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Aberrant memory system connectivity and working memory performance in subjective cognitive decline

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ABSTRACT

Subjective cognitive decline, a perceived worsening of cognitive functioning without objective deficit on assessment, could indicate incipient dementia. However, the neural correlates of subjective cognitive decline as assessed by magnetic resonance imaging remain somewhat unclear. Here, we evaluated differences in functional connectivity across memory regions, and cognitive performance, between healthy older adults aged 50 to 85 with ($n = 35$, $Age = 68.5 \pm 7.7$, 22 female), and without ($n = 48$, $Age = 67.0 \pm 8.8$, 29 female) subjective cognitive decline. We also evaluated neurite density, fractional anisotropy, and mean diffusivity of the parahippocampal cingulum, cingulate gyrus cingulum, and uncinate fiber bundles in a subsample of participants ($n = 37$). Participants with subjective cognitive decline displayed lower average functional connectivity across regions of a putative posterior memory system, and lower retrosplenial-precuneus functional connectivity specifically, than those without memory complaints. Furthermore, participants with subjective cognitive decline performed poorer than controls on visual working memory. However, groups did not differ in cingulum or uncinate diffusion measures. Our results show differences in functional connectivity and visual working memory in participants with subjective cognitive decline that could indicate potential incipient dementia.

1. Introduction

Subjective cognitive decline (SCD) is a putative, preclinical stage of Alzheimer's disease marked by perceived deterioration in cognitive functioning, in any domain, without overt deficit (Jessen et al., 2014a). Self-report of cognitive decline or memory issues constitutes a criterion for mild cognitive impairment (American Psychiatric Association, 2013; Petersen et al., 1999). However, associations between self-perception of cognitive functioning and objective cognitive deficits are complex (Mitchell, 2008). In some instances, cognitive decline may hinder the ability to make correct self-judgments regarding cognition; that is, objective decline could occur without perception of decline (anosognosia). On the other hand, individuals may experience worrisome subjective decline in memory ability, but test within a normal range on neuropsychological assessment. Taken together, these notions diminish the predictive power of cognitive complaints alone, or the lack thereof, for determining *current* dementia status. However, evidence indicates that these cognitive complaints are predictive of *future* decline and may demarcate incipient dementia that precedes mild cognitive impairment (Gifford et al., 2014; Jessen et al., 2010, 2014b; Reisberg et al., 2008, 2010).

As worrisome cognitive complaint may predict future conversion to mild cognitive impairment or probable Alzheimer's disease, it is important to understand the biological properties of this potential preclinical stage to determine targets for preventative intervention. Previous investigations have determined that individuals with SCD exhibit global atrophy patterns similar to Alzheimer's disease (Peter et al., 2014). Furthermore, previous analyses have observed specific volume

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reductions in hippocampus, amygdala, parahippocampal, entorhinal, temporal, and frontal cortices in older individuals with SCD compared to those without (Hafkemeijer et al., 2013; Jessen et al., 2006; Saykin et al., 2006; Striepens et al., 2010; van der Flier et al., 2004). Moreover, longitudinal analysis of hippocampal atrophy predicts SCD development at follow-up measurements, indicating that biological change may underlie perceived deficit in memory (Cherbuin et al., 2015).

Examination of white matter fiber tract diffusion characteristics have also identified features that separate healthy older adults with and without SCD. Most studies to date, except for Yasuno et al. (2015), have observed lower fractional anisotropy and greater mean diffusivity across the white matter, and in the cingulum bundle specifically (Hong et al. (2015); Li et al. (2016)). These results are similar in spatial location and direction to observed results in mild cognitive impairment and Alzheimer's disease (Rose et al., 2006; Salat et al., 2010). Furthermore, decreased fractional anisotropy in the right posterior cingulum bundle associates with lower Mini-Mental State Examination scores, hinting that posterior cingulate white matter is important for higher cognitive function (Bai et al., 2009). Thus, diffusion characteristics of the cingulum could predict conversion from SCD to objective decline.

Although multiple structural MRI studies consistently identify gray matter volume reductions and lower cingulum fractional anisotropy in SCD, limited observations exist in the extant resting-state functional connectivity literature. Yasuno et al. (2015) noted lower connectivity between retrosplenial and medial prefrontal cortices in SCD. However, Hafkemeijer et al. (2013) observed higher default mode network connectivity, including right hippocampus, in SCD. Due to contrasting results in the extant literature, we aimed to evaluate functional connectivity differences between memory regions to better understand brain characteristic differences between healthy older adults with and without SCD using the two cortical memory systems framework of Ranganath and Ritchey (2012). Heterogeneity of the hippocampus, with structural and functional connectivity differences along the long-axis, is a major component of this framework. The anterior hippocampus connects directly to the amygdala, entorhinal, and perirhinal cortex (Poppenk et al., 2013; Ranganath and Ritchey, 2012). Furthermore, the uncinate fasciculus mediates functional connectivity of the anterior hippocampus to orbitofrontal and ventromedial prefrontal cortex through intermediate entorhinal/perirhinal cortex connectivity; though, anatomic studies have not identified direct hippocampal connections through this tract (Von Der Heide et al., 2013). The posterior hippocampus connects directly and indirectly to default mode network cortical regions, i.e., retrosplenial, posterior cingulate, inferior parietal, precuneus, and medial prefrontal cortices (Adnan et al., 2016; Buckner et al., 2008; Kahn et al., 2008; Poppenk et al., 2013; Qin et al., 2016; Ranganath and Ritchey, 2012). Posterior hippocampal connectivity to default mode regions is ultimately mediated by the cingulum bundle (Heilbronner and Haber, 2014). We chose to work within this framework to respect the heterogeneity of the hippocampus and to examine the effect of SCD on connectivity across both memory systems. We hypothesized that average posterior memory system functional connectivity would be lower in older adults with memory complaints compared to those without such complaints. This hypothesis contrasts the results of Hafkemeijer et al. (2013), but agrees with Yasuno et al. (2015), and would be in same direction as results observed in Alzheimer's disease (Greicius et al., 2004). Furthermore, we anticipated lower functional connectivity specifically between medial prefrontal cortex and retrosplenial cortex in SCD, following Yasuno et al. (2015), as well as lower connectivity between posterior hippocampus and retrosplenial cortex, as decreased connectivity between these regions has been observed in Alzheimer's disease and mild cognitive impairment (Greicius et al., 2004; Wang et al., 2006).

We also evaluated uncinate and cingulum diffusion characteristics in SCD with diffusion weighted images, and anticipated lower neurite density and fractional anisotropy, and higher mean diffusivity based on previously noted observations in SCD (Hong et al., 2015; Li et al., 2016). We also compared individuals with and without SCD on a variety of demographic and cognitive measures including Wechsler Memory Scale IV indices, personality, and depression. We anticipated no difference between groups on demographic or cognitive metrics. We also evaluated *APOE ε4* carrier status differences, as *APOE ε4* carrier status is one of the most important risk factors for Alzheimer's disease (Strittmatter et al., 1993), anticipating greater odds of *APOE ε4* status in SCD.

2. Methods

2.1. Participant recruitment

Data were available for 94 participants at the time of analysis; however, we excluded 11 participants due to missing MRI data, MMSE scores <25, left-handedness, or self-report of repetitive thoughts during the resting-state fMRI scan (e.g. counting) on a post-scan questionnaire. One participant used opioid medication prior to the scan session. Thus, T1 structural and resting-state functional images were available for 83 healthy older adults from Detroit, United States, and Leiden, the Netherlands (mean (*M*) age = 68.5 years, standard deviation (*SD*) = 7.6; 51 females). Of the 83 participants, 35 had SCD (*M* age = 68.5 years, *SD* = 7.7; 22 females) and 48 did not (*M* age = 67.0 years, *SD* = 8.8; 29 females). Diffusion images were available for 47 participants scanned in the United States. We excluded 8 participants for reasons listed above, and 2 additional participants because the diffusion software exited in error during processing. Thus, 37 participants composed the analyzed diffusion data set (10 with and 27 without SCD).

Recruitment at Wayne State University occurred through memory clinics, senior centers, and communities around Metro Detroit, Michigan, and at the Leiden University Medical Center through clinics and centers around Leiden in the Netherlands. Review boards approved the study for both sites. Exclusion criteria included a history of neurological and psychiatric disorders, cardiovascular disease, brain injury, cancer, psychotropic medication use, and magnetic resonance contraindications. Individuals categorized as SCD answered "yes" to the following questions: "Do you have memory complaints? If yes, do these complaints worry you?" Participants with SCD had to be worried about their professed memory issues, as previous analysis suggests that it is mainly those who worry about their perceived decline that have an elevated risk of conversion to Alzheimer's disease (Jessen et al., 2010). Most participants with SCD (34 of 35) sought professional medical advice for their complaints prior to participation but were considered cognitively normal at the time. All participants were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971), and had scores ≥ 25 on the Mini-Mental State Examination (Folstein et al., 1975), which is considered within the cognitively normal range (Tombaugh and Mcintyre, 1992). Furthermore, all SCD participants performed in the cognitively normal range as determined by either clinical assessment or performance on Wechsler Memory Scale VI indices of no less than 1.5 standard deviations below the normative mean. All participants provided informed consent prior to participation.

2.2. Demographic and neuropsychological assessment

In Detroit, the Wechsler Abbreviated Scale of Intelligence II (Wechsler and Hsiao-pin, 2011) evaluated participant IQ. In Leiden, the block design, vocabulary, matrix reasoning, and similarities subtests of the Dutch version of the Wechsler Adult Intelligence Scale III (Wechsler, 1997) determined equivalent IQ. We evaluated memory function with the adult battery of the Wechsler Memory Scale IV (Wechsler, 2009). We converted subscale scores to proportional scores by dividing the total subscale score by the maximum possible. We then created auditory, visual, visual working memory, immediate, and delayed memory index scores by averaging subcategories of proportional scores for group comparison, as in Hayes et al. (2017).

Previous investigations have determined positive associations between depression scores and SCD (Balash et al., 2013; de Guzman et al.,

2015; Montejo et al., 2011; Plotkin et al., 1985), and between SCD and neuroticism and conscientiousness (Ponds and Jolles, 1996; Reid and MacLullich, 2006; Slavin et al., 2010). Thus, we evaluated depression with the Geriatric Depression Scale and the Beck Depression Inventory II (Beck et al., 1996; Yesavage et al., 1983) and neuroticism and conscientiousness with the Big Five Inventory (Goldberg, 1990). It is important to note that the Geriatric Depression Scale contains a question that could relate to perceived memory functioning: 14) "Do you feel you have more problems with memory than most?" Therefore, we compared groups with and without this question, and performed a Fisher's Exact test to evaluate differential participant responding to this question. We have previously reported on these measures for a subset of our current sample (Hayes et al., 2017).

2.3. Magnetic resonance imaging data collection

The Detroit scanner was a 3 T Siemens Magnetom Verio full-body magnet (Siemens Medical AG, Erlangen, Germany) with a 32-channel head coil, located at the Wayne State University Magnetic Resonance Research Facility. Participant scanning in the Netherlands occurred at the Leiden Institute for Brain and Cognition on a 3 T Philips Achieva TX scanner with a 32-channel head coil (Philips Healthcare, Best, the Netherlands).

2.3.1. T1-weighted structural images

Detroit parameters: 3D T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) sequence, 176 slices collected parallel to the bicommissural line, repetition time (TR) = 1680 ms, echo time (TE) = 3.51 ms, inversion time = 900 ms, flip angle = 9.0°, pixel bandwidth = 180 Hz/pixel, GRAPPA acceleration factor PE = 2, field of view (FOV) = 256 mm, matrix size = 384 × 384, voxel size = 0.7 × 0.7 × 1.3 mm.

Leiden parameters: 3D T1-weighted gradient echo sequence, 140 slices, TR = 9.7 ms, TE = 4.60 ms, flip angle = 8.0°, FOV = 224 mm, matrix size = 256 × 256, voxel size = 0.88 × 0.88 × 1.20 mm.

2.3.2. Resting-state functional images

Detroit parameters: T2*-weighted echo-planar imaging sequence, 37 slices parallel to bicommissural line, 200 image volumes, TR = 2200 ms, TE = 30 ms, flip angle = 80°, pixel bandwidth = 2232 Hz/pixel, GRAPPA acceleration factor PE = 2, FOV = 220 mm, matrix size = 80 × 80, voxel size = 2.8 mm isotropic.

Leiden parameters: T2*-weighted echo-planar imaging sequence, 38 slices, 200 image volumes, TR = 2200 ms, TE = 30 ms, flip angle = 80°, FOV = 220 mm, matrix size = 80 × 80, voxel size = 2.75 mm isotropic with a 0.275 mm slice gap in the transverse plane.

2.3.3. Diffusion weighted images

Detroit only: multi-band echo-planar imaging sequence, 84 axial slices with 2.00 mm thickness, TR = 3500 ms, TE = 87.0 ms, multi-band acceleration factor = 3, flip angle = 90°, refocus flip angle = 160°, FOV = 200 mm, pixel bandwidth = 1724 Hz/pixel, echo spacing = 0.69 ms, GRAPPA acceleration factor = 2, anterior to posterior phase encoding, diffusion directions = 96 (6 B0), b-values = 1000 (30 directions) & 1800 (60 directions) s/mm^2, matrix size = 100 × 100, voxel size = 2.00 mm isotropic. We acquired all b-values and directions in a single sequence.

2.4. Image processing

Image processing pipelines utilized FMRIB Software Library tools (FSL 5.0.8; https://fsl.fmrib.ox.ac.uk; Jenkinson et al., 2012), Freesurfer 6.0 (http://surfer.nmr.mgh.harvard.edu/; (Dale et al., 1999; Fischl et al., 1999), TRACULA (Yendiki et al., 2011), 3D Slicer (Pieper et al., 2004), AMICO for neurite density maps (Daducci et al., 2015), and in-house Python scripts.

2.4.1. Structural image processing

To prepare for manual hippocampal region of interest placement, realignment of images with 3D Slicer ensured that the bicommissural line was parallel to the y-axis of the voxel-space mesh grid, and corrected for head tilt and yaw (Supplementary Figure 1). Image resampling enforced 0.5 mm isotropic voxels. After realignment and resampling, we extracted non-brain tissue (i.e., skull and meninges) with the FSL brain extraction tool (Smith, 2002), and created gray matter segmentation maps with FSL's automated segmentation tool (Zhang et al., 2001).

2.4.2. Resting-state functional connectivity analysis

Processing included: removal of the first five image volumes to account for early field inhomogeneities, motion correction (Jenkinson et al., 2002), non-brain structure removal (Smith, 2002), spatial smoothing (6 mm FWHM), and 4D-grand-mean-scaling. We used ICA-based Automatic Removal of Motion Artifacts (Pruim et al., 2015) to remove motion artifacts. Images remained in native-space.

We manually defined anterior and posterior hippocampal coordinates in participant structural space to ensure proper placement, following head and body definitions as in Daugherty et al. (2015). The center for the anterior hippocampus along the long axis was the coronal coordinate between the center of the mammillary bodies and the last coronal slice where the uncal apex was visible. The center of the posterior hippocampus was the coronal slice between the uncal apex and the slice where the fornices ascended from the fimbria, visualized as the slice where the temporal (inferior) horn of the lateral ventricle ascended into body of the lateral ventricle in practice. After determining the sagittal coordinates for anterior and posterior hippocampus, a member of the research team (RPV) traced the hippocampal head and body in the corresponding coronal slices and determined sagittal and coronal coordinates by calculating the center of gravity of the tracings (Supplementary Figure 1; reliability estimates in Supplementary Table 2). We based all other memory system regions of interest on prior coordinates in extant literature (Supplementary Table 1). ROI coordinate selection criteria from manuscripts included: 1) suggested involvement of the region in putative anterior or posterior memory systems per Ranganath and Ritchey (2012), and 2) demonstrated functional connectivity to other memory system regions of interest. The tal2icbm tool transformed coordinates originally defined in Talairach to Montreal Neurological Institute space (Lancaster et al., 2007).

Functional connectivity analysis usually involves linear transformation of images to standard space, and signal extraction at specific coordinates. However, individual variability in brain region size and location may remain after transformation. Because of remnant variability, standard space coordinates did not cover the intended regions for some brains in our dataset. Thus, to ensure correct brain region signal extraction, a semi-automated method determined native space coordinates for non-hippocampal regions. For each participant, we transformed coordinates to T1-weighted structural space for visual inspection. If the coordinate was not in the target region after inspection, raters (RPV, PJP, ZJF) moved it the minimal amount necessary to an accurate location. We defined target locations in consultation with atlases (Nolte, 2013; Woolsey et al., 2017). Manual correction procedures are detailed in Supplementary Figures 2-9.

After confirming that coordinates were within desired areas, we generated spherical regions of interest with 6-mm diameters. We then masked the spheres with binarized gray matter segmentation images calculated with the FSL Automated Segmentation Tool (Zhang et al., 2001). Next, we transferred regions from structural to resting-state functional space with the FSL Linear Image Registration Tool (Jenkinson et al., 2002). Resting-state time course extraction followed. We extracted signal from combined left and right regions to form bilateral regions of interest for region-to-region connectivity analysis when appropriate (midline structures did not have left and right ROIs). We then calculated Fisher Z transformed Pearson's r correlations for each connection of interest in native functional space.

2.4.3. Diffusion weighted image analysis

Diffusion images underwent motion and eddy current correction with the FSL Eddy tool (Andersson and Sotiropoulos, 2016), adjusting B-vectors accordingly. Images then underwent affine registration to corresponding T1-weighted images and subsequent affine registration to 1 mm isotropic Montreal Neurological Institute space. Automated tractography requires these affine mappings; however, tract reconstruction and all other analyses occurred in native space. Prior to tractography, Freesurfer brain segmentation and parcellation reconstructed brain anatomy from T1-weighted images (Dale et al., 1999). The automated Bayesian global tractography algorithm in Freesurfer, Tracts Constrained By Underlying Anatomy (TRACULA), automatically reconstructed and labeled major white matter fiber tracts from the diffusion images, utilizing the "ball-and-stick" model of diffusion (Behrens et al., 2007), and anatomic priors (Yendiki et al., 2011).

Thresholded according to default settings (20% the maximum probability value), posterior probability distribution maps for the left and right parahippocampal cingulum, cingulate gyrus cingulum, and uncinate fiber tracts became native-space regions of interest (Fig. 1). After determining regions, we used neurite orientation dispersion and density imaging analysis (NODDI), as implemented in the AMICO python module, to obtain neurite density maps (Daducci et al., 2015; Zhang et al., 2012). The NODDI tissue model compartmentalizes the diffusion signal into supposed intracellular water, extracellular water, and free water. Neurite density serves as interpretation of the fraction of signal compartmentalized to intracellular water. We extracted weighted means of neurite density values for cingulum and uncinate tracts, as well as weighted means for fractional anisotropy and mean diffusivity. Voxel parameter estimates were weighted by the voxel's posterior probability of tract membership prior to weighted mean calculations over regions of interest. Voxels towards the center of a white matter fiber tract had greater posterior probabilities, while voxels further from the center had lower probability of tract membership. Thus, voxels closer to the boundary of white and gray matter contributed less to the weighted means, which limited the potential contribution of partial volume effects to the results.

2.5. Apolipoprotein E genotype

DNA isolation from saliva was performed using the Qiagen EZ1 Advanced Nucleic Acid Purification System in conjunction with the EZ1 DNA Tissue Kit and the EZ1 DNA Tissue Card. The "High-throughput DNA purification with the Qiagen BioRobot™ EZ1" (http://www.dnagenotek.com/US/pdf/MK-AN-006.pdf), an in-house validated procedure, was followed. Apolipoprotein E (APOE) single nucleotide polymorphism (SNP) genotyping was performed for rs429358 and rs7412 using 5 μl of Kapa Probe Fast ABI Prism 2x qPCR Master Mix, 1 μl template DNA, 0.25 μl of 20x TaqMan SNP Genotyping Assays (Applied Biosystems), and 1.25 μl molecular grade water. A CEPH and an in-house control were run along with samples. Samples and controls were run on an Applied Biosystems Quantstudio 12K Flex Real-Time PCR Instrument using the following thermocycling protocol: 95 °C for 5 min and 40 cycles of 95 °C for 5 s and 60 °C for 30 s. We determined *APOE ε4* status for 81 of the 83 participants.

2.6. Statistical models

We used general linear models to evaluate the effects of subjective memory complaint status on average system functional connectivity, as well as connectivity between individual regions, while controlling for age, sex, and test site. Models initially included all two-way interactions, but these were dropped from the final models as they were not significant. We also used general linear models to evaluate the effects of SCD on cingulum and uncinate neurite density, while controlling for age and sex. Test-site was not a covariate for these models as diffusion data collection occurred only in Detroit. Finally, we used general linear models to evaluate the effects of SCD on Wechsler Memory Scale index and verbal fluency scores while controlling for age, sex, test site, and a test site by memory complaint status interaction. We evaluated the models with this interaction included to confirm that there were no systematic group differences across test sites in cognitive performance; but as we observed no significant interactions ($p > .15$), we dropped them from the final models to interpret the predictors as main effects. To examine all other group differences on demographic or neuropsychological metrics we used independent samples t-tests or Fisher's exact tests. We determined significance by correcting for the number of models involved in an analysis topic, dividing .05 by the number of models and then using the resulting alpha level to test for coefficient significance as well as full model significance. We evaluated average anterior and posterior memory system connectivity models at the $\alpha = 0.025$ level. We then evaluated region-to-region functional connectivity, correcting for each of the 42 specific connections measured, at $\alpha = 0.001$. We evaluated neurite density, fractional anisotropy and mean diffusivity each at $\alpha = 0.008$, correcting for each of the 6 tracts evaluated. Finally, we evaluated Wechsler Memory Scale performance, correcting for the 5 memory indices, at $\alpha = 0.01$. The $\alpha = 0.05$ level served as the cutoff for all other neuropsychological and demographic comparisons as they were not the main foci of this analysis, and because we anticipated no systematic group differences for those variables.

3. Results

3.1. Demographics and neuropsychological assessment

Participant demographics and cognitive results are in Table 1. Demographics for the subsample of participants in the diffusion analysis are in Supplementary Table 5. There was no significant age difference, $t(81) = 0.84$, $p = .40$, between participants with SCD ($M = 68.5$, $SD = 7.7$) and controls ($M = 67.0$, $SD = 8.8$). There was also no difference in sex distribution across SCD status, Fisher's exact test $p = .99$, nor difference in the distribution of individuals with SCD across test sites $p = .18$. Participants with SCD did not differ in *APOE ε4* prevalence

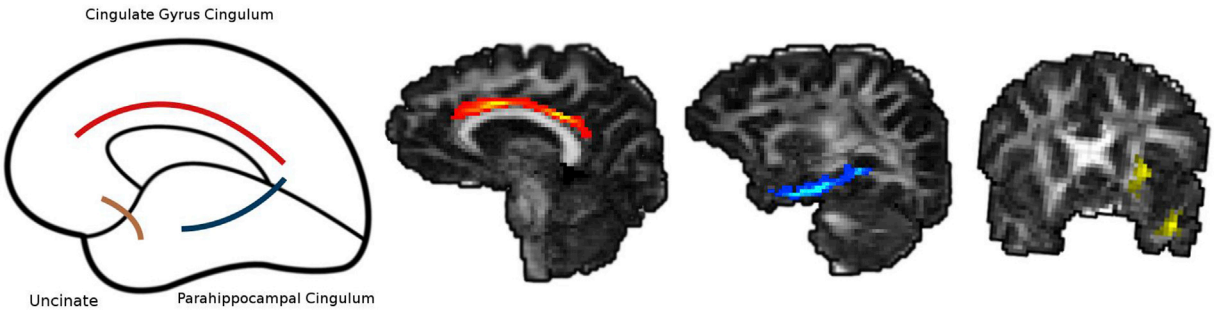

Fig. 1. Cartoon estimation of evaluated fiber tract regions of interest in neurite density analysis, as well as posterior probability distributions of cingulate gyrus cingulum, parahippocampal cingulum, and uncinate fasciculus fiber tracts as determined by TRACULA over an FA map of an example subject.

compared to those without, $p = .22$.

Individuals with SCD had higher Geriatric Depression Scale scores, $t(80) = -2.34$, $p = .02$; however, they were significantly more likely to answer "Yes" to a question directly related to memory functioning ("Do you feel you have more problems with memory than most?"), $p < .001$. After removing this question, the difference between group distributions was no longer significant, $t(80) = -1.73$, $p = .09$. Note that both groups on average were not depressed clinically according to the scale (Yesavage et al., 1983) and did not significantly differ on the Beck Depression Inventory $t(80) = -1.75$, $p = .08$. Furthermore, none of the participants had a history of major depression. We observed no differences between participants with SCD compared to controls on neuroticism $t(79) = -0.64$, $p = .52$, or conscientiousness $t(79) = 1.04$, $p = .30$. Participants with SCD and controls differed neither on IQ measures, $t(73) = 0.01$, $p = .99$, nor Mini-Mental State Examination Scores $t(79) = 1.13$, $p = .26$.

Participants with SCD performed worse on the Wechsler Memory Scale visual working memory index compared to controls ($\beta = -0.23$, $p = .01$, controlling for age, sex, and test site, Supplementary Table 3). SCD status did not significantly relate to other memory indices (Supplementary Table 3). Furthermore, older age associated with poorer performance across all memory indices, and the sample from the Netherlands had better performance across indices.

Table 1
ǂ Cohen's D. ǂǂ Fisher's exact test. ǂǂǂ Beta coefficient from a standardized regression model with age, sex, and test site as included covariates. * Significant at 0.05. ** Significant after multiple comparison correction (Wechsler Memory Scale only).

	Controls	SCD	Effect Size	*p*
Age	66.96 ± 8.79	68.51 ± 7.66	.19ǂ	.40
SCD Distribution across sites	30 DET/18 LEI	16 DET/19 LEI	1.11ǂǂ	.18
Sex distribution across SCD status	29F/19M	22F/13M	.51ǂǂ	.99
Mini Mental State Examination	28.96 ± 1.27	28.65 ± 1.10	.25ǂ	.26
IQ	104.42 ± 15.51	104.40 ± 13.42	<.01ǂ	.99
Memory Functioning Questionnaire Frequency of Forgetting Inverted Mean	2.63 ± .80	3.54 ± .88	1.08ǂ	<.001*
Geriatric Depression Scale	3.42 ± 3.97	5.38 ± 3.44	-.52ǂ	.02*
Geriatric Depression Scale without question 14	3.40 ± 3.39	4.82 ± 3.32	-.39ǂ	.09
GDS 14 "Do you feel you have more problems with memory than most?"	1 Yes/47 No	19 Yes/15 No	7.78ǂǂ	<.001*
Beck Depression Inventory II	4.87 ± 5.37	6.91 ± 4.53	-.39ǂ	.08
Big Five Inventory Neuroticism	18.12 ± 5.71	18.88 ± 4.68	-.14ǂ	.52
Big Five Inventory Conscientiousness	35.50 ± 6.14	34.12 ± 5.22	.23ǂ	.30
Wechsler Visual Memory Index	.52 ± .13	.53 ± .12	-.04ǂǂǂ	.72
Wechsler Auditory Memory Index	.59 ± .11	.57 ± .11	-.14ǂǂǂ	.15
Wechsler Visual Working Memory Index	.48 ± .14	.43 ± .12	-.23ǂǂǂ	.01**
Wechsler Immediate Memory Index	.60 ± .10	.60 ± .09	-.06ǂǂǂ	.56
Wechsler Delayed Memory Index	.52 ± .13	.51 ± .10	-.07ǂǂǂ	.51

3.2. Functional connectivity

3.2.1. Average system connectivity

We observed lower average posterior memory system connectivity in participants with SCD after including age, sex, and test site in the model, and controlling for multiple comparisons ($\alpha = 0.025$). The full model was significant, $F(4, 78) = 12.18$, $p < .001$, with an R^2 of 0.38. SCD status accounted for 4.45% of the variance in average system connectivity, $\beta = -0.22$, $p = .02$, with participants with SCD displaying lower average connectivity. Older age was associated with lower average posterior memory system functional connectivity at trend level, accounting for 3.92% of the variance, $\beta = -0.20$, $p = .03$. The impact of sex on the model was not significant and accounted for 0.12% of the variance, $\beta = 0.04$, $p = .70$. Test site accounted for 28.3% of the variance with participants in Detroit displaying lower average connectivity, $\beta = -0.60$, $p < .001$ (Fig. 2).

Regarding the anterior memory system, the full model was significant, $F(4, 78) = 9.52$, $p < .001$, with an R^2 of 0.33. We found a trend towards lower average anterior memory system functional connectivity in participants with SCD, $\beta = -0.21$, $p = .03$, 4.3% of variance explained, though this result did not survive multiple comparison correction. Age accounted for 5.4% of the variance, with older adults exhibiting significantly lower functional connectivity, $\beta = -0.23$, $p = .01$. Again, sex did not contribute significantly to the model, accounting for 0.11% of the variance, $\beta = 0.04$, $p = .72$. Test site accounted for 22% of the variance, with participants in Detroit displaying significantly lower connectivity, $\beta = -0.53$, $p < .001$.

3.2.2. Region-to-region connectivity

Following the significant difference between groups in average posterior memory system connectivity, we explored group differences in functional connectivity between individual posterior memory system regions with post hoc general linear models. We did not evaluate region-to-region connectivity between anterior memory regions as we did not observe a statistically significant effect of SCD on average anterior memory system connectivity. Controlling for multiple comparisons ($\alpha = .001$), we observed significantly lower connectivity between the precuneus and retrosplenial cortex in participants with SCD, $\beta = -0.35$, $p = .001$, 11.6% of variance explained (Fig. 2). Though, the full model was not significant $F(4, 78) = 4.29$, $p = .003$, $R^2 = 0.18$. Age accounted for 1.18% of variance, which was not significant, $\beta = -0.11$, $p = .29$; furthermore, sex accounted for 0.35% of variance, which was not significant $\beta = 0.07$, $p = .57$. Test site accounted for 7.08% of variance, with participants in Detroit displaying lower functional connectivity, $\beta = -0.30$, $p = .01$; though this was not significant after correction.

3.2.3. Supplemental functional connectivity and visual working memory follow-up analysis

Because of the observed differences in functional connectivity and visual working memory performance between groups, we further explored the relationship between average posterior memory system and retrosplenial-precuneus functional connectivity, and visual working memory performance for the full sample of participants, for the subsample of participants with SCD, and for the subsample of participants without SCD (Supplementary Table 4). Our results did not reveal a significant association between our measures of functional connectivity and visual working memory performance in the total sample or in the subsamples, controlling for age, sex, and test site.

3.3. Diffusion parameters

We did not observe any differences between participants with and without SCD on measures of neurite density, fractional anisotropy, or mean diffusivity for cingulum and uncinate fiber bundles at either the $\alpha = 0.05$ level or the multiple model correction level, $\alpha = 0.008$ (Supplementary Tables 6-8). Furthermore, no age or sex effects on neurite

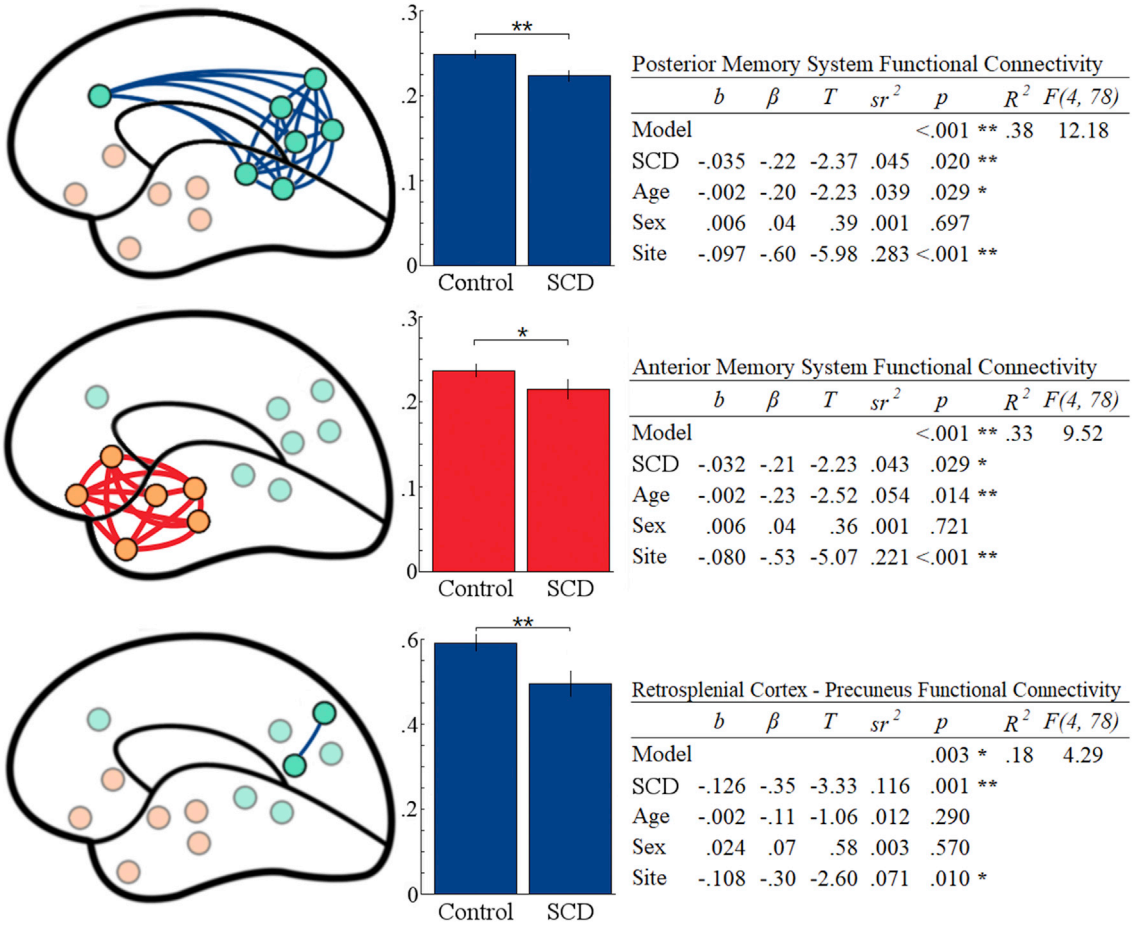

Fig. 2. Top: Average posterior memory system functional connectivity for individuals with and without SCD. Middle: Anterior memory system functional connectivity for individuals with and without SCD. Bottom: Functional connectivity between retrosplenial cortex and precuneus for individuals with and without SCD.

density, fractional anisotropy, or mean diffusivity were observed for the fiber tracts of interest.

4. Discussion

Here, we observed lower average functional connectivity in participants with SCD compared to those without, within a putative posterior memory system (Ranganath and Ritchey, 2012), which largely overlaps with the default mode network. This result is similar to disrupted connectivity observed in Alzheimer's disease (Greicius et al., 2004; Koch et al., 2012) and supports SCD as a pre-mild cognitive impairment stage of Alzheimer's disease. Lower average posterior memory system resting-state functional connectivity could indicate decreased information processing within this system that could influence self-report of memory complaints. While implicated in episodic memory and future planning, default mode network regions, e.g., precuneus, also have a role in self-referential processing and theory of mind (Buckner et al., 2008; Saxe and Kanwisher, 2003). Moreover, the precuneus exhibits distributed network connectivity and has core involvement in integration of self-generated information and external input; and functional imaging studies have determined that recruitment of the precuneus occurs during memory retrieval and self-awareness functioning (Cavanna and Trimble, 2006). In the present analysis, we observed lower functional connectivity between the precuneus and retrosplenial cortex, another important episodic memory region (Vann et al., 2009). This disrupted connectivity may relate to self-awareness of memory processing. Or, it could relate to hippocampal-independent memory retrieval. The implications of lower retrosplenial cortex to precuneus resting-state functional connectivity for SCD remain unclear. In a supplemental follow-up analysis, we did not observe correlations between memory performance and this connection within the full sample, nor within the SCD group alone. Thus, task functional imaging may be necessary to determine the cognitive implications of lower precuneus and retrosplenial connectivity in SCD. Regardless of specific cognitive implications, this disrupted connectivity at wakeful rest may underlie self-reporting of memory issues.

In addition to functional connectivity differences related to SCD status, we also observed age-related connectivity differences. Specifically, we observed lower anterior memory system connectivity, and trend level lower posterior system connectivity, that associated with older age. This age-related lower connectivity in the anterior memory system appears to corroborate previous longitudinal observation that anterior medial temporal lobe connectivity is vulnerable to aging (Salami et al., 2016), but seems to contrast cross sectional findings suggesting that the posterior hippocampus is more sensitive to aging than the anterior hippocampus (Damoiseaux et al., 2016). However, it is important to note that these previous studies examined age-effects across the adult lifespan (age range: 25–80 years and 18–78 years respectively), whereas here we examined age-effects across older age (i.e. 50–85 years). Furthermore, in our previous study, Damoiseaux et al. (2016), we evaluated anterior hippocampal connectivity to default mode regions (i.e. posterior memory system) and not regions specific to the anterior memory system, as was done here.

We observed no associations between memory system functional connectivity and sex, but did consistently observe a site difference, such that average connectivity was lower in the Detroit sample compared to the Leiden sample. Although sequences were almost identical, the

scanners were different, which could have influenced functional connectivity globally. However, there are various other variables that could have influenced overall connectivity differences, such as site differences in hypertension, medication use, body-mass index, racial distribution etc.

Even though we did not anticipate any differences between groups on cognitive measures, as by definition, individuals with SCD perform within the normal range on neuropsychological assessment, we did observe lower visual working memory performance in individuals with SCD. The older adult battery of the Wechsler Memory Scale IV, which is commonly assessed in individuals over 65, does not contain the visual working memory index as there were floor issues during standardization of the spatial addition task (Wechsler, 2009). For the present analysis, we used the standard adult battery and did not encounter floor issues in our sample for the component subtests of the visual working memory index. It is possible that lower visual working memory performance represents executive functioning deficits in SCD as the spatial addition and symbol span subtests that comprise the index require complex mental manipulations of information and discounting of irrelevant stimuli. These manipulations are cognitively demanding, and would recruit the central executive component of the Baddeley working memory model (Baddeley, 2012). As groups did not differ on the visual or immediate memory indices, but did differ on the visual working memory index, the locus of subjective memory complaint related deficit may be within this central executive component. Executive functioning deficit in SCD would relate to an executive component deficit interpretation of Alzheimer's and mild cognitive impairment-related working memory deficits (Huntley and Howard, 2010; Morris and Kopelman, 1986). Our results indicate that challenging visual working memory tests, such as those included in the adult battery of the Wechsler Memory Scale IV, may be sensitive to early cognitive decline. Therefore, inclusion of such tests in clinical assessments should be considered.

In contrast to previously observed white matter fiber tract diffusion parameter differences between healthy older adults with and without SCD (Hong et al., 2015; Li et al., 2016; Selnes et al., 2012, 2013; Yasuno et al., 2015), we did not observe differences between groups in neurite density, fractional anisotropy, or mean diffusivity. Possible reasons for discrepancy across samples could include different operational definitions of subjective decline across studies and differences in other various factors (e.g., medication non-compliance, blood pressure, scanner differences). It is unclear if functional disruption is more sensitive to detect SCD than diffusion parameters; power for our diffusion analyses was lower than for the functional connectivity analyses as there were fewer participants, so we must temper our interpretations of the results of the two modalities in tandem. Regardless, longitudinal analysis could determine if changes in white matter diffusion characteristics follow, or occur in conjunction with, functional brain changes and relate to progression of SCD to objective decline.

A limitation of our functional connectivity analysis was the multi-site/multi-scanner approach. Differences in field heterogeneities and measurement due to site, scanner vendor, and head coil may have influenced site biases for connectivity patterns. Regardless, as there was no difference in the distribution of participants with SCD across sites, and because we controlled for variance related to test site in all our models, it is unlikely that potential issues related to utilizing two scanners from different vendors explain the SCD results. Furthermore, there were no significant interactions between test site and SCD status for any of our analyses, suggesting that systematic site differences do not explain our results. Nevertheless, scanner/site differences were a major source of nuisance variance.

The present analysis is also limited by its cross-sectional approach. Although lower average memory system connectivity was observed at our measurement in adults with SCD, it is possible this lower connectivity might not capture the trajectory of functional connectivity change as subjective impairment progresses to objective decline. Lower connectivity in our sample could have occurred due to cohort effects, and memory system regions may exhibit increased functional coupling in resting-state fMRI at later time points prior to objective decline. Regardless, the present results do corroborate the results from previous analysis of posterior memory components in SCD (Yasuno et al., 2015), and are similar to connectivity results observed in mild cognitive impairment, Alzheimer's disease, and other preclinical dementia (e.g., PiB + or *APOE*-ε4 carrier) studies (Das et al., 2015; Greicius et al., 2004; Koch et al., 2012; Sheline et al., 2010a, 2010b; Zhang et al., 2009). Unfortunately, many of these studies are similarly hindered by the limitations of cross-sectional designs. Therefore, future analyses should track functional change in SCD over time and determine if intrinsic functional connectivity changes associate with change in cognitive performance.

5. Conclusion

We observed lower posterior memory region functional connectivity in SCD, which is similar to previous findings of disrupted connectivity in Alzheimer's disease. Participants with SCD also had poorer visual working memory performance. Our results support SCD as a potential incipient dementia marker. Regardless, longitudinal research must substantiate this claim.

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Conflicts of interest

There are no actual or potential conflicts of interest for any of the authors. None of the author's institutions have contracts relating to the research through which they, or any other organisation, may stand to gain financially now or in the future. There are no other agreements of authors or their institutions that could be seen as involving a financial interest in this work. As listed in the acknowledgments of the manuscript, this work was supported by the Netherlands Organisation for Scientific Research [Veni grant: 016.136.072] to Jessica S. Damoiseaux. The data contained in this manuscript have not been previously published, have not been submitted elsewhere, and will not be submitted elsewhere while under consideration at Neuroimage. As listed in the manuscript, all participants provided written informed consent as approved by local ethics committee. All authors have reviewed the manuscript, approve of its contents, and validate the accuracy of the data.

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Appendix A. Supplementary data

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