Differential neural structures, intrinsic functional connectivity, and episodic memory in subjective cognitive decline and healthy controls

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Abstract

The neural correlates of subjective cognitive decline (SCD; i.e., without objectifiable deficit) remain to be elucidated. Possible causes of SCD include early neurodegeneration related to Alzheimer's disease or functional and structural changes related to sub-clinical depression.

We investigated the relationship between episodic memory performance or memory complaints and structural or functional magnetic resonance imaging (MRI) measures in participants with SCD (n=18) but without psychiatric disorders and healthy controls (n=31).

In SCD, memory complaints were not associated with memory performance but with sub-clinical depression and executive functions. SCD-associated memory complaints correlated with higher amygdala and parahippocampal gyrus (specifically subiculum) gray matter density. In controls, but not in SCD, mesiotemporal gray matter density and superior frontal gyrus functional connectivity predicted memory performance. In contrast, in SCD, only a trend toward a correlation between memory performance and gray matter density in the parietooccipital lobes was observed.

In our memory-clinic sample of SCD, we did not observe incipient neurodegeneration (limited to structural and functional MRI) but rather sub-clinical depression underlying subjective cognitive complaints.

Introduction

Assessing the etiology and prognosis of memory complaints in aging remains challenging, particularly when neuropsychological test performance is within the normal range. On the one hand, memory complaints in cognitively healthy older adults double the annual conversion rate to mild cognitive impairment (MCI) or dementia, compared to people without memory complaints (Mitchell *et al.*, 2014), suggesting an incipient neurodegenerative disease. On the other hand, memory complaints are often linked to psychiatric comorbidity (mainly anxiety and depression), personality characteristics, or medical conditions, e.g., hypothyroidism or anemia (Comijs *et al.*, 2002; Jorm *et al.*, 2004; Blackburn *et al.*, 2014). The clinical term for patients with subjective cognitive complaints with normal test performance is subjective cognitive decline (SCD). In the literature, it has been heterogeneously defined by i) use of memory complaint questionnaires (Dillen *et al.*, 2017; Perrotin *et al.*, 2017), ii) the fact that a memory clinic has been attended (Hafkemeijer *et al.*, 2013; Perrotin *et al.*, 2017; Wirth *et al.*, 2017), or iii) by more extensive criteria including biomarkers such as SCD "plus" (Jessen *et al.*, 2014). To investigate what motivates patients and relatives to attend a memory clinic, we will classify participants as SCD according to definition ii), when complaints do not relate to objectifiable cognitive deficits.

Although biomarkers (i.e., amyloid or tau positron emission tomography, cerebrospinal fluid-based biomarkers) would be of interest in SCD, in many countries, including Germany, such examinations are not performed on healthy individuals. This is mostly due to ethical constraints related to the invasive nature of the examinations. Structural and functional magnetic resonance imaging (MRI) non-invasively provide information about alterations associated with subjective memory complaints. Previous findings on structural changes in SCD are, however, inconclusive: while some studies reported hippocampal atrophy in SCD compared to healthy controls (Reisberg *et al.*, 2008; Scheef *et al.*, 2012; Perrotin *et al.*, 2015) or linked more significant complaints to reduced hippocampal volumes (Stewart *et al.*, 2008), other studies did not find such associations (Jorm *et al.*, 2004; Sun *et al.*, 2016; Wirth *et al.*, 2017).

Atrophy of the medial temporal lobe (MTL) is a hallmark of the most common neurodegenerative disease, i.e., Alzheimer's disease (AD) (Braak and Braak, 1991; Dubois *et al.*, 2010), leading to dementia with predominant episodic memory deficits. We accordingly focus our analyses of structural deficits on the MTL. The MTL communicates with the default-mode network (DMN), which reveals functionally connected brain areas by resting-state fMRI (Greicius *et al.*, 2009). The evidence about changes in the structural and functional connections between the MTL and the DMN, or network changes in SCD in general, is inconsistent: For example, it has been reported that resting-state functional network connectivity in the default-mode network (DMN) decreases

from healthy controls to SCD to MCI, thus linking SCD to Alzheimer's disease (Wang *et al.*, 2013; López-Sanz *et al.*, 2017). However, others reported contradictory findings with increased functional network connectivity of the DMN in SCD compared to controls (Hafkemeijer *et al.*, 2013).

Furthermore, it remains to be established how memory performance is linked to functional neural networks in SCD. Thus far, only a single study assessing functional connectivity (measured by the amplitude of low-frequency fluctuations) reported associations of better verbal episodic memory recognition scores with more robust connectivity in the left inferior parietal lobe in SCD (Sun *et al.*, 2016).

To better understand the neuronal correlates of memory performance in SCD, we here investigated the correlation between memory performance and, based on a literature review, two functional networks previously linked to memory performance: the DMN (Ward *et al.*, 2014; Dillen *et al.*, 2017) and the bilateral frontoparietal control network (Contreras *et al.*, 2017).

We tested two competing theories: if subjective memory complaints are due to incipient AD-related neurodegeneration (as the most frequent neurodegenerative disease leading to dementia), then reduced GM density, hippocampal atrophy, increased white-matter lesion load, a higher APOE ε4 frequency, or altered functional connectivity in memory-relevant networks in SCD participants should be observed. Moreover, in incipient neurodegeneration, we expected a stronger correlation between memory performance, GM density, and functional connectivity in SCD participants than controls (Fouquet *et al.*, 2012; Goerlich *et al.*, 2017). If, however, subjective memory complaints are due to alternative causes, e.g., (sub-) clinical depression, then subjective memory complaint scores should instead be associated with depression scores or brain structures implicated in anxiety regulation, emotions, and self-monitoring, such as the amygdala.

Methods

Participants

Data from 49 participants who had taken part in the more extensive COPCAD study (structural and functional Connectivity alterations in the Posterior Cingulate cortex in Alzheimer's Disease) entered this analysis. General inclusion and exclusion criteria have been described in detail elsewhere (Dillen *et al.*, 2016, 2017). We here provide a summary only. All participants were thoroughly screened for relevant neurological, psychiatric, or medical diseases using medical history, clinical neurological examination, comprehensive blood testing, and contraindications for MRI. Consequently, subjects were excluded if medical conditions could alter cognitive performance, brain structure, or function (e.g., current depressive episode, previous stroke). Of all COPCAD participants (n = 133), only those were selected for the current study, who had a normal structural MRI and normal neuropsychological test scores (i.e., a Mini Mental Examination (MMSE) > 24; each test score not more than 1.5 standard deviations below average of a healthy cohort - adjusted for age, sex, and education, if available; to account for intra-individual variability, exceptions were made if one test only was below -1.5 standard deviations but the average of all tests from the same domain was above -1.5 standard deviations cf. (Dillen *et al.*, 2016)).

Controls were healthy, community-dwelling participants who had not previously attended a memory clinic. They were recruited through flyers, public bulletins, and word-of-mouth advertisement. By contrast, all SCD participants had been recruited through the Memory Clinic Cologne-Jülich at the Department of Neurology, University Hospital Cologne, in cooperation with Institute of Neuroscience and Medicine (INM-3; Cognitive Neuroscience), Research Center Jülich. Please note, the SCD classification applied here differs from the one we applied in previous studies (Dillen *et al.*, 2016, 2017).

FMRI studies are expected to produce strong effects, which is why sample sizes are usually 12 - 20 participants per group (Desmond and Glover, 2002; Szucs and Ioannidis, 2020). Neuroimaging studies on patients often have even smaller sample sizes of 12 - 16 per group (Nellessen *et al.*, 2015). A formal power analysis using G*Power 3.1 (Faul *et al.*, 2007; Erdfelder *et al.*, 2009) yields a high power of .81 for 18 participants for a multiple regression. The parameters used were: test family: t-test; statistical test: linear multiple regression, fixed model, single regression coefficient; one-tailed; effect size f^2: .40 (strong effect); alpha-level: .05, total sample size: 18, number of predictors: 4.

The study had been approved by the ethics committee of the University Hospital of Cologne and was performed following the World Medical Association's declaration of Helsinki in its latest form from October 2013 (World Medical Association, 2013). All participants had signed written

informed consent before participation, and healthy controls were paid a small fee to compensate for transportation and lunch.

Neuropsychological testing

A comprehensive cognitive test battery (in German) assessed memory, executive functions, language, attention, and visuospatial abilities (cf. Table 2). This battery included the MMSE total score (Folstein, Folstein and McHugh, 1975; Kessler, Markowitsch and Denzler, 2000), the verbal learning memory test (VLMT; total of learning steps 1-5, delayed recall step 7, corrected recognition), logical memory (immediate and delayed recall, recognition), design memory (immediate and delayed recall, recognition) and symbol span (total) subtests of the Wechsler memory scale IV (Wechsler, 2009), digit span (total of forward and backward) and digit symbol substitution (DSST) subtest totals of the Wechsler adult intelligence scale (WAIS-III (Wechsler, 1997), Trail making test part A and B in seconds (Reitan, 1958), Stroop test (Stroop, 1935) in seconds (word reading, color naming, interference), word fluency test total of category and “S” words (Aschenbrenner, Tucha and Lange, 2000), brief test of attention total (Schretlen, Bobholz and Brandt, 1996), and the "Leistungsprüfsystem" +50 mental rotation subtest total (Horn, 1983). Depression was examined using the Hamilton Depression Scale with a cutoff score of <17 (Hamilton, 1960). Furthermore, we quantified subjective age-related memory complaints using a German translation of the brief six-item self-rating questionnaire MAC-Q (Crook, Feher and Larrabee, 1992). The latter was chosen as it is one of the most frequently used questionnaires for subjective memory complaints (Rabin *et al.*, 2015). Respondents answered six different questions with a five-point Likert scale, whether they perceived their memory as being "much better", "somewhat better", "about the same", "somewhat poorer", or "much poorer" compared to high school or college level. This leads to a range between 7 (no subjective concern) to 35 (most serious subjective concern) points. Twenty-five points or more indicate the presence of increased levels of subjective cognitive complaints (Crook, Feher and Larrabee, 1992). Neuropsychological testing and MR imaging were performed within three months (on average 13.1 ± 28.0 days). Neuropsychological data were 99.8 % complete (one value of design memory delayed recall and one value of digit symbol substitution test = DSST were missing).

Statistical analyses: demographics, brain pathology markers, and neuropsychological testing

Statistical analyses were performed using the software R version 3.2.3 (https://cran.r-project.org/). Group differences between controls and SCD in years of education and age were assessed using a Mann-Whitney-U test because age and years of education were non-normally

distributed (Shapiro-Wilk Normality Test each $p < .05$). Proportional differences between the groups in sex and APOE ε4 status were tested using a chi-squared test. ST (psychologist in neuroimaging research for his master thesis) assessed the white matter lesion load using the Scheltens total score (Scheltens et al. 1992). NN (neurologist in training) assessed the MTL atrophy using the Scheltens MTL atrophy scale (Scheltens, Leys, *et al.*, 1992). The raters were blinded to diagnosis, filenames, subject names, and any further personal or medical information, and ratings were performed in a pseudo-randomized order across all participants. To test for between-group differences in the Scheltens white matter lesions scale total score, the mean Scheltens MTL atrophy scale score, and the neuropsychological test scores, analyses of covariance (ANCOVA) were performed with the additional package "ez" version 4.3 (http://CRAN.R-project.org/package=ez). For these analyses, group was the factor, and age, sex, and years of education served as covariates of no interest. A general linear model, such as an ANCOVA, can be used if covariates of no interest are to be removed (Hohenfeld *et al.*, 2017). Here, normality as an assumption of ANCOVA was not considered. The possible influence on results was expected to be low since an AN(C)OVA is robust against normality distribution violations (Feir-Walsh and Toothaker, 1974; Schmider *et al.*, 2010). As a measure of effect size for the ANCOVAs mentioned above, eta squared generalized was calculated (Olejnik and Algina, 2003). It states the proportion of explained variance by a variable of interest of the total data variance after correcting for covariates. Neuropsychological test group differences were reported at a significance level of $p < .05$ after applying a false discovery rate (FDR) correction for multiple comparisons (Benjamini and Hochberg, 1995).

Associations between memory complaints, neuropsychological test scores, and depressive traits

To examine the relationship between memory complaints and neuropsychological tests or depressive traits (HAMD), we performed multiple regressions across groups with each test as the dependent variable and MAC-Q values as the independent variable, correcting for age, sex, and education years. Results were thresholded at $p < .05$, corrected for multiple comparisons using FDR correction.

Image acquisition

Scans were performed on a 3.0 T whole-body scanner (Siemens MAGNETOM Trio System, Erlangen, Germany). We used an eight-channel head coil with a positron emission tomography insert (Herzog *et al.*, 2011). Participants lay in a supine position, head first, while foam pads

carefully limited head movements. All participants reported that they felt comfortable at the beginning and during the measurements. High-resolution anatomical images were acquired using a 3D MPRAGE sequence (TR 2250 ms, TE 3.03 ms, FA 9°). They consisted of 176 sagittal slices of 1 mm isotropic voxels with an in-plane matrix of 256 × 256. FLAIR images were collected with the following parameters: TR = 12900 ms, TE = 111 ms, TI = 2370 ms, FA =130°, 48 transversal slices of 3 mm thickness and 0.5 x 0.5 mm in-plane resolution. For the 7-minute resting-state fMRI, participants were asked to keep their eyes open, avoid falling asleep, and hold still. Functional images were collected with a T2*-weighted, single-shot echo-planar imaging sequence with repetition time = 3000 ms, echo time = 30 ms, flip angle = 90°, field of view = 200 x 200 mm^2, matrix = 80 x 80, voxel resolution = 2.5 x 2.5 x 2.8, gap = 0.28 mm. The slice order was descending. With a distance factor of ten percent, we ensured that cross-talk between slices and motion-related spin history artifacts were kept to a minimum. We acquired 140 volumes, each consisting of 50 oblique slices covering the whole brain. Sliced were tilted with an angle of around -30° to the cerebellar tentorium line. This ensured an orientation perpendicular to the longitudinal axis of the hippocampus and full-brain coverage.

Voxel-based morphometry

Structural images were analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and the vbm8 toolbox (http://www.neuro.uni-jena.de/vbm/). They were segmented into GM, white matter, and cerebrospinal fluid and then normalized to the Montreal Neurological Institute (MNI) space with modulation for nonlinear normalization only. Furthermore, they were smoothed with an isotropic Gaussian at full-width-at-half-maximum of 8.6 mm^3 to ensure comparability with other ongoing analyses (not shown).

Whole-brain gray matter and medial temporal lobe masks

A whole-brain GM mask (excluding the brainstem and cerebellum) was created, averaging the smoothed GM volume maps and thresholding the resulting image at 0.2 because it visually included all cortical and subcortical areas. The mask was then resliced to a 2 mm isotropic resolution and restricted all analyses to voxels with GM only. Additionally, for the region-of-interest analyses, an MTL mask was created combining thresholded Harvard Oxford Atlas probability maps (Desikan *et al.*, 2006) of the bilateral amygdala, hippocampus, and parahippocampal gyrus at 20 percent, and multiplying it with the binary GM mask specified before (see Fig. 1).

Functional magnetic resonance imaging preprocessing

The first five images were discarded to allow for stabilization of the magnetic field. The remaining 135 images were preprocessed using FSL's MELODIC (multivariate exploratory linear optimized decomposition into independent components) toolbox version 3.1 (www.fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC, (Beckmann and Smith, 2004)). Images were realigned to correct for head motion using the motion correction linear image registration tool (Jenkinson *et al.*, 2002). Movement parameters (maximum absolute, and maximum and mean relative displacement) were not normally distributed, as revealed by a Shapiro-Wilk normality test (all $p < .05$). Thus, a Mann-Whitney-U test was used, which unveiled no group differences (all $p > .12$). Images were then spatially smoothed with an 8-mm full width at half maximum Gaussian kernel to decrease spatial noise. Afterward, they were resampled to 3 mm isotropic voxels and temporally smoothed using a high-pass filter at 0.02 Hz to reduce the effect of low-frequency drifts. Slice timing correction was performed to correct for timing delays of different slices. Each participant's functional image was registered to her/his high-resolution image (3 degrees of freedom (DOF), translation only) and then to their high-resolution anatomical image (6 DOF, rigid body) with the correlation ratio cost function and a normal search using the linear image registration tool first (Jenkinson *et al.*, 2002). We then applied a single-subject ICA denoising using MELODIC ICA to regress out artifactual components (Quigley *et al.*, 2002; Kiviniemi *et al.*, 2003). Many artifactual components, such as physiological noise, occur at the same low frequency of <0.1 Hz as the spontaneous fluctuations measured by resting-state fMRI. Thus, it is important to identify and remove them objectively. We used a fully automated tool provided by FSL (FMRIB's ICA-based Xnoiseifier) (Salimi-Khorshidi *et al.*, 2014), which detects artifactual components from spatial ICA using MR acquisition characteristics, as well as temporal and spatial features such as the sagittal sinus, cerebrospinal fluid, and white matter, and motion regressors. The classifier was trained on hand-labeled components from five participants with SCD and five controls to avoid a group bias in noise component selection. Noise components were selected following published recommendations (Kelly *et al.*, 2010; Griffanti *et al.*, 2017). Based on the information criterion, a conservative threshold of five was chosen for FIX. Consecutively, noise components were regressed out. Furthermore, motion-related artifacts were reduced using 24 motion-regressors based on realignment parameters (Friston, Williams, *et al.*, 1996; Power *et al.*, 2014). Brain extraction of structural images was performed by multiplying the structural and functional images with a binary brain-extracted mask derived from tissue maps calculated in vbm8 since this approach was more reliable than BET-based brain extraction integrated in FSL, the results of which had not been satisfactory on visual inspection, which is a known problem

(Popescu *et al.*, 2012). The brain-extracted high-resolution anatomical images were then registered to the MNI152 standard template (12 DOF; affine) and further refined with the nonlinear image registration tool with a 10 mm^3 warp resolution (Andersson *et al.*, 2007) and resampled to a 3 mm^3 resolution. Using the same normalization parameters, the co-registered functional images were normalized to MNI space, resulting in an isotropic 2 mm resolution as a compromise between higher-resolution structural and lower-resolution functional images.

Functional magnetic resonance imaging processing

After preprocessing, an exploratory group-level ICA was performed with MELODIC to detect independent brain networks (components). With a pre-defined number of 20 components, large-scale, intrinsically connected networks were generated without *a priori* assumptions of regional distribution. Defining 20 components has two advantages over an automatic estimation of the number of components. First, networks are more large-scale, and the investigator does not need to define between-node connections of interest (Abou-Elseoud *et al.*, 2009). Second, networks are more reproducible between subjects and studies (Pendse, Borsook and Becerra, 2011).

The set of spatial maps from the group-average analysis was used to generate subject-specific versions of the spatial maps and associated time series, using dual regression (Filippini *et al.*, 2009). First, for each subject, the group-average set of spatial maps was regressed (as spatial regressors in a multiple regression) into the subject's 4D space-time dataset. This procedure resulted in a set of subject-specific time series, one per group-level spatial map. Next, those time series were regressed (as temporal regressors, again in a multiple regression) into the same 4D dataset, resulting in a set of subject-specific spatial maps, one per group-level spatial map. We then, based on a literature review, visually selected the bilateral, so-called frontoparietal control networks (Damoiseaux *et al.*, 2006; Thomas Yeo *et al.*, 2011; Contreras *et al.*, 2017), which have been consistently reproduced in the ICA literature and have also been linked to memory functions (Damoiseaux *et al.*, 2006; Contreras *et al.*, 2017). We also selected a DMN component (Beckmann *et al.*, 2005; Thomas Yeo *et al.*, 2011) encompassing the anterior cingulate, medial and lateral parietal (reaching into the occipital lobe) cortices, which is affected in early Alzheimer's disease (Agosta *et al.*, 2012; Koch *et al.*, 2012). To be more region-specific, a mask was generated encompassing voxels with FSL's default of $p < .5$ for component thresholding, multiplied by the whole-brain GM mask described above to exclude non-GM voxels.

General imaging analysis

Imaging analyses were all performed using the FMRIB Software Library FSL v5.0.10 (https://fsl.fmrib.ox.ac.uk, (Jenkinson *et al.*, 2012)) and randomise v2.9 (Winkler *et al.*, 2014). Data quality control was achieved by visually inspecting each data set after each (pre-)processing step. Results were reported at a threshold of $p < .05$, family-wise error (FWE)-corrected with threshold-free cluster enhancement (TFCE), which is more sensitive and interpretable for finding neural activation patterns than voxel- and cluster-based correction methods (Smith and Nichols, 2009). However, TFCE relies on supporting information from surrounding voxels, which might be missing when including narrow GM masks. Therefore, voxel-wise FWE corrections ($p < .05$) showing highly significant results with small spatial extent (Friston, Holmes, *et al.*, 1996) were also considered, when TFCE-corrected results were not significant (applied in one case: a positive correlation of episodic memory and the left frontoparietal control network ICN in controls). Anatomical regions were labeled using the Harvard Oxford Cortical and Subcortical Atlas integrated in FSL. However, a shortcoming is its low precision regarding MTL cytoarchitectonic substructures. To be more specific, a MTL cytoarchitectonic allocation was considered (Amunts *et al.*, 2005; Eickhoff *et al.*, 2005, 2006, 2007). Using FSL's randomize permutation-testing tool, imaging analyses were corrected for age, sex, and education as nuisance regressors in all general linear models. Additionally, analyses with ICNs also included mean relative displacement as a nuisance regressor to reduce the effects of motion further.

To visualize brain-behavior relationships, peak voxel values were extracted and plotted against memory performance using R and the package ggplot2 v2.2.1. To test for group differences in the brain-behavior associations, the multiple regressions of episodic memory on GM density or ICNs included an interaction term group by episodic memory or group by MAC-Q value, respectively, in randomise. P-values were extracted from the peak voxel (see Figure 3). For visualization purposes, we used the MNI152 template in a 0.5 mm isotropic resolution to overlay statistical results on brain sections and the brain-extracted MNI152 template in a 1 mm isotropic resolution for whole-head three-dimensional renderings. All brain-based figures were created in Mango v4.0.1 (http://rii.uthscsa.edu/mango/) and arranged in the GNU Image Manipulation Program v2.8.18 (https://www.gimp.org/).

[FIGURE 1 ABOUT HERE]

Group differences in gray matter density and intrinsic connectivity networks

The first analyses were group differences in GM density in the MTL and the ICNs using ANCOVAs. In post-hoc exploratory analyses, group differences in GM density were also performed with the whole-brain GM mask to avoid overlooking results outside the MTL.

Episodic memory performance or subjective memory complaints related to imaging

Within each group (controls, SCD), voxel-wise multiple regression analyses were used to find associations between either GM density or ICA functional connectivity values with A) a composite score of episodic memory performance (average z-transformed values of delayed recall of the verbal learning test, logical memory, and design memory, cf. Table 2) or B) memory complaints operationalized as MAC-Q (Cacciamani *et al.*, 2017).

We performed interaction analyses to test whether the slopes of correlation between episodic memory and GM density or ICNs differed between groups on a voxel-wise level. Due to a lack of power, the same interactions were also assessed in the significant within-group correlations' peak voxels.

Since there were no significant associations of EM with GM density or ICNS within the SCD group (see results section), we performed post-hoc regressions of episodic memory on GM density and ICNs separately for HAMD, attention, and DSST scores in FSL to test whether other cognitive domains or affective status could explain variance. In additional post-hoc analyses, regressions of MAC-Q on GM density or ICNs were corrected for HAMD in SCD since the MAC-Q values correlated with affective status in SCD.

Link between entorhinal cortex gray matter density and functional network connectivity

As stated in the introduction, we were interested in the interplay of cortical integrity (operationalized *via* mean GM density in the entorhinal cortex within the Jülich atlas mask thresholded at 25 % probability) and any of the three ICNs. Therefore, voxel-wise multiple regressions between mean entorhinal cortex GM density and ICNs in either group were performed.

Multiple regression to evaluate the best prediction of episodic memory

As a final post-hoc-analysis to compare the predictive effect of different factors on episodic memory, an additional multiple regression was performed. The model regressed age, sex, education years, mean relative displacement, HAMD, and functional connectivity values (from the respective peak voxel of the significant clusters obtained correlating episodic memory and the

frontoparietal control network ICNs) of the left and right superior frontal gyrus and right entorhinal cortex GM density (from the peak voxel of the significant cluster obtained correlating episodic memory and GM density) on episodic memory function (cf. Table 5).

Results

Demographic information

Results are also shown in Table 1. There were no significant group differences concerning sex, age, or education years (all p ≥ .05, respectively). Controls (n = 31, 10 females, 21 males) were 63.4 ± 6.7 (range 50 - 72) years old while SCD participants (n = 18, 11 females, 7 males) were 65.1 ± 8.0 (range 51 - 76) years old. Controls had 14.8 ± 4.2 (range 8 - 25) and SCD participants had 12.8 ± 3.5 (range 8 - 18) years of education.

Genetics and brain pathology markers

Results are also shown in Table 1. In controls, 5 out of 29 (17%; 2 data missing) had at least one APOE ε4 allele. In the group of SCD participants, this was true for 5 out of 18 (28%). This difference was not significant (uncorrected p = .62). Scheltens total scores for white matter hyperintensities were 5.8 ± 4.2 (range 1 - 19) in controls and 5.5 ± 3.5 (range 1 - 12) in SCD (uncorrected p = .29). Scheltens MTL atrophy scores were 0.6 ± 0.5 (range 0 - 1.5) in controls and 0.7 ± 0.5 (range 0 - 1) in SCD (uncorrected p = .55).

Group differences in neuropsychological testing

Neuropsychological test results are displayed in Table 2. SCD participants performed worse than controls in the verbal learning test immediate recall, trail making test A, trail making test B, Stroop interference, word fluency, and the digit symbol substitution test. Notably, all participants performed within normal ranges. SCD participants, however, had increased MAC-Q and HAMD scores.

Group differences in gray matter density and functional networks

There were no group differences in GM density in the MTL ROI or on the whole-brain level (FWE-corrected p > .05). There were also no group differences in the DMN or frontoparietal control network ICNs connectivity z values (FWE-corrected p > .05).

Associations between memory complaints, neuropsychological test scores, and depressive traits

MAC-Q values correlated positively with HAMD scores (corrected p = .011, standardized ß = .48). MAC-Q values did not correlate with memory scores or other non-memory domain scores (all corrected and uncorrected p > .05).

Subjective memory complaints and medial temporal lobe structures

MAC-Q values did not correlate with MTL GM density in controls. In SCD, however, GM density in the left anterior amygdala (FWE-corrected $p < .05$; 168 mm^3; x = -14, y = -2, z = -16;) and in the right posterior hippocampal formation (subiculum; FWE-corrected $p < .05$; 192 mm^3; x = 20, y = -26, z = -12) correlated positively with MAC-Q values (cf. Figure 2), i.e., more complaints were associated with higher GM density. The group by episodic memory interaction was significant in a cluster encompassing the left amygdala, hippocampal body, and subiculum (FWE-corrected $p < .05$; 3464 mm^3; x = 18, y = 0, z = -14), indicating a stronger correlation in SCD than in controls. When correcting for HAMD scores, the correlation between MAC-Q and GM density of the left anterior amygdala in the SCD group revealed a trend only (FWE-corrected $p = .065$), while the cluster in the right subiculum remained significant.

Objective episodic memory performance and gray matter density

Voxel-wise multiple regressions (correcting for age, sex, and education) confirmed a positive association between the episodic memory composite score and GM density in the right hippocampus and entorhinal cortex (Figure 3; FWE corrected $p < .05$; 3272 mm^3; x = 32, y= -20, z= -10), as well as in the left hippocampus, entorhinal cortex, and amygdala (Figure 3; FWE corrected $p < .05$; 6880 mm^3; x = -20, y = -20, z = -30) in controls. There was no significant association between the objective episodic memory composite score and GM density in SCD. There was still no such association when adding depression scores, executive function, or attention to the regression models. There was a group by episodic memory interaction in the right superficial amygdala FWE corrected $p < .05$; 48 mm^3; x = 20, y= -8, z= -10), as well as the entorhinal cortex peak voxel ($p = .0002$), confirming a stronger and more positive relationship between episodic memory and GM density in controls compared to SCD participants. Post-hoc analyses on the whole-brain level were performed with a more liberal threshold of $p < .001$ uncorrected and a cluster size of $n \geq 10$ contingent voxels, after excluding three SCD participants with the highest HAMD scores (outliers with more than two standard deviations above study mean). In controls, beyond the MTL, clusters for positive correlations between the episodic memory composite score and GMD were found in the frontal lobes and left putamen. In SCD, such positive correlations were found mostly in parietooccipital areas, namely in the left precentral gyrus, right lingual gyrus, right precuneus, and right superior parietal lobule (cf. Table 3).

Objective episodic memory performance and functional brain networks

Voxel-wise multiple regressions (correcting for age, sex, education, and mean relative displacement) confirmed a positive association between the episodic memory composite score in the right superior frontal gyrus of the left frontoparietal control network in controls (FWE-corrected $p < .05$; 328 mm^3; x = 22, y = 20, z = 60). In the left frontoparietal control network, connectivity within the right superior frontal gyrus predicted episodic memory performance in controls (FWE-corrected $p < .05$; 24 mm^3; x = -10, y = 38, z = 48). There was no significant association between episodic memory performance and intrinsic connectivity of the DMN or frontoparietal control networks in SCD participants. There was still no such association when adding depression scores, executive function, or attention to the regression models.

Besides, there was an interaction between group and episodic memory performance on connectivity in the left and right superior frontal gyri peak voxels ($p = .015$ and $p = .0016$, respectively), indicating a more robust positive relationship in controls compared to SCD.

Post-hoc analyses on the whole-brain level with a more liberal threshold of $p < .001$, uncorrected, and ≥ 10 contingent voxels, after excluding three SCD participants with the highest HAMD scores revealed FC correlates of episodic memory in SCD (N = 15, see Table 4) more prominently in posterior brain regions and not in the frontal lobe. Specifically, positive correlations were found in SCD participants in the right intracalcarine sulcus of the DMN ICN, and in the left superior temporal gyrus, left supramarginal gyrus, and left postcentral gyrus of the left frontoparietal control network ICN.

Link between entorhinal cortex gray matter density and functional network connectivity

Voxel-wise multiple regressions (correcting for age, sex, education, and motion) showed a positive association between mean entorhinal cortex GM density and z values in the bilateral lingual gyri DMN ICN in controls (Fig. 6; FWE-corrected $p < .05$; right: 3960 mm^2, x = 12, y = -46, z = -2; left: 424 mm^2, x = -12, y = -48, z = -2). There was no such association between GM density and functional network connectivity in SCD participants. Specifically, there was a group by GM density interaction in the bilateral lingual gyrus of the DMN ICN (FWE-corrected $p < .05$; right: 4072 mm^3, x = 12, y = -64, z = 10; left: 344 mm^3, x = -14, y = -50, z = -2) indicating a stronger and more positive relationship in controls compared to SCD.

No other associations between GM density and functional network connectivity were found in either group.

Multiple regression to evaluate the best prediction of episodic memory function

As revealed by multiple regression, age, and right and left superior frontal gyri functional connectivity were, with high statistical significance and moderate to strong effects, the best predictors for episodic memory performance in controls. Full results are presented in Table 5.

[TABLES 1 - 5 ABOUT HERE]

[FIGURES 2 - 5 ABOUT HERE]

Discussion

Memory complaints in clinically-defined SCD participants without diagnosed psychiatric comorbidities were not associated with memory deficits or degeneration of structural integrity or functional brain networks. Instead, memory complaints were associated with sub-clinical depression and increased GM density in regions previously implicated in self-awareness and fear processing. Interestingly, we observed that the link between episodic memory and structure (GM density) or functional connectivity involving the MTL and frontal regions observed in normal controls was weaker and comprised rather untypical parietooccipital brain regions in SCD.

Relationship between memory complaints, objective neuropsychological testing, and subclinical depression

On a behavioral level, SCD participants did not even show subtle AD-typical cognitive deficits, which would typically affect episodic memory retention (Dubois *et al.*, 2007). Instead, SCD participants performed worse than controls in attention and executive functions such as processing speed or selective attention. These cognitive functions rely on the frontal and parietal lobes' structural and functional integrity and are typically affected in depression (Beats, Sahakian and Levy, 1996; Veiel, 1997; Austin *et al.*, 1999; Koenigs and Grafman, 2009). Alternatively, these non-memory deficits might mediate the relationship between complaints and memory and reflect higher-order cognitive processes (Hertzog *et al.*, 2003; Lee *et al.*, 2012).

Analogously, MAC-Q scores did not correlate with any objective memory score but rather with depressive traits. This lack of correlation between MAC-Q and memory scores is consistent with recent studies (Mattos *et al.*, 2003; Slavin *et al.*, 2010; Buckley *et al.*, 2013; Iuliano *et al.*, 2017). MAC-Q scores have mostly been linked to affective states and partially to personality traits, such as higher neuroticism (Slavin *et al.*, 2010; dos Santos *et al.*, 2012; Reid *et al.*, 2012; Coutinho *et al.*, 2016). All this is in line with previous reports that medical help-seeking in SCD could primarily be associated with anxiety and subclinical depression (Perrotin *et al.*, 2017).

Memory complaints relate to larger mesiotemporal structures in subjective cognitive decline

There was no atrophy in SCD compared to controls. Furthermore, in correlational analyses, there was no subtle GM density reduction in participants with higher MACQ scores (in either group), which could indicate neurodegenerative disease. However, in SCD, memory complaints correlated positively with GM density in the superficial layer of the left amygdala and the subiculum. With its structural connections to the Nucleus basalis of Meynert, the amygdala's superficial layers are relevant for memory formation, emotion regulation, and sensory information

integration (Benninghoff and Drenckhahn, 2004; Kukolja *et al.*, 2011). In patients with an anxiety disorder and depression, the amygdala show hyperresponsiveness toward emotionally negative stimuli (Siegle *et al.*, 2002; Stein *et al.*, 2002, 2007; Phan *et al.*, 2006; Dannlowski *et al.*, 2007; Etkin and Wager, 2007). Consistent with this, higher amygdala volume was associated with higher social interaction anxiety in healthy women (Günther *et al.*, 2018) and anxious arousal in healthy adolescents (Castagna *et al.*, 2017). Moreover, the amygdala increase activity during explicit self-relevant information processing (Rameson, Satpute and Lieberman, 2010) or self-reflection (Herwig *et al.*, 2010). When correcting this regression of complaints on GM density for depressive traits (HAMD), the association of SCD and amygdala structure remained significant at the trend-level.

Taken together, prior evidence supports the interpretation of our data that in SCD, the amygdalae could constitute a neural correlate for increased anxious and depressive traits as a cause for a more negative estimation of one's memory function. Increased GM density in the subiculum may be related to its known role in episodic memory (Squire, Stark and Clark, 2004; Philippi *et al.*, 2016), internal awareness (Vanhaudenhuyse *et al.*, 2011), and self-referential information processing (Su *et al.*, 2010).

Link between cortical integrity, intrinsic functional connectivity, and episodic memory

As expected, GM density in several MTL structures, including the hippocampus, parahippocampal gyrus, and amygdala, predicted episodic memory performance in controls (Nyberg *et al.*, 1996; Scoville and Milner, 2000; Squire, Stark and Clark, 2004; Hartley and Harlow, 2012; Kühn and Gallinat, 2013; Hirjak *et al.*, 2017). In contrast, this correlation was not found in SCD. Correlations of memory scores and neural correlates are usually more robust in patients with a neurodegenerative disease than in cognitively normal controls (Fouquet *et al.*, 2012; Philippi *et al.*, 2016; Goerlich *et al.*, 2017; Olsen *et al.*, 2017). Thus, our data do not support the hypothesis that SCD results from incipient neurodegeneration. Exploratory analyses suggested that GM density in regions distant from the MTL and frontal lobe structures were associated with objective memory performance in SCD compared to healthy controls. These regions were more posteriorly located, such as the medial and lateral parietal, occipital, and lateral temporal regions in SCD instead of the MTL, frontal poles, and superior frontal gyrus in controls.

Rather than being disrupted (i.e., no functional link), the link between structure and memory performance was most prominent in parietal and occipital lobes instead of MTL and frontal lobes in SCD and controls (in the exploratory analyses). These more posteriorly located cortical regions are also relevant for episodic memory performance (Spaniol *et al.*, 2009; Rugg and Vilberg, 2013).

There was no evidence for altered intrinsic connectivity in SCD compared to controls as an early indicator for neural dysfunction, in analogy to GM density. This finding seems at odds with previous data that suggested decreased DMN connectivity in SCD. These studies interpreted those DMN dysfunctions as indicative of early neurodegeneration at the transition from SCD to mild cognitive impairment or Alzheimer's dementia (Wang *et al.*, 2013; Dillen *et al.*, 2017; López-Sanz *et al.*, 2017). The most parsimonious explanation for this discrepancy may be the different SCD classification used in our study (memory-clinic population vs. community-based sample). In the control group, superior frontal connectivity in the frontoparietal control networks predicted memory performance, consistent with the observation that connectivity within these frontoparietal regions is relevant for memory consolidation (Takashima *et al.*, 2009) and episodic memory retrieval (Rugg and Vilberg, 2013). Again, this correlation was group-specific and not present in the SCD group. In *post-hoc* analyses after excluding participants with elevated depression scores, associations of intrinsic connectivity and episodic memory function in SCD were found in the right visual cortex within the DMN and in the left superior temporal gyrus as well as the left lateral parietal cortex within the left frontoparietal control network. In analogy to the GM density results, associations were found in more posterior regions than in healthy controls, suggesting altered intrinsic connectivity networks in SCD compared to controls. Our results support the notion that posterior regions such as the parietal cortex (Sun *et al.*, 2016) might be more actively involved in memory processing in SCD than in controls. Importantly, these trends were only observed when controlling for depression in the SCD group. The negative influence of depressive traits on memory has been well established (Beats, Sahakian and Levy, 1996; Austin *et al.*, 1999; Rock *et al.*, 2014). Specifically, depression has been shown to alter frontal lobe activity during rest in the dorsolateral prefrontal cortex (Fitzgerald *et al.*, 2006; Northoff, 2016).

Overall, the best predictor for episodic memory function in controls was age, followed by superior frontal gyrus functional connectivity within the frontoparietal control network ICNs. No such associations were present in SCD. One reason for this could have been that episodic memory function in SCD was influenced by variance based on other factors, such as personality traits, sub-clinical depression, and anxiety. However, adding nuisance variables containing depressive scores, executive function, and attention in the regression models did not re-establish the link between episodic memory and MTL cortical integrity, the frontoparietal control network, or DMN intrinsic connectivity in our data.

Link of entorhinal cortical integrity and the default-mode network

In controls, the entorhinal cortex structural integrity was predictive of lingual gyrus functional connectivity z values within the default-mode network. The lingual gyrus is a region of the extended default-mode network and has previously been associated with episodic memory (Kukolja *et al.*, 2016; Richter *et al.*, 2018). Thus, our finding is consistent with previous results that related entorhinal cortex structure to the default-mode network connectivity in healthy older adults (Ward *et al.*, 2015). In contrast, in SCD, no association of entorhinal cortex structure and default-mode connectivity was found.

In sum, in a memory clinic-derived sample, we did not find evidence that SCD without psychiatric comorbidity is an indicator of incipient neurodegeneration. However, more than just observing an absence of evidence, we discovered an association of episodic memory and brain morphology in the opposite direction than expected from neurodegeneration: the association was weaker in SCD than in controls. Whether the prevalence of occult or asymptomatic neurodegenerative disease is different between the SCD and the control groups cannot be elucidated based on the present data as neurodegenerative biomarkers were not assessed due to ethical considerations; this warrants further investigation. However, it is noteworthy that both groups were thoroughly screened for relevant neurological, psychiatric, or medical diseases using medical history, clinical neurological examination, comprehensive blood testing, and structural MRI.

Additionally, we observed the most robust association of memory complaints with sub-clinical depression, not episodic memory, brain atrophy, or brain dysfunction. A novel finding is the association of increased amygdala GM density with memory complaints in SCD as a putative neural correlate of increased awareness or altered self-monitoring. Future studies with greater sample sizes and different SCD definitions are warranted. These studies should also focus on more homogenous subgroups of SCD, which may help to define SCD patients at risk for specific neurodegenerative diseases.

Limitations

Sampling was uneven between groups, and sample sizes were modest. Due to ensuing power restrictions, no subgroup analyses were possible. Furthermore, this cross-sectional study investigated the relationship between neuropsychological performance and self-rating questionnaires with multimodal imaging in a specialized memory clinic cohort. Unfortunately, no quantitative data on anxiety scores or personality traits were collected, limiting the understanding of confounding factors in neuropsychological testing in SCD. Finally, biomarkers (amyloid and tau

proteins) and longitudinal outcomes of the participants were not assessed. Therefore, the potential predictive value of subjective memory complaints (or lack thereof) and their relation to Alzheimer's disease or dementias of other forms could not be assessed.

Conclusions

In conclusion, the data do not disclose an association of SCD and incipient neurodegeneration. Instead, our data, based on a community-serving memory clinic, suggest that SCD without diagnosed psychiatric disorders may be associated with sub-clinical depressive traits.

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Disclosure

The authors report no conflicts of interest.

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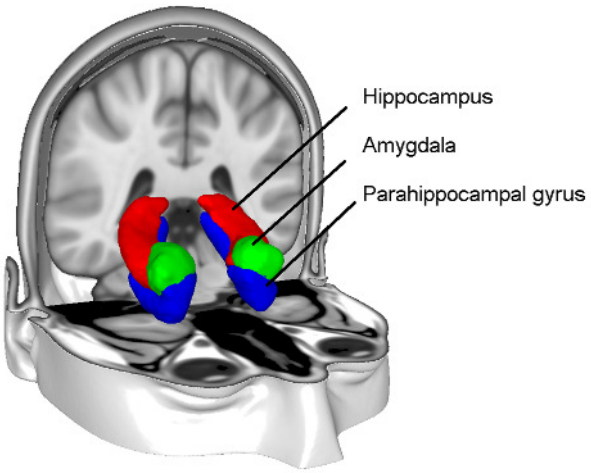

Figure 1. Medial temporal lobe mask. Voxel-wise multiple regressions of the gray matter density maps were restricted to the medial temporal lobe encompassing the hippocampus, parahippocampal gyrus, and amygdala. The mask was created based on volume maps provided by the standardized Harvard-Oxford Anatomical Atlas. For visualization purposes, macroscopic anatomical regions are color-coded.

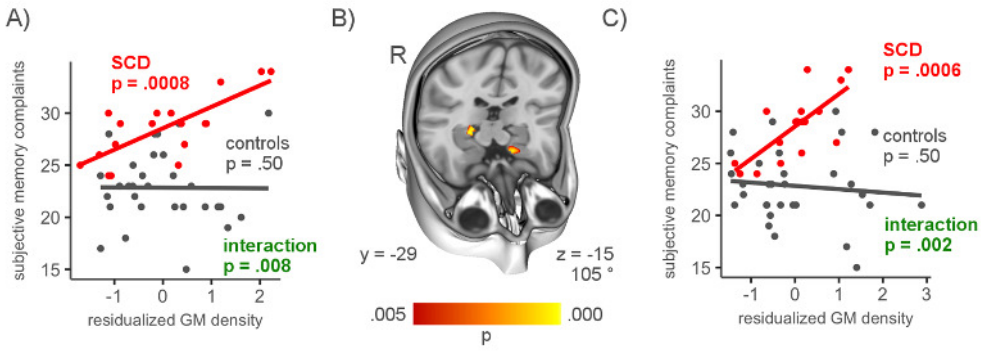

Figure 2. Amygdala and subiculum gray matter density were positively associated with subjective memory complaints in the group with a subjective cognitive decline only. A voxel-wise multiple regression (correcting for age, sex, education) confirmed a positive correlation of gray matter (GM) density within the medial temporal lobe mask in the group with subjective cognitive decline (SCD) only (B). The two peak p values were found in the left amygdala and the right subiculum, two regions associated with memory, emotion regulation, and self-awareness. GM density values were extracted in the respective voxels, residualized for age, sex and education and plotted against subjective memory complaint scores (MAC-Q values) (A for right subiculum and C for left amygdala, superficial layers). This association was not found in controls. In both peak voxels, we found a significant group by MAC-Q values interaction, rendering the association of GM density and subjective memory complaints specific for the SCD group. Both clusters survived family-wise error-correction (FWE) for multiple comparisons ($p < .05$). Cluster characteristics are described in Table 3. Axial cut section is oblique with an angle of 105° towards the coronal section.

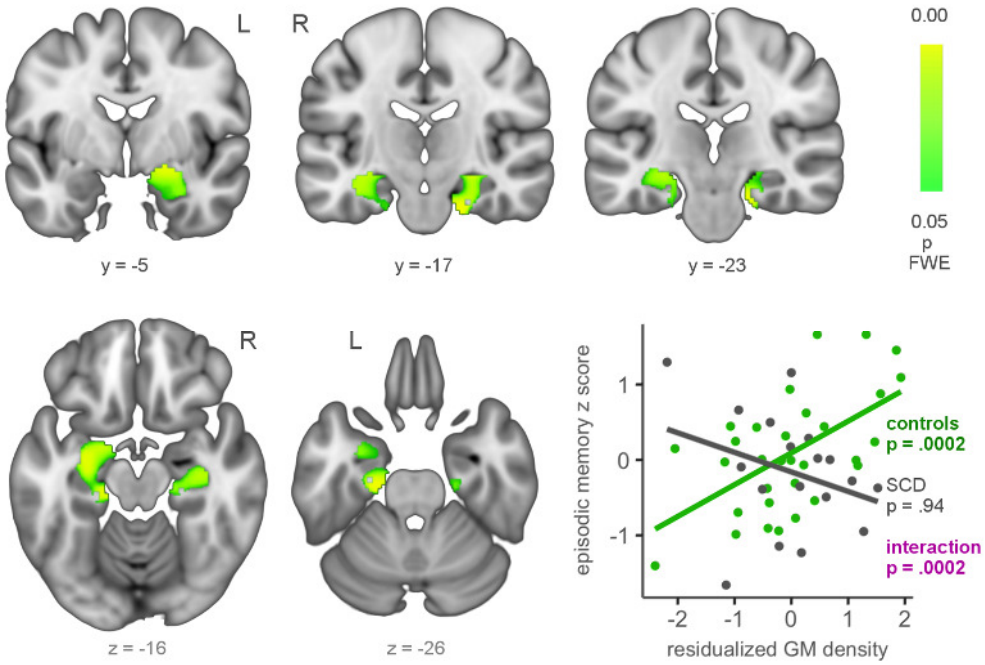

Figure 3. Medial temporal lobe structures were positively associated with episodic memory in controls only. A voxel-wise multiple regression (correcting for age, sex, education) confirmed a positive correlation of episodic memory function and gray matter (GM) density within the medial temporal lobe mask in 31 controls. The peak p-value was found in the left entorhinal cortex, where GM density values were extracted, residualized for age, sex and education, and plotted against memory scores. This association was not found in participants with subjective cognitive decline (SCD). In the peak voxel (x = -20, y = -20, z = -30), we found a significant group by episodic memory function interaction, showing that the association of GM density and episodic memory was specific for the control. Results are reported at $p < .05$, family-wise error-corrected (FWE) for multiple comparisons. Cluster characteristics are described in Table 3.

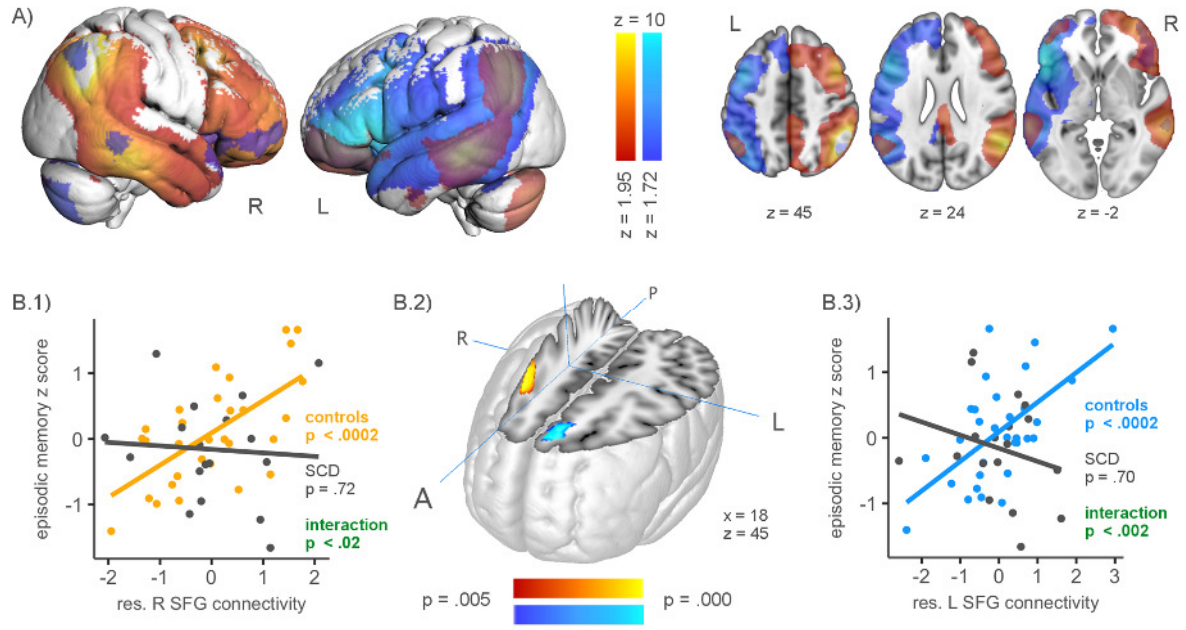

Figure 4. Frontoparietal control networks were positively associated with episodic memory in controls only. A group independent component analysis found two spatial components comprising left- (blue) and right-lateralized (red) frontoparietal control networks previously linked to memory performance (A). A voxel-wise multiple regression (correcting for age, sex, education, and head movement) found a positive association of episodic memory z scores with component z values in the superior frontal gyri (SFG) in the left (blue) and right-lateralized (red-yellow) frontoparietal control networks in controls (B.2). The association was not present in participants with subjective cognitive decline (SCD). Specifically, there was a significant group by episodic memory function interaction displayed in the scatterplots of peak voxel values (B.1 for right-lateralized functional network: x = -10, y = 38, z = 48; and B.3 for left-lateralized functional network: x = 22, y = 20, z = 60; residualized component z values). Voxel-wise results survived family-wise error-correction (FWE) with corrected p < .05. Cluster characteristics are described in Table 3.

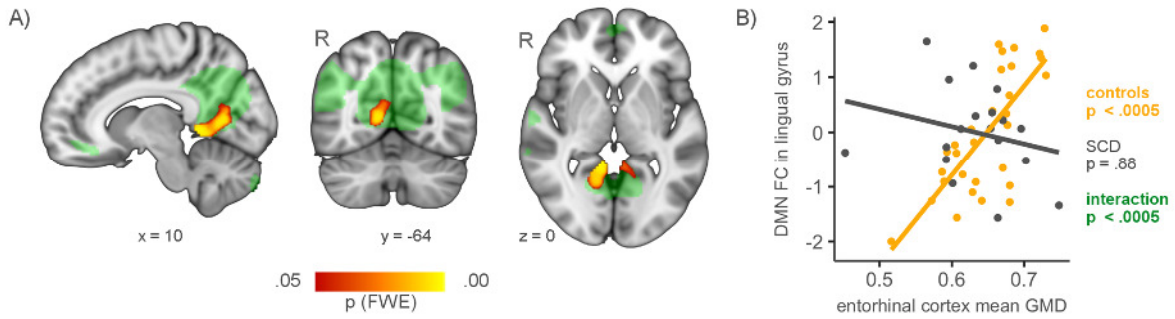

Figure 5. Entorhinal cortex integrity was positively associated with default-mode network functional connectivity in controls only. A voxel-wise multiple regression (correcting for age, sex, education, and motion) confirmed a positive correlation of mean entorhinal cortex gray matter density (GMD) in the bilateral lingual gyri of the default-mode network (DMN, green area) in 31 controls (A). In the peak voxel (x = 12, y = -46, z = -2), FC z values were extracted, residualized for age, sex and education and plotted against functional mean entorhinal cortex GMD values. This association was not found in participants with subjective cognitive decline (SCD). In the peak voxel, we found a significant group by entorhinal cortex GMD and DMN functional connectivity (FC) interaction, showing that the association of entorhinal cortex GMD and DMN FC was specific for the control group (see scatter plot B). Results are reported at $p < .05$, family-wise error-corrected (FWE) for multiple comparisons.