Rhythm" OR DE "Theta Rhythm"))) OR (DE "Magnetoencephalography")) OR (DE "Positron Emission Tomography")) OR (DE "Single Photon Emission Computed Tomography")

S4

S2 OR S3

S5

S1 AND S4

S6

S5 NOT ((epilepsy OR "multiple sclerosis" OR "parkinson's disease" OR "frontotemporal dementia"))

S7

S6 Limiters - Scholarly (Peer Reviewed) Journals; Language: English; Age Groups: Middle Age (40-64 yrs), Aged (65 yrs & older), Very Old (85 yrs & older); Population Group: Human; Methodology: BRAIN IMAGING
Search modes - Find all my search terms