Neuroimaging in subjective cognitive decline

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CHAPTER 6

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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"I don't remember
lighting this cigarette
and I don't remember
if I'm here alone
or waiting for someone." (L. Cohen)

ABSTRACT

Background. Subjective cognitive decline (SCD) and a family history of Alzheimer's disease (AD) both 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). Participants were categorized as having SCD if they reported that their memory was becoming worse (SCD[+]). We used extensive neuropsychological assessment to investigate 5 different cognitive domains performance at baseline (n=124) and one 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. At follow-up, immediate and delayed memory improved across groups, but the improvement in immediate memory was reduced in SCD[+] compared to SCD[-] (all $p<0.05_{FDR}$). When compared to SCD[-], SCD[+] subjects showed increased pDMN-MTMS connectivity ($p<0.05_{FDR}$). Higher connectivity between the MTMS and 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 $p<0.05_{FDR}$).

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.

INTRODUCTION

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 six-fold increased risk of clinical progression to dementia in cognitively normal individuals,[1] whereas a family history of AD dementia gives a two- to three-fold increased risk.[2–4] First-degree relatives with AD dementia as well as 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 increased risk of incident clinical progression.[12,13] Additionally, 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 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] So far cross-sectional memory clinic studies have shown increased DMN connectivity in SCD patients compared to AD patients and controls.[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 PREVENT-AD cohort study we investigated (i) whether SCD is associated with altered brain connectivity in the medial temporal memory system (MTMS), anterior ventral DMN (avDMN) and pDMN and (ii) whether brain connectivity, SCD, or both are related to objective cognitive performance.

METHODS

Study population. Data used in the preparation of this article were obtained from the Pre-symptomatic Evaluation of Novel or Experimental Treatments for Alzheimer's Disease (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 multi-modal biomarkers of Alzheimer's disease may be measured and used in pre-symptomatic persons at high risk of subsequent AD dementia to trace the progression of the disease process and to measure 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 MRI and resting-state functional (rsf)MRI from the PREVENT-AD cohort.[25] Briefly, volunteer participants in this cohort were aged 60 or older (55 or older 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, neurological and cognitive assessment using the Montreal Cognitive Assessment (MoCA) and Clinical Dementia Rating (CDR) 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 (RBANS).[27] Persons with questionable cognitive deficits were referred for full neuropsychological assessment. The IRB of 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 same question. Furthermore, the Everyday Cognition Questionnaire (Ecog) 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 visuo-spatial skills.[30] In addition, neuroticism and depressive symptoms were measured using the 44-item Big Five Inventory (BFI)[31] and 15-item geriatric depression scale (GDS) respectively.[32] Neuropsychological assessment and brain imaging were done on the same day, and most individuals completed the SCD interview on a different day (5 months ± 3 SD), with a maximum of one year between assessments.

Table 1. Demographic and clinical data

Baseline data	NO SCD n=56	SCD n=68	p-value	Follow-up data NO SCD n=29	Follow-up data SCD n=30	
Age (years)	64±5 (55-76)	64±5 (55-77)	p=0.89	65±6	65±6	p=0.79
Education (years)	15±3 (7-23)	16±4 (10-24)	p=0.11	14±4	15±4	p=0.12
Gender (%females)	71%	62%	p=0.34	78%	67%	p=0.29
APOE ε4 genotype (% ε4/ ε4 carriers)	30% (0%)	42% (4%)	p=0.26 (p=0.11)			
GDS	2±2 (0-6)	2±2 (0-11)	p=0.89			
Neuroticism	19±7 (8-36)	19±8 (8-34)	p=0.61			
Parent history (%)	96%	91%	p=0.24			
Sibling history (%)	7%	12%	p=0.39			
rsfMRI volumes (n)	244±56 (56-300)	236±59 (86-300)	p=0.46			
Everyday Cognition Questionnaire						
Memory	10±2 (8-14)	12±3 (8-18)	p<0.001			
Language	10±2 (9-18)	11±2 (9-22)	P<0.01			
Attention	4 ±1 (4-7)	5±2 (4-12)	p=0.001			
Organization skills	6±1 (5-8)	6±1 (4-12)	p=0.06			
Planning	5±0 (5-7)	5±1 (5-8)	p=0.92			
Visuo-spatial	7±1 (6-10)	8±2 (5-17)	p=0.07			
Neuropsychological assessment						
Immediate Memory	100±12 (69-123)	102±10 (78-120)	p=0.01	108±11 (85-126)	104±9 (85-117)	p<0.01
Visuo-spatial	96±14 (66-112)	97±16 (64-131)	p=0.87	95±15 (72-126)	97±15 (60-131)	p=0.73
Language	101±8 (83-120)	102±10 (85-127)	p=0.51	98±6 (87-111)	100±9 (79-120)	p=0.89
Attention	104±14 (75-138)	104±14 (72-142)	p=0.54	105±14 (82-125)	104±16 (72-142)	p=0.41
Delayed Memory	101±7 (81-116)	103±9 (***81***-124)	p=0.06	107±7 (95-121)	104±7 (86-121)	p=0.04
Total Cognition	100±9 (84-122)	101±10 (83-127)	p=0.03	103±11 (85-128)	102±9 (88-123)	p=0.03

Data are presented as mean±SD (min-max) or percentages. *APOE* = Apolipoprotein; SCD, subjective cognitive decline. Neuropsychological data was acquired using the repeatable battery for the assessment of neuropsychological status (RBANS). 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 to SCD[-]. Displayed p-values were unadjusted for multiple-comparisons. Baseline and follow-up demographic data were comparable. GDS, neuroticism and Everyday Cognition questionnaires were not repeated at follow-up.

Neuropsychological assessment. Objective cognitive performance was assessed at one annual visit (n=124) and again a year later (n=59) using an equivalent alternate version of the RBANS (12 months ± 1 SD).[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). RBANS 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 (Supplementary Table S1).

MRI acquisition. MRI data acquisition procedures have been documented elsewhere.[33] In brief, MRI scans were acquired using Magnetom Tim Trio (Siemens) operating at 3-Tesla. Structural T1-weighted images were obtained using a GRE sequence (TR=2300ms; TE =2.98ms; FA=9°; matrix size=256x256; voxel size=1x1x1 mm3; 176 slices). For rsfMRI scans, we acquired two consecutive functional T2*-weighted images for 5 minutes each with a blood-oxygen-level-dependent (BOLD) sensitive, single-shot echo planar sequence (TR=2000ms; volumes=150; TE=30ms; FA=90°; matrix size=64x64; voxel size=4x 4x4 mm^3; 32 slices). Dummy scans were used to obtain a steady-state magnetization, these volumes were automatically rejected during data acquisition.

Image analysis. rsfMRI data were preprocessed with default settings using the Neuroimaging Analysis Kit v0.12.17 (http://niak.simexp-lab.org), using GNU Octave (v4.0), and the Minc toolkit v0.3.18 http://www.bic.mni.mcgill.ca/ServicesSoftware/MINC), running on Guillimin. Briefly, functional images were motion-corrected, time-filtered (0.01Hz high-pass cut-off), non-linearly spatially normalized (Montreal Neurological Institute ICBM152), re-sampled (3mm isotropic), and smoothed at 6mm FWHM. 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 (FD) was automatically calculated by NIAK to assess excessive motion between frames (in reference to group-wise averages). For each frame exceeding an FD of 0.5 millimeter, the individual frame was removed (scrubbed), along with one adjacent frame prior, and two consecutive frames after. Images passed quality control if: i) functional and structural images were correctly registered (spatial correlation r>0.75, NIAK preprocessing report); ii) no spatial normalization or image artefacts were present during visual inspection; iii) at least one out of two functional scans with a minimum of 50 frames (100s) remained after scrubbing procedures. Overall, 14 subjects failed QC procedures (8 excluded due to 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 (supplementary table S2). Demographic characteristics of the current fMRI subsample were similar to the entire PREVENT-AD Cohort.[25] A functional

parcellation scheme was generated with bootstrap analysis of stable clusters (BASC)[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, posterior inferior parietal and ventromedial prefrontal cortex (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 BASC-generated template is that it provides regions with a principled and maximized resting-state network stability at different resolutions.[37] The template can be found 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 AAL 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 1 or 2 runs), were extracted using Matlab (R2012b). Six connectivity estimates were extracted: pDMN with the rest of the brain (measured as one ROI representing all cortical parcels excluding the pDMN parcel) (1), avDMN with the rest of the brain (2), MTMS with the rest of the brain (3), and interconnectivity among pDMN-MTMS ROIs (4), pDMN-avDMN ROIs (5) and MTMS-avDMN ROIs (6) (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 dorsal medial prefrontal cortex (dmPFC) was used as a control region within the DMN network since this subdivision is unimpaired until later stages of AD.[18]

APOE 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 APOE genotype. The DNA was amplified using reverse transcriptase–PCR, 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'-CGGACATGGAGGACG-3' (rs429358) and 5'-CGATGACCTGCAGAAG-3' (rs7412).

Statistical analyses. Statistical analyses were performed with SPSS version 20.0.0 (IBM Corp., Armonk New York, U.S.). Clinical, imaging (quality control; i.e. rsfMRI number of volumes, frame displacement), and demographic variables were analyzed with t-tests for continuous variables and χ^2 tests for discrete variables. In order to investigate the main effect association 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 (GDS) and neuroticism (model 3), and for mean cortical thickness (model 4), as these could confound connectivity results (37–40). To make sure 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 (Supplementary 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*time interaction, whereas the models for the effects of connectivity on cognition included terms for subject as a random effect, time, connectivity and connectivity*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*time, connectivity*time, and time*connectivity*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 (Supplementary 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 Ecog domains of memory, attention and language ($p<0.05$), but not on other cognitive domains (all $p>0.05$). Age, education, gender and *APOE* ε4 genotype were comparable between SCD[-] and SCD[+], as were neuroticism and depressive symptoms (all $p>0.05$).

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 $p>0.05_{FDR}$; Table 2). Furthermore, SCD[+] had *increased* connectivity between the pDMN and the MTMS ($\beta = 0.26$, $p<0.05_{FDR}$), but

Table 2. Effects of SCD status on functional brain connectivity

ROIs with the rest of the brain		SCD status Std Beta (p-value)
pDMN-rest of the brain	Model 1	0.14 (0.17)
	Model 2	0.17 (0.11)
	Model 3	0.17 (0.09)
	Model 4	0.13 (0.16)
MTMS-rest of the brain	Model 1	0.15 (0.12)
	Model 2	**0.17 (0.049)**
	Model 3	0.17 (0.053)
	Model 4	**0.18 (0.049)**
avDMN-rest of the brain	Model 1	-0.14 (0.16)
	Model 2	-0.14 (0.16)
	Model 3	-0.15 (0.13)
	Model 4	-0.14 (0.14)
Between ROIs		
pDMN-MTMS	Model 1	**0.23 (0.02)***
	Model 2	**0.26 (<0.01)***
	Model 3	**0.26 (<0.01)***
	Model 4	**0.23 (<0.01)***
pDMN-avDMN	Model 1	0.03 (0.72)
	Model 2	0.02 (0.82)
	Model 3	0.02 (0.87)
	Model 4	0.04 (0.66)
MTMS-avDMN	Model 1	0.00 (0.97)
	Model 2	-0.01 (0.91)
	Model 3	-0.02 (0.83)
	Model 4	-0.01 (0.89)

Data are presented as standardized β estimates with corresponding p-values. β's for SCD status represent the estimated additional change in connectivity if individuals report SCD. Model 1 is adjusted for age, gender, 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, GDS 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. p<0.05 significant standardized β estimates are displayed in bold. *, p<0.05FDR significant.

not between the pDMN-avDMN or the MTMS-avDMN (all $p>0.05_{FDR}$) (Figure 1B). The effects did not change after additional adjustment for depressive symptoms or degree of neuroticism, or mean cortical thickness (Table 2, model 3 and model 4 respectively). The connectivity between the dmPFC (control region) and our *a priori* defined ROIs, as

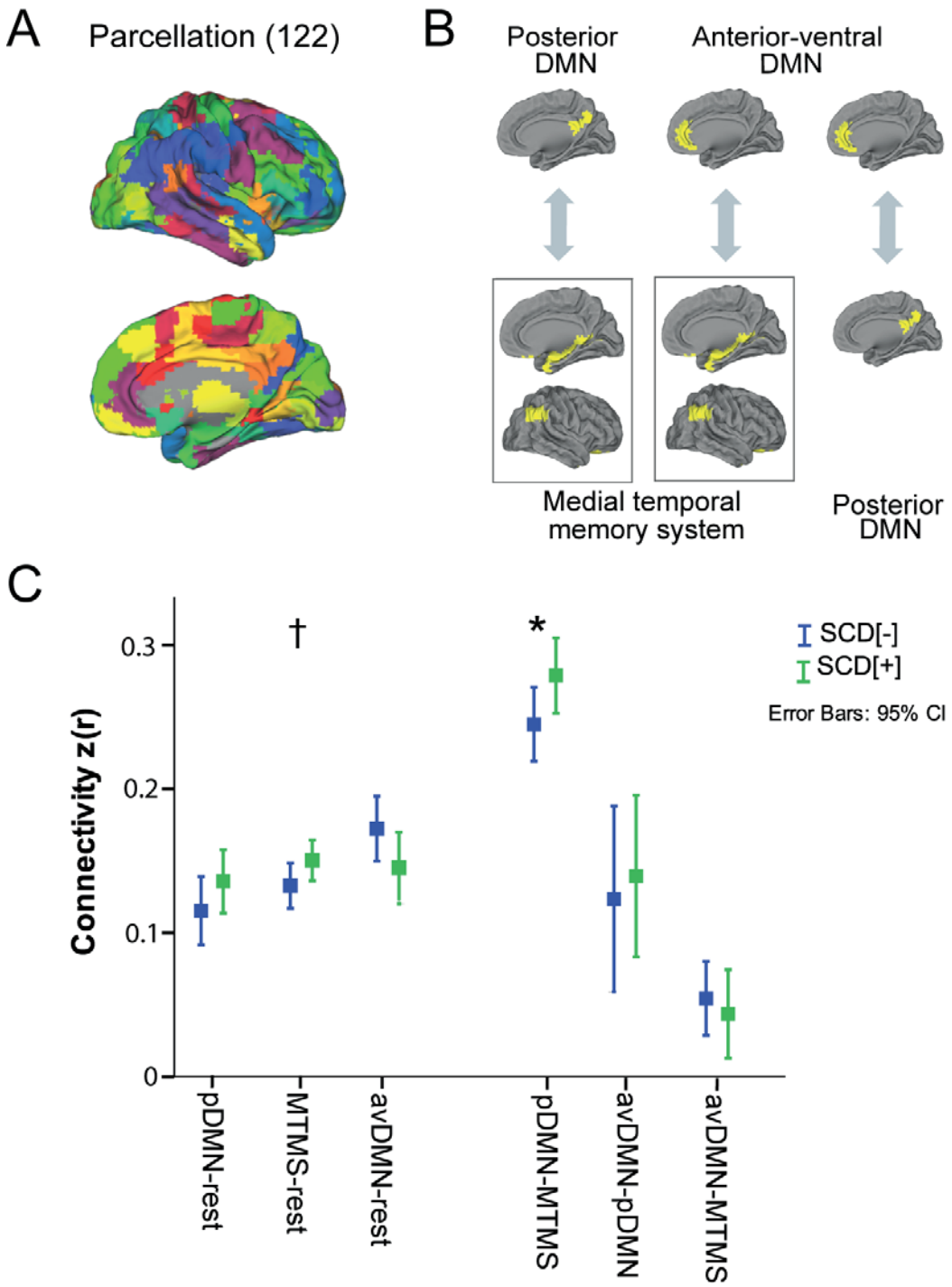

Figure 1. Functional brain parcellation (A). Regions of interest (ROIs) [left to right]: 1) posterior default mode network (pDMN) with medial temporal memory system (MTMS) 2) anteroventral DMN (avDMN) and MTMS, 3) avDMN and pDMN (B). Connectivity separated for SCD status. The left panel represents connectivity between the ROIs and the rest of the brain and the right panel represents connectivity between ROIs (C). Analyses were adjusted for age, gender, frame displacement and APOE ε4. †, p<0.05 uncorrected; *, p<0.05$_{FDR}$. MTMS consisted of the hippocampus, parahippocampus, retrosplenial, inferior parietal and ventromedial prefrontal cortex. Data are presented as mean+95% confidence intervals.

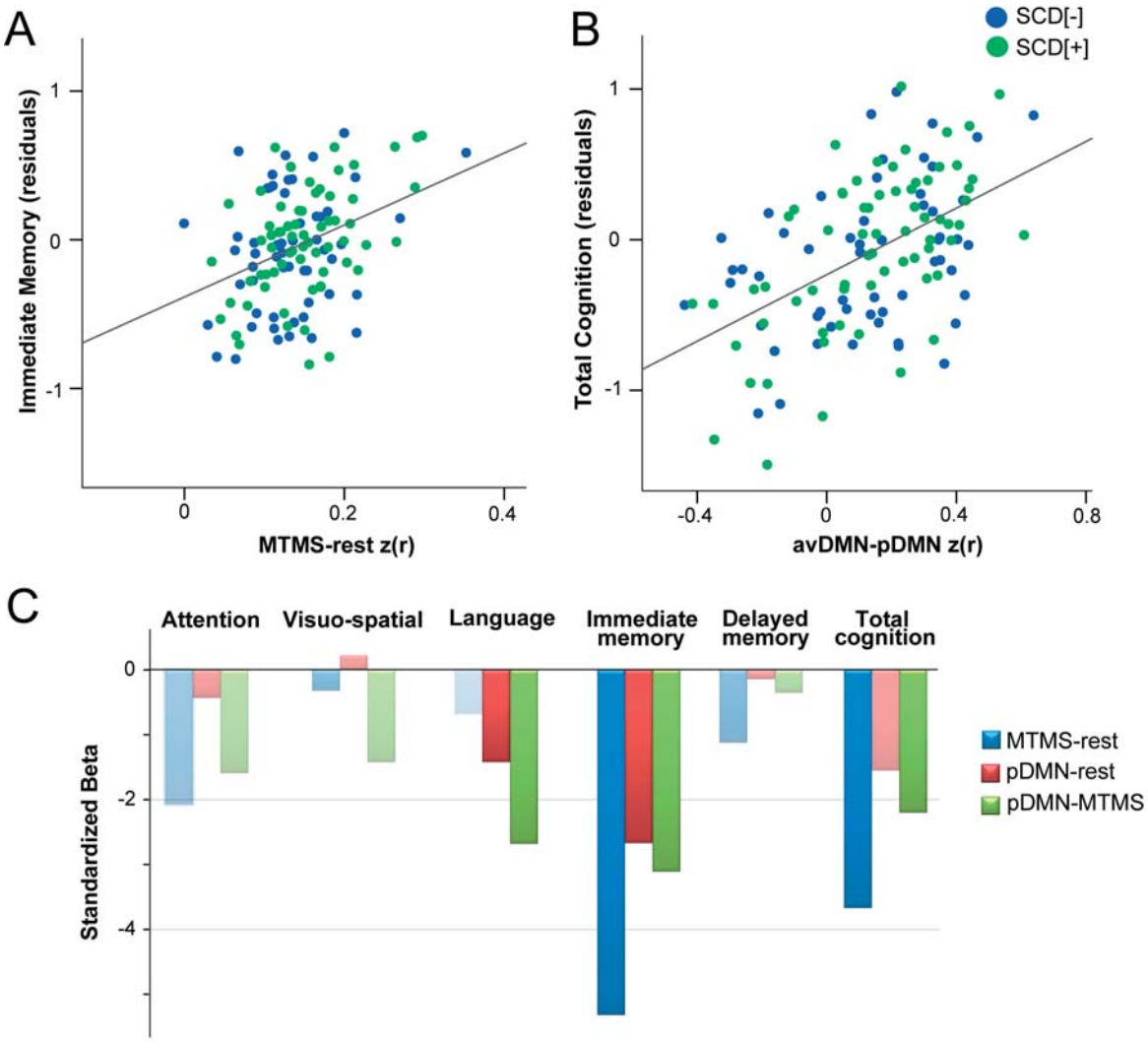

Figure 2. Associations between MTMS and the rest of the brain (all parcels excluding the MTMS parcels) and immediate memory recall (A). Associations between avDMN-pDMN connectivity and global cognition. Standardized beta estimates for connectivity measures on longitudinal cognitive performance (non-significant [p>0.05] beta estimates are displayed transparent) (C). Cognitive scores have been Z-transformed so that the variances are 1, and standardized beta 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.

well as the connectivity between the dmPFC 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>0.05), nor did the minimum number of volumes affect our results (Table 1 and supplementary materials Table S2).

SCD in relation to cognition. At baseline, *comparable* performance was found between SCD[-] and SCD[+] on all cognitive domains (all $p>0.05_{FDR}$; Table 1). At follow-up, immediate

(β=0.40, $p<0.05_{FDR}$) and delayed (β=0.46, $p<0.05_{FDR}$) memory improved across groups, but the extend of immediate memory improvement was reduced in SCD[+] compared to SCD[-] (β= -0.64, $p<0.05_{FDR}$).

Brain connectivity in relation to cognition. We performed linear mixed models to investigate the effects of connectivity on cognition (Table 3). Higher connectivity between MTMS and the rest of the brain was associated with better baseline immediate memory (β=7.58, $p<0.05_{FDR}$), attention (β=6.51, $p<0.05_{FDR}$), and global cognition (β=7.02, $p<0.05_{FDR}$). Likewise, higher pDMN-avDMN connectivity was associated with better baseline language function (β=2.17, $p<0.05_{FDR}$) and global cognition (β=1.79, $p<0.05_{FDR}$). In contrast, higher connectivity between the MTMS and the rest of the brain and pDMN-MTMS connectivity were associated with lower immediate memory over time (β= -3.33 and β= -5.32 respectively, both $p<0.05_{FDR}$). There were no associations between MTMS-avDMN connectivity, avDMN or pDMN with the rest of the brain and baseline or longitudinal cognition (all $p>0.05_{FDR}$).

Table 3. Associations between brain connectivity and cognition

Cognitive domain / Connectivity		Visuo-spatial	Immediate Memory	Language	Attention	Delayed Memory	Total Cognition
pDMN-rest	BL	0.76 (.70)	2.71 (.17)	2.14 (.32)	1.47 (.23)	-0.89 (.60)	2.41 (.17)
	FU	0.23 (.86)	**-2.67 (.04)**	-1.42 (.32)	-0.43 (.70)	0.14 (.99)	-1.55 (.18)
MTMS-rest	BL	0.54 (.86)	**7.58 (.01)***	2.71 (.40)	**6.51 (.01)***	-2.82 (.27)	**7.02 (.01)***
	FU	-0.32 (.88)	**-5.32 (.01)***	-0.68 (.76)	-2.07 (.07)	-1.12 (.52)	**-3.67 (.04)**
avDMN-rest	BL	1.55 (0.41)	-1.55 (.41)	0.14 (.95)	2.90 (.09)	0.91 (.57)	1.30 (.44)
	FU	-0.98 (0.45)	1.16 (.37)	0.20 (.88)	**-0.52 (.62)**	-1.28 (.23)	-0.18 (.87)
pDMN-MTMS	BL	-1.60 (.35)	**3.58 (.04)**	**3.67 (.047)**	1.58 (.32)	0.84 (.58)	2.65 (.08)
	FU	-1.42 (.25)	**-3.11 (.01)***	**-2.68 (.04)**	-1.59 (.11)	-0.35 (.74)	**-2.20 (.03)**
pDMN-avDMN	BL	1.24 (.10)	-0.04 (.95)	**2.17 (.01)***	**1.38 (.04)**	0.74 (.26)	**1.79 (.01)***
	FU	-0.44 (.38)	-0.12 (.82)	**-1.22 (.03)**	-0.47 (.26)	-0.76 (.08)	**-0.89 (.04)**
MTMS-avDMN	BL	0.75 (.60)	-0.35 (.82)	0.01 (.99)	1.91 (.17)	2.47 (.06)	1.48 (.28)
	FU	0.03 (.98)	0.08 (.94)	0.28 (.80)	-0.47 (.58)	-1.55 (.07)	-0.27 (.75)
SCD	BL	-0.06 (.87	**0.89 (.01)**	0.25 (.51)	0.20 (.54)	0.59 (.05)	**0.68 (.03)**
	FU	0.08 (.73)	**-0.64 (.01)***	-0.04 (.89)	-0.17 (.41)	**-0.42 (.04)**	**-0.45 (.03)**

Data are presented as standardized beta estimates+ p-value (p<0.05 are in bold). Hyphenation "rest" implicates the rest of the brain representing all cortical parcels, excluding the one of interest, used as one single ROI. *, FDR-corrected p-values ($p<0.05_{FDR}$). Linear mixed models between connectivity and cognition were adjusted for age, sex, education, and contained an interaction term for connectivity*time. Abbreviations: BL, baseline; FU, follow-up

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 $p<0.05_{FDR}$) and pDMN-MTMS connectivity (β= -3.37 $p<0.05_{FDR}$), but not SCD status, were associated with lower cognitive performance over time. There were no significant 3-way interaction effects between time*connectivity*SCD.

Connectivity between a priori defined ROIs and all other brain parcels**.** For exploratory purposes, we assessed the relationship between the pDMN, the avDMN and the MTMS and all other brain parcels. No results survived $p<0.05_{FDR}$ correction. Using a more lenient statistical threshold of $p<0.005$, we found that, compared to SCD[-], SCD[+] showed increased pDMN connectivity in relation to the bilateral middle cingulate cortex and left inferior parietal, and increased MTMS connectivity in relation to bilateral precuneus, middle cingulate, posterior cingulate, inferior occipital and left inferior parietal cortex (Supplementary 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 prior to 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 BOLD time-series between the pDMN and other regions of interest. In keeping with

prior results, we found increased connectivity between the pDMN and medial temporal memory system (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, resting-state (rs)fMRI studies on cognitively intact individuals have found both 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 controls and patients with AD.[22–24] It is hypothesized that prior to 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 pre-dementia stages across imaging modalities with rsfMRI, magnetoencephalography and cerebral metabolism (i.e. FDG-PET).[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 lower immediate memory and global cognition over time. Similarly, our data indicates 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 individuals with SCD when compared to individuals without SCD. Others have shown that memory clinic patients with SCD have poorer memory functioning over time compared to controls.[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 are able to 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 and tau 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. Last, 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.

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 therefore 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.

SUPPLEMENTARY MATERIALS

https://www.sciencedirect.com/science/article/pii/S2451902217302306?via%3Dihub

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