Archival Report

Biological Psychiatry: CNNI

Subjective Cognitive Decline Is Associated With Altered Default Mode Network Connectivity in Individuals With a Family History of Alzheimer's Disease

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ABSTRACT

BACKGROUND: Both subjective cognitive decline (SCD) and a family history of Alzheimer's disease (AD) portend risk of brain abnormalities and progression to dementia. Posterior default mode network (pDMN) connectivity is altered early in the course of AD. It is unclear whether SCD predicts similar outcomes in cognitively normal individuals with a family history of AD.

METHODS: We studied 124 asymptomatic individuals with a family history of AD (age 64 ± 5 years). Participants were categorized as having SCD if they reported that their memory was becoming worse (SCD^+). We used extensive neuropsychological assessment to investigate five different cognitive domain performances at baseline (n = 124) and 1 year later (n = 59). We assessed interconnectivity among three a priori defined ROIs: pDMN, anterior ventral DMN, medial temporal memory system (MTMS), and the connectivity of each with the rest of brain.

RESULTS: Sixty-eight (55%) participants reported SCD. Baseline cognitive performance was comparable between groups (all false discovery rate-adjusted p values $> .05$). At follow-up, immediate and delayed memory improved across groups, but the improvement in immediate memory was reduced in SCD^+ compared with SCD^- (all false discovery rate–adjusted p values $< .05$). When compared with SCD^-, SCD^+ subjects showed increased pDMN–MTMS connectivity (false discovery rate–adjusted $p < .05$). Higher connectivity between the MTMS and the rest of the brain was associated with better baseline immediate memory, attention, and global cognition, whereas higher MTMS and pDMN–MTMS connectivity were associated with lower immediate memory over time (all false discovery rate–adjusted p values $< .05$).

CONCLUSIONS: SCD in cognitively normal individuals is associated with diminished immediate memory practice effects and a brain connectivity pattern that mirrors early AD-related connectivity failure.

Keywords: Alzheimer's disease, Cognition, Default mode network connectivity, Family history of dementia, Resting-state functional MRI, Subjective cognitive decline

https://doi.org/10.1016/j.bpsc.2017.11.012

Subjective experience of cognitive decline (SCD) and a family history of Alzheimer's disease (AD) are two risk factors for dementia. SCD is associated with a three- to sixfold increased risk of clinical progression to dementia in cognitively normal individuals (1), whereas a family history of AD dementia gives a two- to threefold increased risk (2–4). First-degree relatives with AD dementia and self-perceived decline are two relatively common phenomena in cognitively normal individuals (5), but individuals with both risk factors may not necessarily develop AD dementia. The aim of this study is to investigate whether SCD is informative in individuals with a family history of AD, and might therefore help predict who will develop dementia.

AD dementia takes years to develop, during which time one may observe gradual cognitive, structural, and functional brain changes (6,7). Memory clinic studies have shown that persons with SCD have hypometabolism in the precuneus (8), decreased gray matter volumes (9,10), and cortical thinning in medial temporal regions (11), which may be related to an increased risk of incident clinical progression (12,13). In addition, in normal individuals, a family history of AD dementia is associated with decreased regional brain volumes (14–16). Others have demonstrated that connectivity changes involving the posterior default mode network (pDMN), comprising largely the posterior cingulate cortex, are evident in the earliest stages of AD dementia (17,18). It has been suggested that brain hyperconnectivity in the pDMN compensates for early pathophysiological processes but later gives way to global brain hypoconnectivity, perhaps resulting from sustained

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ISSN: 2451-9022

excitotoxicity (18,19). Functional brain changes may precede structural abnormalities and clinical symptoms and may therefore serve as a potential early AD biomarker (20,21). Thus far, cross-sectional memory clinic studies have shown increased DMN connectivity in SCD patients compared to AD patients and control subjects (22,23). By contrast, others found that decreased connectivity in resting state and visual networks was related to a higher degree of cognitive complaints across individuals with preclinical and prodromal AD (24). It remains unclear whether SCD is related to DMN connectivity in relatively young community-dwelling individuals with a family history of AD, and whether altered functional connectivity is predictive of early cognitive changes.

In the longitudinal Pre-symptomatic Evaluation of Novel or Experimental Treatments for Alzheimer's Disease (PREVENT-AD) cohort study we investigated 1) whether SCD is associated with altered brain connectivity in the medial temporal memory system (MTMS), anterior ventral DMN (avDMN) and pDMN, and 2) whether brain connectivity, SCD, or both are related to objective cognitive performance.

METHODS AND MATERIALS

Study Population

Data used in the preparation of this article were obtained from the PREVENT-AD program (http://www.douglas.qc.ca/page/prevent-alzheimer) data release 3.0 (November 30, 2016). The primary goal of PREVENT-AD is to test whether serial determination of multimodal biomarkers of AD may be measured and used in presymptomatic persons who are at high risk of subsequent AD dementia to trace the progression of the disease process and to measure the effects of any potentially preventive treatment interventions. We studied a convenience sample of 124 asymptomatic individuals who were not enrolled in any treatment studies with available information on SCD (1), structural magnetic resonance imaging (MRI) and resting-state functional MRI (rsfMRI) from the PREVENT-AD cohort (25). Briefly, volunteer participants in this cohort were 60 years of age or older (≥55 years if their age was within 15 years of their youngest affected relative's dementia onset) and were required to have at least 6 years of formal education, to demonstrate fluency in either English or French, and to be in good general health. They were required to have a parental or multiple-sibling family history of AD dementia, documented either by a diagnosis of AD from a specialist or by a reported history of "AD-like dementia." The latter was defined as a memory or other cognitive deficit from uncertain causes that had an insidious onset and evolved gradually to a state of cognitive disability sufficient to cause impaired daily functioning (26). Participants underwent a screening physical and neurological and cognitive assessment using the Montreal Cognitive Assessment and Clinical Dementia Rating scale. Their annual visits include a 1.5-hour sequence of MRI acquisitions and more extensive psychometric assessment using the Repeatable Battery for Assessment of Neuropsychological Status (27). Persons with questionable cognitive deficits were referred for full neuropsychological assessment. The Institutional Review Board of the McGill Faculty of Medicine approved the study. All participants provided written informed consent for each stage of study.

SCD Assessment

We used a single validated "SCD question" that has a positive predictive value for AD (1,28,29) to classify participants as either SCD^- or SCD^+. During a structured interview, participants were classified as having SCD^+ if they answered "yes" to the question "Do you think your memory is becoming worse?" Conversely, participants were classified SCD^- if they responded "no" to this question. Furthermore, the Everyday Cognition Questionnaire was administered to all participants and was used to investigate the degree of self-reported cognitive complaints in the following cognitive domains: memory, language, attention, planning, organization skills, and visuospatial skills (30). In addition, neuroticism and depressive symptoms were measured using the 44-item Big Five Inventory (31) and 15-item Geriatric Depression Scale respectively (32). Neuropsychological assessment and brain imaging were done on the same day, and most individuals completed the SCD interview on a different day (mean ± standard deviation [SD], 5 ± 3 months), with a maximum of 1 year between assessments.

Neuropsychological Assessment

Objective cognitive performance was assessed at one annual visit (n = 124) and again a year later (n = 59) using an equivalent alternative version of the Repeatable Battery for Assessment of Neuropsychological Status (12 ± 1 months) (27). This battery provides a global cognitive score consisting of five composite index scores: immediate and delayed memory, attention, language, and visuospatial functioning (from a total of 12 individual tests). Repeatable Battery for Assessment of Neuropsychological Status composite scores were Z-transformed using initial scores as a reference. Baseline neuropsychological data was comparable between subjects with one time point compared to those with two time points (Supplemental Table S1).

MRI Acquisition

MRI data acquisition procedures have been documented elsewhere (33). In brief, MRI scans were acquired using a 3T Magnetom Tim Trio (Siemens Corp., Erlangen, Germany). Structural T1-weighted images were obtained using a gradiet recalled echo sequence (repetition time 2300 ms; echo time 2.98 ms; fractional anisotropy 9°; matrix size 256 × 256; voxel size 1 × 1 × 1 mm^3; 176 slices). For rsfMRI scans, we acquired two consecutive functional T2*-weighted images for 5 minutes each with a blood oxygen level–dependent sensitive, single-shot echo-planar sequence (repetition time 2000 ms; volumes = 150; echo time 30 ms; fractional anisotropy 90°; matrix size 64 × 64; voxel size 4 × 4 × 4 mm^3; 32 slices). Dummy scans were used to obtain a steady-state magnetization, and these volumes were automatically rejected during data acquisition.

Image Analysis

rsfMRI data were preprocessed with default settings using the Neuroimaging Analysis Kit (version 0.12.17, available at http://niak.simexp-lab.org), using GNU Octave (version 4.0), and the Minc toolkit (version 0.3.18, available at http://www.bic.mni.mcgill.ca/ServicesSoftware/MINC), running on Guillimin. Briefly, functional images were motion-corrected, time-filtered

(0.01-Hz high-pass cut-off), nonlinearly spatially normalized (Montreal Neurological Institute International Consortium for Brain Mapping 152), resampled (3-mm isotropic), and smoothed at 6 mm full width at half maximum. In addition, a regression of confounds was performed to account for slow time drifts, high frequencies, motion parameters, average signal of the white matter, and the ventricles (http://niak.simexp-lab.org/pipe_preprocessing.html) (33). As part of the preprocessing, frame displacement was automatically calculated by Neuroimaging Analysis Kit to assess excessive motion between frames (in reference to groupwise averages). For each frame exceeding a frame displacement of 0.5 mm, the individual frame was removed (scrubbed), along with one adjacent frame before and two consecutive frames after. Images passed quality control if 1) functional and structural images were correctly registered (spatial correlation $r > .75$, Neuroimaging Analysis Kit preprocessing report); 2) no spatial normalization or image artefacts were present during visual inspection; and 3) at least one out of two functional scans with a minimum of 50 frames (100 s) remained after scrubbing procedures. Overall, 14 subjects failed quality control procedures (8 excluded because of insufficient frames in both runs, 6 excluded due to image artefacts), leaving 124 for analysis (118 with two runs, 6 with one). Results were essentially unchanged when restricting to individuals with two runs, or rsfMRI acquisitions with more than 100 and 180 volumes (Supplemental Table S2). Demographic characteristics of the current fMRI subsample were similar to those of the entire PREVENT-AD cohort (25). A functional parcellation scheme was generated with bootstrap analysis of stable clusters (34,35) on the Cambridge sample of the 1000 Functional Connectomes Project, and the following regions of interest (ROIs) defined a priori were used (18,36): pDMN, avDMN, and MTMS, the latter consisting of the hippocampus, parahippocampus, retrosplenial, and posterior inferior parietal and ventromedial prefrontal cortices (Figure 1). These ROIs have previously been shown to play a role in the cascading network failure related to AD (18), with the pDMN showing the earliest vulnerability. The advantage of a bootstrap analysis of stable clusters–generated template is that it provides regions with a principled and maximized resting-state network stability at different resolutions (37) (the template is available at https://figshare.com/articles/Group_multiscale _functional_template_generated_with_BASC_on_the_Cambridge_sample/1285615). The parcellation template with 122 parcels was superimposed on an Automated Anatomical Labeling brain atlas to select our a priori defined ROIs (Figure 1B). Subsequently, single-subject regional Fisher *Z*-transformed Pearson correlation values, based on the average time series of all voxels between ROIs (of either one or two runs), were extracted using MATLAB software (The MathWorks, Inc., Natick, MA). Six connectivity estimates were extracted: 1) pDMN with the rest of the brain (measured as one ROI representing all cortical parcels excluding the pDMN parcel); 2) avDMN with the rest of the brain; 3) MTMS with the rest of the brain; and interconnectivity among 4) pDMN–MTMS ROIs, 5) pDMN–avDMN ROIs, and 6) MTMS–avDMN ROIs (Figure 1). The rationale for investigating connectivity between each ROI in relation to the rest of the brain is because DMN regions exhibit a great geodesic cortical distance and support an overarching organization of large-scale connectivity, which could be vulnerable for neuropsychiatric conditions (38). The dorsomedial prefrontal cortex was used as a control region within the DMN network because this subdivision is unimpaired until later stages of AD (18).

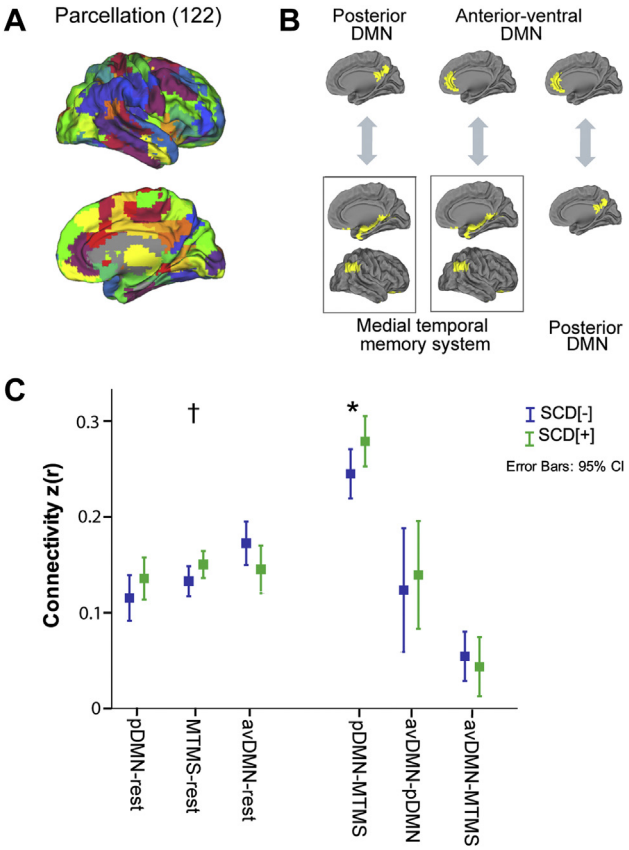

Figure 1. **(A)** Functional brain parcellation. **(B)** Regions of interest (left to right): posterior default mode network (pDMN) with medial temporal memory system (MTMS); anteroventral DMN (avDMN) and MTMS; and avDMN and pDMN. **(C)** Connectivity separated for subjective cognitive decline (SCD) status. The left side of part C represents connectivity between the regions of interest and the rest of the brain; the right side of part C represents connectivity between the regions of interest. Analyses were adjusted for age, gender, frame displacement, and apolipoprotein E ε4 genotype. †Uncorrected $p < .05$; *false discovery rate–corrected $p < .05$. MTMS consisted of the hippocampus, parahippocampus, retrosplenial, and inferior parietal and ventromedial prefrontal cortices. Data presented as mean ± 95% confidence intervals (CIs).

Apolipoprotein E ε4 Genotype

DNA was extracted from buffy coat samples using the QiaSymphony DNA kit (Qiagen, Toronto, Canada), and subsequently the PyroMark Q96 pyrosequencer (Qiagen) was used to determine the apolipoprotein E (*APOE*) genotype. The DNA was amplified using reverse transcriptase–polymerase chain reaction, forward primers 5′-ACGGCTGTCCAAGGAGCTG-3′ (rs429358) and 5′-CTCCGCGATGCCGATGAC-3′ (rs7412), and reverse biotinylated primers 5′-CACCTCGCCGCGGTACTG-3′ (rs429358) and 5′-CCCCGGCCTGGTACACTG-3′ (rs7412). The DNA was sequenced with these primers: 5′-CGGACAT GGAGGACG-3′ (rs429358) and 5′-CGATGACCTGCAGAAG-3′ (rs7412).

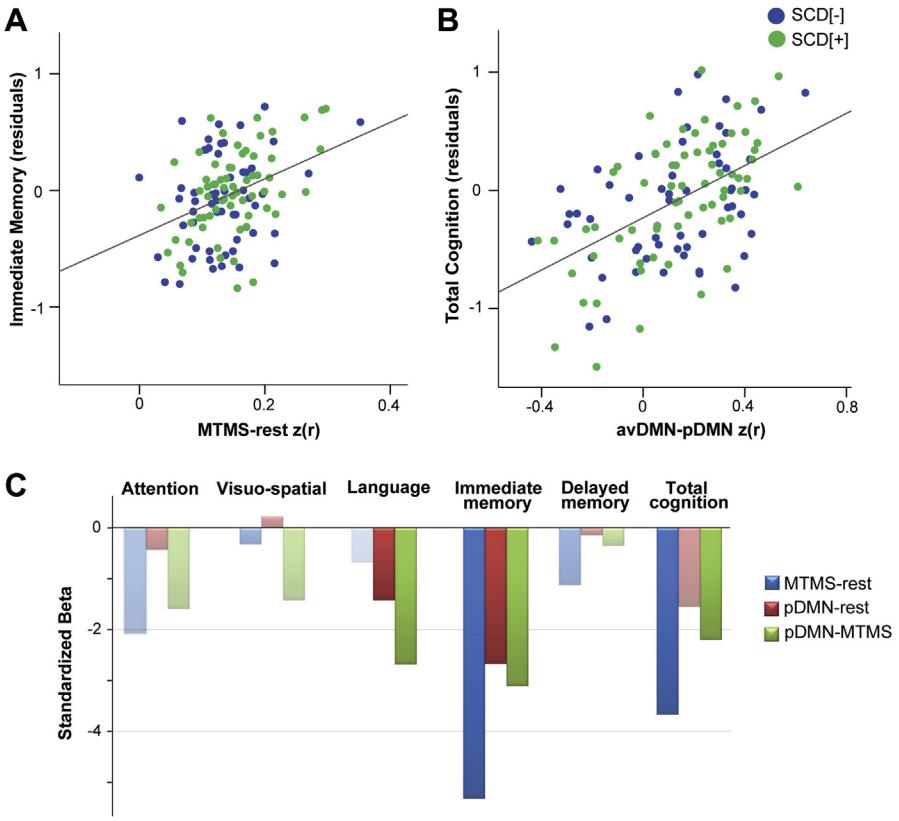

Figure 2. **(A)** Associations between medial temporal memory system (MTMS) and the rest of the brain (all parcels excluding the MTMS parcels) and baseline immediate memory recall. **(B)** Associations between anterior ventral default mode network (avDMN) and posterior DMN (pDMN) connectivity and baseline global cognition. **(C)** Standardized β estimates for connectivity measures on longitudinal cognitive performance (nonsignificant [$p > .05$] β estimates are displayed as transparent). Cognitive scores have been *Z*-transformed so that the variances are 1, and standardized β estimates refer to how many standard deviations cognition will change, per standard deviation increase in the connectivity variable. Residuals of fixed predicted effects were used for scatterplots. SCD, subjective cognitive decline.

Statistical Analyses

Statistical analyses were performed with SPSS software (version 20.0.0; IBM Corp., Armonk NY). Clinical, imaging (quality control; i.e., rsfMRI number of volumes and frame displacement), and demographic variables were analyzed with *t* tests for continuous variables and χ^2 tests for discrete variables. To investigate the main effect of SCD with connectivity (i.e., single-subject Fisher *Z*-transformed regional Pearson correlations), we performed separate univariate linear regression analyses between SCD (independent variable) and strength of connectivity in a priori defined ROIs (dependent variable). Analyses were adjusted for age, gender, and head movement during rsfMRI (frame displacement) (model 1). We additionally adjusted for *APOE* ε4 genotype (model 2). In secondary analyses, we adjusted for depressive symptoms (Geriatric Depression Scale) and neuroticism (model 3), and for mean cortical thickness (model 4), because these could confound connectivity results (39–42). To ensure that our rsfMRI results were not reflective of atrophy patterns, we also compared regional cortical thickness estimates (based on the Desikan-Killiany Atlas) between SCD^+ and SCD^-, which did not show any differences (Supplemental Table S3) (43,44). In a second set of analyses, we investigated the associations of SCD and connectivity with cognition. To do so, we performed linear mixed models to investigate the separate main effects of connectivity and SCD (independent variables) on baseline and follow-up cognitive functioning (dependent variables) for each cognitive domain (45). The models for the effects of SCD on cognition included terms for subject as a random effect, time, SCD status, and SCD by time interaction, whereas the models for the effects of connectivity on cognition included terms for subject as a random effect, time, connectivity and connectivity by time interaction. In a post hoc analysis, we sought to investigate the joint effects of SCD status and connectivity on cognitive decline. The models included terms for subject as a random effect, SCD by time, connectivity by time, and time by connectivity by SCD. The models were adjusted for age, education and gender. Standardized betas were reported if $p < .05$. The false discovery rate (FDR) procedure was used to correct for multiple testing in all analyses (46). Residualized data (fixed effects) were used to create scatterplots. For exploratory purposes, and to investigate whether other brain regions showed altered connectivity between SCD groups (independent variable), regression analyses (adjusted for age, gender, head movement, and *APOE* ε4 genotype) were performed between our three a priori defined ROIs and all other brain parcels (Supplemental Figure S1).

RESULTS

Descriptive and Clinical Data

Demographic and clinical data are shown in Table 1. Sixty-eight (55%) participants reported SCD (SCD^+). Compared to participants without SCD (SCD^-), they reported more cognitive complaints on the Everyday Cognition Questionnaire domains of memory, attention, and language ($p < .05$), but not

Table 1. Demographic and Clinical Data

	Baseline Data			Follow-up Data		
	No. SCD, n = 56	SCD, n = 68	p	No. SCD, n = 29	SCD, n = 30	p
Age, Years	64 ± 5 (55–76)	64 ± 5 (55–77)	.89	65 ± 6	65 ± 6	.79
Education, Years	15 ± 3 (7–23)	16 ± 4 (10–24)	.11	14 ± 4	15 ± 4	.12
Female Gender, %	71	62	.34	78	67	.29
APOE ε4 Genotype (% ε4/ε4 Carriers)	30 (0)	42 (4)	.26 (.11)			
Geriatric Depression Scale Score	2 ± 2 (0–6)	2 ± 2 (0–11)	.89			
Neuroticism	19 ± 7 (8–36)	19 ± 8 (8–34)	.61			
Parent History, %	96	91	.24			
Sibling History, %	7	12	.39			
rsfMRI Volumes, n	244 ± 56 (56–300)	236 ± 59 (86–300)	.46			
Everyday Cognition Questionnaire						
Memory	10 ± 2 (8–14)	12 ± 3 (8–18)	<.001			
Language	10 ± 2 (9–18)	11 ± 2 (9–22)	<.01			
Attention	4 ± 1 (4–7)	5 ± 2 (4–12)	.001			
Organization skills	6 ± 1 (5–8)	6 ± 1 (4–12)	.06			
Planning	5 ± 0 (5–7)	5 ± 1 (5–8)	.92			
Visuospatial	7 ± 1 (6–10)	8 ± 2 (5–17)	.07			
Neuropsychological Assessment						
Immediate memory	100 ± 12 (69–123)	102 ± 10 (78–120)	.01	108 ± 11 (85–126)	104 ± 9 (85–117)	<.01
Visuospatial	96 ± 14 (66–112)	97 ± 16 (64–131)	.87	95 ± 15 (72–126)	97 ± 15 (60–131)	.73
Language	101 ± 8 (83–120)	102 ± 10 (85–127)	.51	98 ± 6 (87–111)	100 ± 9 (79–120)	.89
Attention	104 ± 14 (75–138)	104 ± 14 (72–142)	.54	105 ± 14 (82–125)	104 ± 16 (72–142)	.41
Delayed memory	101 ± 7 (81–116)	103 ± 9 (81–124)	.06	107 ± 7 (95–121)	104 ± 7 (86–121)	.04
Total cognition	100 ± 9 (84–122)	101 ± 10 (83–127)	.03	103 ± 11 (85–128)	102 ± 9 (88–123)	.03

Data are presented as mean ± SD (range) or percentages. Neuropsychological data were acquired using the Repeatable Battery for the Assessment of Neuropsychological Status. p Values of baseline neuropsychological data were acquired with linear mixed models, and p values of the follow-up data reflect relative cognitive changes between baseline and follow-up of SCD^+ compared with SCD^- patients. Displayed p values were unadjusted for multiple comparisons. Baseline and follow-up demographic data were comparable. Geriatric Depression Scale, neuroticism, and Everyday Cognition Questionnaires were not repeated at follow-up.

APOE, apolipoprotein E; rsfMRI, resting-state functional magnetic resonance imaging; SCD, subjective cognitive decline.

on other cognitive domains (all $p > .05$). Age, education, gender, and *APOE* ε4 genotype were comparable between SCD^- and SCD^+, as were neuroticism and depressive symptoms (all $p > .05$).

SCD and Brain Connectivity

To investigate the effect of SCD on connectivity, we performed linear regression analyses. Compared to SCD^-, SCD^+ showed comparable connectivity between the pDMN, avDMN, MTMS, and the rest of the brain (all models adjusted for age, gender, frame displacement, and *APOE* ε4; all $p > .05_{FDR}$ (Table 2). Furthermore, SCD^+ had increased connectivity between the pDMN and the MTMS ($\beta = .26$, $p < .05_{FDR}$), but not between the pDMN–avDMN or the MTMS–avDMN (all $p > .05_{FDR}$) (Figure 1B). The effects did not change after additional adjustment for depressive symptoms, degree of neuroticism, or mean cortical thickness (Table 2, models 3 and 4, respectively). The connectivity between the dorsomedial prefrontal cortex (control region) and our a priori defined ROIs, as well as the connectivity between the dorsomedial prefrontal cortex and the rest of the brain, were comparable between SCD^- and SCD^+. There were no significant differences in the number of volumes remaining after image preprocessing between SCD^- and SCD^+ (all $p > .05$), nor did the minimum number of volumes affect our results (Table 1 and Supplemental Table S2).

SCD in Relation to Cognition

At baseline, comparable performance was found between SCD^- and SCD^+ on all cognitive domains (all $p > .05_{FDR}$) (Table 1). At follow-up, immediate ($\beta = .40$, $p < .05_{FDR}$) and delayed ($\beta = .46$, $p < .05_{FDR}$) memory improved across groups, but the extend of immediate memory improvement was reduced in SCD^+ compared to SCD^- ($\beta = -.64$, $p < .05_{FDR}$).

Brain Connectivity in Relation to Cognition

We performed linear mixed models to investigate the effects of connectivity on cognition (Table 3 and Figure 2). Higher connectivity between MTMS and the rest of the brain was associated with better baseline immediate memory ($\beta = 7.58$, $p < .05_{FDR}$), attention ($\beta = 6.51$, $p < .05_{FDR}$), and global cognition ($\beta = 7.02$, $p < .05_{FDR}$). Likewise, higher pDMN–avDMN connectivity was associated with better baseline language function ($\beta = 2.17$, $p < .05_{FDR}$) and global cognition ($\beta = 1.79$, $p < .05_{FDR}$). In contrast, higher connectivity between the MTMS and the rest of the brain and pDMN–MTMS connectivity were associated with lower immediate memory over

Table 2. Effects of Subjective Cognitive Decline Status on Functional Brain Connectivity

	Model	SCD Status Standard β (*p* Value)
ROIs With the Rest of the Brain		
pDMN–Rest of the Brain	1	.14 (.17)
	2	.17 (.11)
	3	.17 (.09)
	4	.13 (.16)
MTMS–Rest of the Brain	1	.15 (.12)
	2	.17 (.049)[a]
	3	.17 (.053)
	4	.18 (.049)[a]
avDMN–Rest of the Brain	1	−.14 (.16)
	2	−.14 (.16)
	3	−.15 (.13)
	4	−.14 (.14)
Between ROIs		
pDMN–MTMS	1	.23 (.02)[a,b]
	2	.26 (<.01)[a,b]
	3	.26 (<.01)[a,b]
	4	.23 (<.01)[a,b]
pDMN–avDMN	1	.03 (.72)
	2	.02 (.82)
	3	.02 (.87)
	4	.04 (.66)
MTMS–avDMN	1	.00 (.97)
	2	−.01 (.91)
	3	−.02 (.83)
	4	−.01 (.89)

Data are presented as standardized β estimates with corresponding *p* values. β values for SCD status represent the estimated additional change in connectivity if individuals reported SCD. Model 1 is adjusted for age, gender, and frame displacement. Model 2 is adjusted for age, gender, frame displacement, and *APOE* ε4. Model 3 is adjusted for age, gender, frame displacement, *APOE* ε4, Geriatric Depression Scale, and neuroticism. Model 4 is adjusted for age, gender, frame displacement, *APOE* ε4, and mean cortical thickness. The rest of the brain represents all cortical parcels, excluding the one of interest, used as one single ROI.

APOE, apolipoprotein E; avDMN, anterior ventral default mode network; MTMS, medial temporal memory system; pDMN, posterior default mode network; ROI, region of interest; SCD, subjective cognitive decline.

[a] $p < .05$.

[b] Significant false discovery rate–corrected *p* values ($p < .05_{FDR}$).

time (β = −3.33 and β = −5.32, respectively; both $p < .05_{FDR}$). There were no associations between MTMS–avDMN connectivity, avDMN, or pDMN with the rest of the brain and baseline or longitudinal cognition (all $p > .05_{FDR}$).

Simultaneous Effects of Brain Connectivity and SCD in Relation to Cognition

As a post hoc analysis we performed linear mixed models to investigate the joint effects of connectivity and SCD on cognitive performance. Higher connectivity between MTMS and the rest of the brain (β = −5.39, $p < .05_{FDR}$) and pDMN–MTMS connectivity (β = −3.37, $p < .05_{FDR}$), but not SCD status, were associated with lower cognitive performance over time. There were no significant three-way interaction effects between time by connectivity by SCD.

Connectivity Between A Priori Defined ROIs and All Other Brain Parcels

For exploratory purposes, we assessed the relationship between the pDMN, avDMN, MTMS, and all other brain parcels. No results survived $p < .05_{FDR}$ correction. Using a more lenient statistical threshold of $p < .005$, we found that compared with SCD^-, SCD^+ showed increased pDMN connectivity in relation to the bilateral middle cingulate and left inferior parietal cortices and increased MTMS connectivity in relation to bilateral precuneus, middle cingulate, posterior cingulate, inferior occipital, and left inferior parietal cortices (Supplemental Figure S1).

DISCUSSION

We found that self-perceived cognitive decline is associated with increased connectivity between AD vulnerable regions. Moreover, increased brain connectivity was related to better baseline cognitive performance but to a reduced rate of cognitive performance over time in individuals with SCD compared to those without SCD. Our findings suggest that SCD is an informative parameter in cognitively normal individuals with a family history of AD.

Both family history of AD and SCD are associated with an increased risk of incident progression to dementia (1,2). AD pathogenesis takes years to develop, and it is hypothesized that functional abnormalities precede clinical symptoms (6). For this reason, it is conceivable that functional connectivity changes in individuals at risk may occur before extensive structural brain damage and objective cognitive decline (20). Combining both subjective and objective cognitive functioning in relation to brain connectivity could lead to a better understanding of early processes related to cognitive decline, and potentially lead to a better selection for future preventive strategies or disease-modifying therapies.

Others have shown that pDMN hyperconnectivity is associated with AD risk factors in cognitively normal individuals and could therefore reflect an early disease mechanism related to future cognitive decline (23,47–51). Hyperconnectivity may be expressed as increasing temporal covariance of metabolically active brain regions and is considered to occur after damage to neural systems as a result of brain plasticity (52). In the current study, we defined connectivity within a single subject by means of a correlation of resting-state blood oxygen level–dependent time series between the pDMN and other ROIs. In keeping with previous results, we found increased connectivity between the pDMN and the MTMS in individuals with SCD (20,53). Moreover, when we additionally adjusted for cortical thickness these associations remained essentially unchanged, suggesting that these associations explain variance in brain connectivity beyond cortical atrophy. So far, rsfMRI studies on cognitively intact individuals have found increased (20,23,48,49,53), decreased (18,39), and mixed (47) pDMN connectivity in relation to the presence of AD risk factors. Furthermore, memory clinic studies have demonstrated altered brain connectivity in patients with SCD compared to control subjects and patients with AD (22–24). It is hypothesized that

Table 3. Associations Between Brain Connectivity and Cognition

Cognitive Domain Connectivity		Visuospatial	Immediate Memory	Language	Attention	Delayed Memory	Total Cognition
pDMN–Rest of the brain	BL	.76 (.70)	2.71 (.17)	2.14 (.32)	1.47 (.23)	−.89 (.60)	2.41 (.17)
	FU	.23 (.86)	−2.67 (.04)[a]	−1.42 (.32)	−.43 (.70)	.14 (.99)	−1.55 (.18)
MTMS–Rest of the brain	BL	.54 (.86)	7.58 (.01)[a,b]	2.71 (.40)	6.51 (.01)[a,b]	−2.82 (.27)	7.02 (.01)[a,b]
	FU	−.32 (.88)	−5.32 (.01)[a,b]	−.68 (.76)	−2.07 (.07)	−1.12 (.52)	−3.67 (.04)[a]
avDMN–Rest of the brain	BL	1.55 (.41)	−1.55 (.41)	.14 (.95)	2.90 (.09)	.91 (.57)	1.30 (.44)
	FU	−.98 (.45)	1.16 (.37)	.20 (.88)	−.52 (.62)[a]	−1.28 (.23)	−.18 (.87)
pDMN–MTMS	BL	−1.60 (.35)	3.58 (.04)[a]	3.67 (.047)[a]	1.58 (.32)	.84 (.58)	2.65 (.08)
	FU	−1.42 (.25)	−3.11 (.01)[a,b]	−2.68 (.04)[a]	−1.59 (.11)	−.35 (.74)	−2.20 (.03)[a]
pDMN–avDMN	BL	1.24 (.10)	−.04 (.95)	2.17 (.01)[a,b]	1.38 (.04)[a]	.74 (.26)	1.79 (.01)[a,b]
	FU	−.44 (.38)	−.12 (.82)	−1.22 (.03)[a]	−.47 (.26)	−.76 (.08)	−.89 (.04)[a]
MTMS–avDMN	BL	.75 (.60)	−.35 (.82)	.01 (.99)	1.91 (.17)	2.47 (.06)	1.48 (.28)
	FU	.03 (.98)	.08 (.94)	.28 (.80)	−.47 (.58)	−1.55 (.07)	−.27 (.75)
SCD	BL	−.06 (.87	.89 (.01)[a]	.25 (.51)	.20 (.54)	.59 (.05)	.68 (.03)[a]
	FU	.08 (.73)	−.64 (.01)[a,b]	−.04 (.89)	−.17 (.41)	−.42 (.04)[a]	−.45 (.03)[a]

Data presented as standardized β estimates (*p* value). "Rest" implicates the rest of the brain representing all cortical parcels, excluding the one of interest, used as one single region of interest. Linear mixed models between connectivity and cognition were adjusted for age, sex, education, and contained an interaction term for connectivity by time.

avDMN, anterior ventral default mode network; BL, baseline; FU, follow-up; MTMS, medial temporal memory system; pDMN, posterior default mode network; SCD, subjective cognitive decline.

[a] $p < .05$.

[b] Significant false discovery rate–corrected *p* values ($p < .05_{FDR}$).

before a global connectivity failure, brain regions of high activity could accelerate pathology (54,55) or reflect an attempted compensation of early pathophysiological processes (19). While there is controversy about the interpretation of connectivity patterns, pDMN hyperconnectivity has been demonstrated in predementia stages across imaging modalities with rsfMRI, magnetoencephalography, and cerebral metabolism (i.e., fluorodeoxyglucose positron emission tomography) (23,47–51,54,56–61). Our findings further support the idea that pDMN hyperconnectivity, particularly between the pDMN and MTMS, could be one the earliest network changes related to AD, especially since none of our participants showed any signs of cognitive impairment at baseline or follow-up. Others showed that higher pDMN connectivity is related to better concurrent global cognition along the AD spectrum (18). We extend these findings by showing that higher pDMN–MTMS connectivity was associated with better concurrent cognitive performance but with lower immediate memory and global cognition over time. Similarly, our data indicate that higher connectivity between the MTMS and the rest of the brain is also involved in early cognitive changes, and that these associations were independent of SCD status. Previous research has shown that the MTMS becomes engaged when decisions involve constructing a mental scene based on memory (36). We furthermore provide evidence that the degree of MTMS connectivity is also related to immediate recall of verbal information, attention, and global cognition. Taken together, our findings suggest that hyperconnectivity is related to better concurrent cognitive performance, but could have a detrimental effect over time in cognitively normal individuals. These findings could reflect decline during normal aging or resemble one of the earliest changes related to AD.

Baseline cognitive performance was comparable between individuals with and without SCD. Over time, when looking across groups, immediate and delayed memory improved, likely reflecting memory-selective practice effects that often occur in cognitively normal individuals (62). The amplitude of the immediate memory recall improvement was, however, reduced in SCD^+ individuals when compared with SCD^- individuals. Others have shown that SCD^+ memory clinic patients have poorer memory functioning over time compared to control subjects (8,63). One explanation is that learning abilities (i.e., practice effects) tend to weaken in individuals with SCD, and might be an early form of learning "stagnation," which is in line with evidence that practice effects diminish in preclinical AD (64,65). We hypothesize that individuals who report self-perceived cognitive decline can preserve memory function for some time, but deteriorate in the long run. Notwithstanding, future studies are necessary to fully elucidate early stages of cognitive changes.

A strength of our study is that it investigated self-perceived decline in a unique sample of individuals with a family history of AD in conjunction with state-of-the-art imaging techniques. Several limitations also warrant attention. First, our follow-up duration was relatively short, and none of the participants in this sample showed incident clinical progression. Nonetheless, we did find altered connectivity related to cognitive decline in regions vulnerable to AD. Unfortunately, other biomarkers such as amyloid-β and tau protein levels that could further corroborate evidence of AD pathogenesis have not yet been acquired. Some studies have proposed that connectivity changes might even precede measurable pathology (18,47,54,55). In this regard, our results may be potentially relevant. Second, cognitive complaints in community-dwelling individuals could be caused by a myriad of factors. Self-perceived decline could be a reflection of underlying neurodegenerative disease but could also be induced by mental illness, substance abuse, sleep disturbances, neuroticism, and normal aging (5). Family history in itself could also induce anxiety and worries for AD. We therefore adjusted our

connectivity models for depressive symptoms and neuroticism, but this did not change the results. Nevertheless, future research should investigate whether family history could affect the phenotype of cognitive complaints. Finally, because we studied asymptomatic individuals with a family history of AD, it is unclear whether our findings can be extrapolated to community-dwelling persons without a family history of AD.

In sum, SCD in cognitively normal individuals at elevated risk of AD is associated with a brain connectivity pattern that mirrors early AD-related connectivity failure. Our findings illustrate that SCD in individuals with a family history of AD is a relevant phenomenon that may foreshadow subsequent cognitive decline. Future studies may elucidate the nature of SCD in cognitively normal individuals who have a family history of AD and may disentangle the concomitant effects with other biomarkers in relation to AD pathogenesis.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by Alzheimer Nederland Fellowship Grant No. WE.15-2016-03 (to SCJV), Gieske-Strijbis Fonds, a Canada Research Chair, a Canadian Institutes of Health Research Foundation Grant, a Canada Fund for Innovation Grant, and a joint Alzheimer Society of Canada and Brain Canada Research Grant (to SV), a Gieske-Strijbis Fonds Research Grant (to WvdF and SCJV), a fellowship from the Alzheimer Society of Canada and Fonds de recherche Santé Québec (to APB), and a Canada Research Chair Grant (to JB). PREVENT-AD was launched in 2011 as a $13.5 million, 7-year public–private partnership using funds provided by McGill University, the Fonds de Recherche du Québec–Santé, an unrestricted research grant from Pfizer Canada, the Levesque Foundation, the Douglas Hospital Research Centre and Foundation, the Government of Canada, and the Canada Fund for Innovation. Private sector contributions are facilitated by the Development Office of the McGill University Faculty of Medicine and by the Douglas Hospital Research Centre Foundation (http://www.douglas.qc.ca/).

WvdF has received research funding and speaker honoraria from Boehringer Ingelheim; all funds were paid to her institution. PS received grant support for the institution (Umc Alzheimer center) from GE Healthcare, Danone Research, and Merck. In the past 2 years, PS has received speaker's fees (paid to the institution) from Lilly, GE Healthcare, Lundbeck, Danone, and Jansen AI-Pfizer. The other authors report no biomedical financial interests or potential conflicts of interest.

The computational resources used to perform the data analysis were provided by Compute Canada (https://computecanada.ca) and McGill's Centre for High-Performance Computing (http://www.hpc.mcgill.ca), which is funded in part by the Natural Sciences and Engineering Research Council of Canada (Major Resources Support), Fonds de recherche du Québec – Nature et technologies, and McGill University. The funding sources had no role in the design and conduct of the study, in the collection, analysis, interpretation of the data or in the preparation, review or approval of the manuscript. Finally, we would like to acknowledge the participants of the PREVENT-AD cohort for dedicating their time and energy to help us collect these data.

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We acknowledge all members of the Pre-symptomatic Evaluation of Novel or Experimental Treatments for Alzheimer's Disease (PREVENT-AD) research group for their contribution (in alphabetical order [last name, first name]): Aisen Paul; Anthal Elena; Appleby Melissa; Ayranci Gülebru; Barkun Alan; Beaudry Thomas; Bellec Pierre; Benbouhoud Fatiha; Bohbot Veronique; Brandt Jason; Breitner John; Carmo Leopoldina; Carrier Charles Edouard; Chakravarty Mallar; Cheewakriengkrai Laksanun; Collins Louis; Courcot Blandine; Couture Doris; Craft Suzanne; Cuello Claudio; Dadar Mahsa; Dansereau Christian; DasSamir; Dauar-Tedeschi Marina; Dea Doris; Debacker Clement; Desautels Rene; Dubuc Sylvie; Duclair Guerda; Dufour Marianne; Eisenberg Mark; El-Khoury Rana; Etienne Pierre; Evans Alan; Faubert Anne-Marie; Ferdinand Fabiola; Fonov Vladimir; Fontaine David; Frappier Josée; Frenette Joanne; Gagne Guylaine; Gauthier Serge; Gervais Valérie; Giles Renuka; Gonneaud Julie; Gordon Renee; Hoge Rick; Hyman Bradley; Ituria-Medina Yasser; Jack Clifford; Kat Justin; Kazazian Christina; Khachaturian Zaven; Knopman David; Kostopoulos Penelope; Labonte Anne; Lafaille-Magnan Marie-Elyse; Lee Tanya; Leoutsakos Jeannie-Marie; Lepage Claude; Leppert Illana; Madjar Cécile; Mahar Laura; Maillet David; Maltais Jean-Robert; Mathieu Axel; Mathotaarachchi Sulantha; Maultaup Gerhard; Mayrand Ginette; Meyer Pierre-François; Michaud Diane; Miron Justin; Montine Thomas; Morris John; Münter Lisa-Marie; Nair Vasavan; Near Jamie; Newbold-Fox Holly; Orban Pierre; Page Véronique; Pascoal Tharick; Petkova Mirela; Picard Cynthia; Pichet Binette Alexa; Pogossova Galina; Poirier Judes; Pruessner Jens; Rajah Natasha; Rioux Pierre; Rosa-Neto Pedro; Sager Mark; Saint-Fort Eunice Farah; Savard Mélissa; Sperling Reisa; Tabrizi Shirin; Tam Angela; Tardif Christine; Tariot Pierre; Teigner Eduard; Theroux Louise; Thomas Ronald; Toussaint Paule-Joanne; Tremblay-Mercier Jennifer; Tuwaig Miranda; Vallee Isabelle; Venugopalan Vinod; Verfaillie Sander; Villeneuve Sylvia; Vogel Jacob; Wan Karen; Wang Seqian; and Yu Elsa. The investigators of the PREVENT-AD program contributed to the design and implementation of PREVENT-AD and/or provided data but did not participate in analysis or writing of this report.

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Received Sep 30, 2017; revised Nov 20, 2017; accepted Nov 22, 2017.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2017.11.012.

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