Journal of Alzheimer's Disease 77 (2020) 1067–1076
DOI 10.3233/JAD-200299
IOS Press

Identification of Earlier Biomarkers for Alzheimer's Disease: A Multimodal Neuroimaging Study of Individuals with Subjective Cognitive Decline

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Handling Associate Editor: Andrew Saykin

Accepted 30 June 2020

Abstract.
Background: Individuals with subjective cognitive decline (SCD) are thought to be the earliest along the cognitive continuum between healthy aging and Alzheimer's disease (AD).
Objective: The current study used a multi-modal neuroimaging approach to examine differences in brain structure and function between individuals with SCD and healthy controls (HC).
Methods: 3T high-resolution anatomical images and resting-state functional MRI scans were retrieved for 23 individuals with SCD and 23 HC from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database.
Results: The SCD and HC groups were not significantly different in age or education level. Voxel-based morphometry results did not show significant differences in grey matter volume between the groups. Functional MRI results revealed significantly greater functional connectivity in the default mode network in regions including the bilateral precuneus cortex, bilateral thalamus, and right hippocampal regions in individuals with SCD relative to controls. Conversely, those with SCD showed decreased functional connectivity in the bilateral frontal pole, caudate, angular gyrus, and lingual gyrus, compared to HC.
Conclusion: Findings revealed differences in brain function but not structure between individuals with SCD and HC. Overall, this study represents a crucial step in characterizing individuals with SCD, a group recognized to be at increased risk for AD. It is imperative to identify biomarkers of AD prior to significant decline on clinical assessment, so that disease-delaying interventions may be delivered at the earliest possible time point.

Keywords: Alzheimer's disease, magnetic resonance imaging, neuroimaging, subjective cognitive decline

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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INTRODUCTION

Globally, the number of individuals aged 60 and older is expected to double to nearly 2.1 billion by 2050 [1]. Although increased longevity can create opportunities for positive and active community engagement for older adults, these opportunities can be hampered by health issues associated with aging. Indeed, research suggests that age is the strongest risk factor for the development of Alzheimer's disease (AD), the most common form of dementia [2]. Mirroring the aging population, the number of individuals with dementia, currently estimated at 50 million, is expected to reach 131.5 million by 2050 [3].

AD is a neurodegenerative disorder which includes clinical impairments in memory and other cognitive domains (e.g., executive functions) [4]. In addition to impairing the patient's quality of life, AD can lead to burdens for caregivers [5], and economic consequences, societally [6]. At this time, there is no cure for AD and the available pharmacological treatments only provide temporary symptomatic relief [7]. Unsuccessful clinical trials aimed at decelerating the progression of AD at the mild to moderate stages have fostered increasing interest in the earlier preclinical stages of AD [8]. Therefore, a major aim is to identify individuals who are likely to progress to AD before measurable symptoms develop and there is evidence that studying individuals with subjective cognitive decline (SCD)—who are considered to fall earlier along the continuum between healthy aging and mild cognitive impairment (MCI)—can advance this objective.

Individuals with SCD have a self-perceived decline in one or more cognitive domains, but perform within normal limits on standardized neuropsychological assessment [9]. Importantly, research to date has found that as many as 60% of individuals with SCD are likely to convert to a diagnosis of MCI and AD over a 15-year period [10]. In light of these findings, the International Working Group (IWG), US National Institute of Aging – Alzheimer's Association (NIA-AA), and SCD-Initiative (SCD-I) agree that this pre-clinical stage of AD is likely to have detectable biomarkers [11–13].

An ideal biomarker for AD at the stage of SCD would be non-invasive and easily repeatable, as is magnetic resonance imaging (MRI). To date, the vast majority of MRI-based research on SCD has focused on changes in brain structure. This is likely because the gold standard MRI biomarker for AD is based on the identification of atrophy in medial temporal lobe structures [14]. Similar studies focused on individuals with SCD have revealed atrophy in multiple grey matter structures, including the hippocampus [15, 16], left medial frontal gyrus [16], right precentral gyrus [16], entorhinal cortex [17, 18], and the amygdala [17]. However, findings have been mixed, with some studies finding no differences between individuals with SCD and healthy controls [19].

An additional potential MRI biomarker, which has been less studied, is functional connectivity [11]. Early on in the disease process of AD, the brain may be able to functionally compensate for neuropathological changes, allowing an individual to perform within normal limits on standardized cognitive testing [13]. As a result, it is possible that such changes in function, as measured by functional MRI (fMRI), may be detectable prior to changes in brain structure. While many methods exist to study functional connectivity, a common approach uses a seed-based analysis. This type of analysis identifies functional connectivity in regions of the brain that are correlated with the seed region [20]. The posterior cingulate cortex is a common seed or region of interest (ROI) that has been used to study alterations in functional connectivity in the default mode network (DMN) [21–25] and applied in individuals with early AD [21, 26–28].

Thus far, few studies have examined both brain structure and function in individuals with SCD. Notably, Wang et al. [19] and Hafkemeijer et al. [29] examined both brain atrophy and resting state functional connectivity in individuals with SCD compared to healthy controls with mixed results. Specifically, Wang and colleagues [19] found that individuals with SCD had no significant differences in brain structure, but decreased DMN connectivity, relative to healthy controls. In contrast, Hafkemeijer et al. [29] found that individuals with SCD showed structural atrophy in regions including the right amygdala, bilateral precuneus, cuneus, anterior cingulate cortex, and medial prefrontal cortex along with increased levels of functional connectivity in the DMN compared to healthy controls. It has been posited that increased functional connectivity is related to compensation, which helps individuals with SCD maintain cognitive scores within normal limits as measured by neuropsychological assessments [30]. Others have suggested that the cause of these alterations in functional connectivity may be attributed to a compensatory mechanism that is enacted when there is a failure of proper functioning within medial temporal regions [31]. The Scaffolding Theory of Aging and Cognition (STAC) [32, 33]

also describes functional compensation mechanisms (increased functional connectivity) to possibly assist in maintaining normal cognitive status in individuals with structural atrophy. Further investigations of functional connectivity using resting state fMRI are needed to evaluate its utility in early detection of AD.

Taken together, more research is needed that uses a multimodal approach in the same individuals to better understand the relationship between brain structure and function and what each technique may contribute to understanding biomarkers for SCD. Based on both the findings of previous studies and theoretical models, we expected those with SCD to 1) show regional atrophy compared to healthy controls, and 2) show increased resting state fMRI functional connectivity in the DMN compared to healthy controls.

METHODS

Data collection

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

Participant selection

All participants were selected from the ADNI-2 database. The SCD group was drawn from the significant memory complaints (SMC) cohort that was included in ADNI-2 to focus on the gap between healthy elderly controls and individuals with MCI. A total of 23 individuals with SCD (mean age = 72.9 years, SD = 5.4) and 23 healthy elderly controls (mean age = 74.3, SD = 5.0) were included. The current sample is thought to be representative of the broader ADNI groups, as both the SCD and healthy elderly control groups are predominantly comprised of participants in the 70–79 years age range; consistent with the mean age values for these groups in this study.

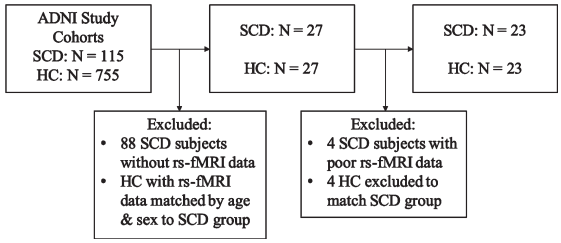

Fig. 1. Flow diagram of participant selection. ADNI, Alzheimer's Disease Neuroimaging Initiative; SCD, Subjective Cognitive Decline; HC, Healthy Controls.

Table 1
Participant Demographics

	HC	SCD	HC versus SCD
Age	74.3 ± 5.0	72.9 ± 5.4	$p = 0.39$
Years of Education	16.0 ± 2.5	16.7 ± 3.0	$p = 0.35$
APOE ε4 (ε4 + /ε4–)[†]	6/14	7/15	
Sex (M/F)	11/12	11/12	

HC, healthy controls; SCD, Subjective Cognitive Decline. [†]Missing data of 4 participants (3 HC, 1 SCD).

The ADNI database recruits participants from 57 sites across Canada and the United States of America. In this study, the SCD group was comprised of subjects from 9 sites and healthy controls from 11 sites. The ADNI database consists of over 2,500 individuals with varying diagnoses. The final sample size for the current study included the maximum number of participants that met the inclusion criteria (those in the SMC group that had both structural and functional MRI data). Please see Fig. 1 for a flow chart of participant selection and Table 1 for participant demographics. For more information on group classifications, including all additional eligibility criteria, please consult the ADNI-2 procedures manual [34].

Image acquisition

MRI data were retrieved from the ADNI-2 database. All images were acquired on 3 Tesla Philips MRI scanners. Whole-brain anatomical MRI scans were acquired sagittally, with a T1-weighted MPRAGE sequence, with the following parameters: a repetition time (TR) of 7 ms, an echo time of 3 ms, voxel size of $1 \times 1 \times 1.2$ mm, and a flip angle of 9°. fMRI scans were obtained during resting state (with eyes open). Resting state fMRI scans were 7

min in duration and obtained with a T2*-weighted echo-planar imaging sequence with the following parameters: a repetition time of 3000 ms, an echo time of 30 ms, 140 volumes, 48 slices, voxel size of $3.3 \times 3.3 \times 3.3$ mm, and a flip angle of 80°.

Data analysis

Image preprocessing

All data obtained from the ADNI database were in DICOM format. All structural and functional images were converted from DICOM to NIFTI format using dcm2niix in the MRIcroGL application [35]. 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) [36]. Non-brain tissue in the raw T1 images was removed using the automated Brain Extraction Tool [37], followed by manual verification and optimization for each subject.

VBM analysis

A structural whole brain VBM analysis was conducted to compare grey matter densities between individuals with SCD and healthy controls. The brain extracted images were segmented into grey matter, white matter, and cerebrospinal fluid, based on voxel intensity, and a study-specific grey matter template was created. Next, the grey matter probability images were affine-registered (with FSL's FLIRT) to the GM ICBM-152 and then re-registered to the affine GM template using non-linear registration (with FSL's FNIRT) and the native grey matter images were non-linearly registered to the created study-specific template. Following this step, the images were smoothed (3 mm) and the randomize function was run (for permutation testing). Within FSL, a general linear model (GLM) approach was implemented to compare those with SCD to the healthy controls and differences were examined at the $p < 0.05$ level with threshold free cluster enhancement (corrected for multiple comparisons).

Seed-based resting state fMRI functional connectivity analysis

A seed-based approach was used to examine functional connectivity in the DMN. The FEAT function was used to pre-process the data including skull removal (using the Brain Extraction Tool [37]), motion correction (using MCFLIRT [38]), and high-pass temporal filtering (using Gaussian-weighted least-squares straight line fitting with $\sigma = 50.0$ s). No smoothing was applied. Registration of the functional data to the high-resolution structural image was carried out using the boundary-based registration algorithm [39]. Registration of the high-resolution structural images to standard space was carried out using FLIRT [38, 40] and then further refined using FNIRT nonlinear registration [41, 42]. Next, the posterior cingulate cortex region of interest (ROI or seed) was registered to individual space. This ROI/seed was created based on ROIs from previous studies and included a 10-voxel spherical ROI was created centered on the following MNI coordinates: –2, –51, 27 [43, 44]. The FEAT function was used to examine the DMN, the posterior cingulate cortex ROI/seed and to regress out the lateral ventricle signal to correct for confounding noise. Specifically, the mean blood oxygen level-dependent signal time series was extracted from the posterior cingulate seed region and used as the model response function in a general linear model analysis. This allowed for examination of functional connectivity in the DMN through the detection of voxels with timeseries that correlate with that measured in the posterior cingulate seed. The time-series statistical analysis was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction [45].

Finally, a higher-level between-group analysis was conducted to compare resting state functional connectivity in the DMN between the SCD group and controls. The higher-level analysis was carried out using a fixed effects model, by forcing the random effects variance to zero in FLAME (FMRIB's Local Analysis of Mixed Effects) [46–48]. Z (Gaussianised T/F) statistic images were thresholded non-parametrically using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $p = 0.05$ [49].

RESULTS

VBM

The VBM analysis did not reveal any significant differences between those with SCD relative to healthy controls in grey matter density ($p = 0.18$).

Functional connectivity

The SCD group showed both increased and decreased functional connectivity in different regions of the DMN compared to healthy controls (Fig. 2). Specifically, cluster-level group comparisons

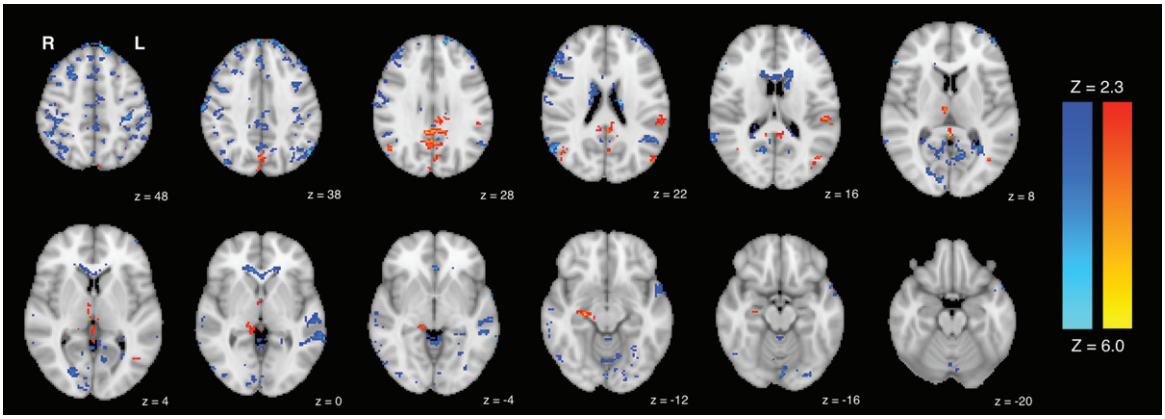

Fig. 2. Results of group level comparisons showing significant functional connectivity in the DMN in those with SCD relative to healthy controls. The color red represents increased functional connectivity and blue represents decreased functional connectivity in the DMN in those with SCD compared to healthy controls.

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

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

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

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

revealed that individuals with SCD have increased functional connectivity compared to healthy controls in the right hippocampus and right posterior division of the parahippocampal gyrus, bilaterally in the thalamus and precuneus cortex (see Table 2 for peak coordinates). In contrast, those with SCD exhibited decreased functional connectivity compared to healthy controls in the right superior frontal gyrus, right occipital pole, and right superior temporal gyrus, left superior temporal gyrus in the posterior division, left precuneus cortex, left precentral gyrus, left occipital fusiform gyrus, left temporal pole, and left cerebellum. Lastly, healthy controls displayed bilateral increases in functional connectivity in the frontal pole, caudate, angular gyrus, and lingual gyrus relative to healthy controls (see Table 3 for peak coordinates of these areas). To further illustrate group differences, Fig. 3 displays boxplots of mean z scores for each subject that were extracted from clusters that were activated at a threshold of $Z > 2.3$.

DISCUSSION

The present study represents a valuable step toward characterizing brain structure and function in SCD. The first hypothesis was that there would be decreased brain tissue density in those with SCD compared to healthy controls; however, no significant differences were detected between these groups. The second hypothesis was that there would be

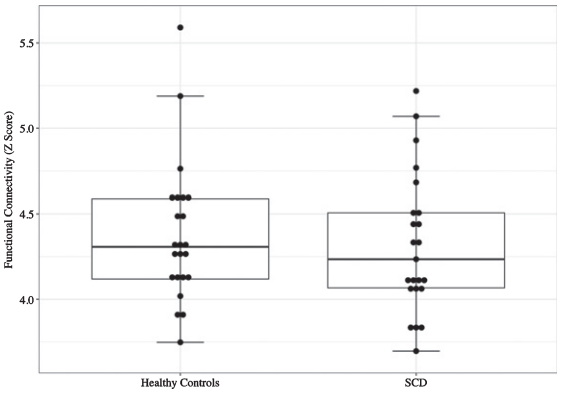

Fig. 3. Boxplots of functional connectivity for the DMN in SCD and healthy controls. For each subject, mean z scores were extracted from clusters that were activated at a threshold of $Z > 2.3$. Boxplots show median, lower and upper quartile, and sample minimum and maximum.

increased resting state fMRI functional connectivity in the DMN in those with SCD compared to healthy controls; the results revealed both increased and decreased functional connectivity between the groups in specific regions. These results are further discussed in the context of the existing literature below.

VBM

The structural analyses did not reveal any differences in the density of grey matter in individuals with SCD compared to healthy controls. These findings are consistent with several other studies that investigated brain structure in SCD and did not detect atrophy [19, 50]. In contrast, Saykin et al. [16] found bilateral medial temporal atrophy in individuals with SCD and MCI compared to healthy controls. Furthermore, the current findings are in contrast with several other studies that found reductions in the volume of the entorhinal cortex [17, 18, 51], hippocampus [15, 16, 51], left medial frontal gyrus [16], right precentral gyrus [16], and the amygdala [17], specific to individuals SCD. It is likely that these mixed reports are due to methodological differences across studies, particularly with regards to sample characteristics. For instance, Wang et al. [19] showed no significant differences between individuals with SCD and healthy controls in grey matter structure; however, the groups were not significantly different in age, sex, education, or *APOE* ε4 status (similar to the current study). In comparison, the aforementioned study by Saykin et al. [16], which detected grey matter atrophy in individuals with SCD, included significantly more females (28 females to 12 males). A more recent study by Wang et al. [19] specifically investigated sex differences in those with SCD and found females with SCD to show increased atrophy in the entorhinal cortex, medial temporal lobes, hippocampus, and fusiform compared to their male counterparts; therefore, it is possible that sex differences have led to mixed findings between studies. Similarly, other studies with positive findings have had significant differences between their groups of interest in terms of recruitment source [18, 51], *APOE* ε4 status [16], and indices of depression symptoms [18]. Another important source of variability between studies relates to the characterization of the SCD group. In particular, some studies define SCD by broadly asking one question about subjective concerns [15, 51], while others involve full questionnaires and/or informant reports [16, 18, 19]. This issue has led the SCD-I to codify "SCD-plus": a group with elevated risk specific for AD based on factors such as *APOE* ε4 status and subjective decline in memory, as opposed to other domains of function; providing an important framework for moving forward [9].

Functional connectivity

Given that changes in brain function may precede measurable changes in brain structure, the current study also examined differences in functional connectivity in the DMN between individuals with SCD and healthy controls. Results revealed that individuals with SCD have regional increased and decreased resting state functional connectivity compared to healthy controls. Specifically, areas of increased functional connectivity included the right hippocampus, right posterior division of the parahippocampal gyrus, bilateral thalamus, and bilateral precuneus cortex. The latter findings are consistent with those of Hafkemeijer and colleagues [29] who found increased functional connectivity in similar areas in those with SCD compared to healthy controls. Chiesa et al. [52] found increased resting state functional connectivity between the anterior basal forebrain and posterior cingulate cortex as well as between the posterior basal forebrain and the postcentral gyrus, dorsal cingulate cortex, temporal cortex, and anterior insulae.

Interestingly, Sperling et al. [53] demonstrated a positive relationship between increased functional connectivity in the precuneus and posterior cingulate and amyloid-β levels, a known neuropathological biomarker related to AD. In general, these findings are congruent with other studies showing increased

functional connectivity across the DMN in other cognitively normal individuals who also possess risks of developing AD, such as those with autosomal dominant AD mutation carriers [54], *APOE* ε4-carriers [55], and individuals with high levels of amyloid-β deposition [53].

Unexpectedly, the present study also revealed areas of decreased functional connectivity in the DMN, specific to the right superior frontal gyrus, right occipital pole, right superior temporal gyrus, left superior temporal gyrus in the posterior division, left precuneus cortex, left precentral gyrus, left occipital fusiform gyrus, left temporal pole, and left cerebellum, as well as bilateral decreases in the frontal pole, caudate, angular gyrus, and lingual gyrus. The findings of the current study contrast those of Hafkemeijer et al. [29], Chiesa et al. [52], and Sperling et al. [53] as these studies did not find the SCD group to show decreased functional connectivity at resting state compared to healthy controls. However, there are several reports in the literature of decreased connectivity in the DMN in specific regions when individuals with SCD are compared to healthy controls. In particular, Wang and colleagues [19] found decreased connectivity in the right hippocampus and Viviano et al. [56] described decreased connectivity across regions within the posterior memory system as well as between the lower retrosplenial cortex and precuneus in those with SCD compared to healthy controls. It has been theorized that decreases of functional connectivity seen in later stages of AD may be preceded by past evidence of increased functional connectivity that seemed to be a compensatory mechanism at one point in time [57]. Hence, it is thought that when the threshold of neuronal damage is met, an individual with SCD will transition to MCI as they are no longer able to compensate functionally and begin to show objective cognitive impairment [58, 59]. Within this theoretical context, the regions with decreased connectivity may represent areas throughout the DMN that are no longer able to compensate.

Notably, a number of studies have found contrasting results regarding functional connectivity in those with SCD compared to HC. For example, Hu et al. [60] found both increased functional connectivity between the midline core network and superior medial frontal cortex and decreased functional connectivity between the dorsal medial prefrontal subnetwork and the right hippocampus. A graph theory study by Li et al. [30] found increased levels of degree centrality in the medial temporal lobe and decreased degree centrality in the inferior parietal gyrus. Another investigation by Dong et al. [50], found individuals with SCD to show increased relative functional connectivity strength in the left posterior cingulate cortex and precuneus, as well as increased absolute functional connectivity strength in regions associated with the DMN. In light of the mixed findings in this area, further investigation of altered functional connectivity will be an important step in characterizing these early changes in the brain related to AD. In particular, longitudinal studies that track conversions from SCD to MCI will be helpful in characterizing the expected patterns of change in functional connectivity along the continuum of AD.

Limitations and future directions

The present study had several limitations. First, the sample size was relatively small. Although the sample size within this study is not out of the norm for neuroimaging studies investigating SCD, it would be valuable to expand the sample size to increase the generalizability of the findings to the greater population. Second, this study was cross-sectional, in the future it would be valuable to conduct these types of analyses longitudinally to investigate which individuals with SCD are most at risk of converting to a diagnosis of MCI or AD. Third, this study did not examine differences in AD biomarkers, such as *APOE* ε4, amyloid-β, and tau levels across the SCD participants. Incorporating these biomarkers of AD pathogenesis in individuals with SCD would be useful to determine if these individuals with this subjective change in cognitive abilities are in fact presenting with the hallmark biomarkers of AD.

In light of the limitations of the current study, there are multiple directions for future research. First, additional research is needed on larger sample sizes to better characterize *in vivo* biomarkers in SCD (with greater power and generalizability). These investigations should use the SCD-Plus framework and take a longitudinal approach to understand differences between those who convert and those who are stable over time.

Second, future research should use multi-modal approaches to look at differences between individuals with SCD and healthy controls in multiple functional connectivity networks (e.g., frontoparietal and salience networks). Studying structural and functional connectivity in the same individuals will be key for understanding the earliest changes in the brain that are related to AD pathology. Along with multimodal neuroimaging approaches, future studies

should also examine differences in AD biomarkers, such as *APOE* ε4, amyloid-β, and tau levels and sex differences in SCD participants. Incorporating these biomarkers of AD pathogenesis in individuals with SCD would be useful to determine if these individuals with this subjective change in cognitive abilities are in fact presenting with the hallmark biomarkers of AD.

Third, previous studies that have hypothesized increased functional connectivity to reflect a compensatory mechanism in early AD are becoming dated. Future studies should be conducted to replicate these findings to strengthen this hypothesis.

Fourth, future studies would benefit from comparing additional groups along the AD continuum, including healthy controls, SCD, MCI, and AD groups. Examining multiple groups along the AD continuum could help to identify subtle differences between these different stages that we would otherwise not see when only looking at a subset of groups along this continuum.

Conclusion

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

ACKNOWLEDGMENTS

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (http://www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. Funding for secondary analyses of the ADNI database was supported by the University of Victoria and the Canada Graduate Scholarship Masters Award.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/20-0299r1).

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