Lifelong experiences as a proxy of cognitive reserve moderate the association between connectivity and cognition in Alzheimer's disease

Ersin Ersoezlue*[1], Boris-Stephan Rauchmann*[1,3,29], Thomas Schneider-Axmann[1], Michael Wagner[4,5], Tommaso Ballarini[4,5], Maia Tatò[1], Julia Utecht[1], Carolin Kurz[1], Boris Papazov[1], Selim Guersel[1], Lena Burow[1], Gabriele Koller[1], Sophia Stöcklein[2], Daniel Keeser[1], Claudia Bartels[6], Frederic Brosseron[4,5], Katharina Buerger[3,7], Arda Cetindag[8], Peter Dechent[9], Laura Dobisch[10], Michael Ewers[3], Klaus Fliessbach[4,5], Ingo Frommann[4,5], John D. Haynes[11], Michael T. Heneka[4,5], Daniel Janowitz[3], Ingo Kilimann[12,13], Luca Kleinedam[4], Christoph Laske[14,15], Franziska Maier[16], Coraline D. Metzger[10,17,18], Matthias H. Munk[14,15], Oliver Peters[8,19], Lukas Preis[19], Josef Priller[19,20,21], Alfredo Ramirez[4,5,22], Sandra Roeske[4], Nina Roy[4], Klaus Scheffler[23], Anja Schneider[4,5], Annika Spottke[4,24], Eike J. Spruth[20], Stefan Teipel[12,13], Jens Wiltfang[6,13,25], Steffen Wolfsgruber[4,5], Renat Yakupov[10], Emrah Duezel[10,17], Frank Jessen[4,16,26], Robert Perneczky[1,3,27,28,29]

1. Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany
2. Department of Radiology, University Hospital, LMU Munich, Munich, Germany
3. German Center for Neurodegenerative Diseases (DZNE, Munich), Munich, Germany
4. German Center for Neurodegenerative Diseases (DZNE) Bonn, Bonn, Germany
5. Department for Neurodegenerative Diseases and Geriatric Psychiatry, University Hospital Bonn, Germany
6. Department of Psychiatry and Psychotherapy, University Medical Center Goettingen, University of Goettingen, Goettingen, Germany
7. Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Munich, Germany
8. Charité – Universitätsmedizin Berlin, Department of Psychiatry and Psychotherapy, Campus Benjamin Franklin, Berlin, Germany
9. MR-Research in Neurology and Psychiatry, Georg-August-University Göttingen, Germany
10. German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany
11. Bernstein Center for Computational Neuroscience, Charité — Universitätsmedizin, Berlin, Germany
12. German Center for Neurodegenerative Diseases (DZNE), Rostock, Germany
13. Department of Psychosomatic Medicine, Rostock University Medical Center, Rostock, Germany
14. German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany
15. Section for Dementia Research, Hertie Institute for Clinical Brain Research and Department of Psychiatry and Psychotherapy, University of Tübingen, Tübingen, Germany
16. Department of Psychiatry, University of Cologne, Medical Faculty, Cologne, Germany
17. Institute of Cognitive Neurology and Dementia Research (IKND), Otto-von-Guericke University, Magdeburg, Germany
18. Department of Psychiatry and Psychotherapy, Otto-von-Guericke University, Magdeburg, Germany
19. German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany
20. Department of Psychiatry and Psychotherapy, Charité, Berlin, Germany
21. Department of Psychiatry and Psychotherapy, Klinikum rechts der Isar, Technical University Munich, Munich, Germany

22. Division of Neurogenetics and Molecular Psychiatry, Department of Psychiatry, University of Cologne, Medical Faculty, Cologne, Germany
23. Department for Biomedical Magnetic Resonance, University of Tübingen, Tübingen, Germany
24. Department of Neurology, University of Bonn, Bonn, Germany
25. Neurosciences and Signaling Group, Institute of Biomedicine (iBiMED), Department of Medical Sciences, University of Aveiro, Aveiro, Portugal
26. Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Köln, Germany
27. Munich Cluster for Systems Neurology (SyNergy) Munich, Munich, Germany
28. Ageing Epidemiology Research Unit (AGE), School of Public Health, Imperial College London, London, UK
29. Sheffield Institute for Translational Neurology (SITraN), University of Sheffield, Sheffield, UK

*These two authors contributed equally and are sharing the co-first authorship.

#Corresponding author:
Prof. Dr. Robert Perneczky
Division of Mental Health of Older Adults, Department of Psychiatry and Psychotherapy
Ludwig-Maximilians-Universität München, Nußbaumstr. 7, 80336 Munich, Germany
Tel.: +49 89 4400-53439, Fax: +49 89 4400-53413, Email: robert.perneczky@med.lmu.de

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ABSTRACT

Alzheimer's disease (AD) is associated with alterations in functional connectivity (FC) of the brain. The FC underpinnings of CR, i.e. lifelong experiences, are largely unknown. Resting-state FC and structural MRI were performed in 76 CSF amyloid-β (Aβ) negative healthy controls and 152 Aβ positive individuals as an AD spectrum cohort (ADS; 55 with subjective cognitive decline, SCD; 52 with mild cognitive impairment; 45 with AD dementia). Following a region-of-interest (ROI) FC analysis, intrinsic network connectivity within the default-mode network (INC-DMN) and anti-correlation in INC between the DMN and dorsal attention network (DMN:DAN) were obtained as composite scores. CR was estimated by education and Lifetime Experiences Questionnaire (LEQ). The association between INC-DMN and MEM was attenuated by higher LEQ scores in the entire ADS group, particularly in SCD. In ROI analyses, higher LEQ scores were associated with higher FC within the DMN in ADS group. INC-DMN remains relatively intact despite memory decline in individuals with higher lifetime activity estimates, supporting a role for functional networks in maintaining cognitive function in AD.

1. INTRODUCTION

Structural and functional brain alterations during aging and disease depend on interactions between individual genetic backgrounds and cumulative effects of lifestyle behaviors and other external influences (Mesulam, 2000; Sperling et al., 2011). Therefore, cognitive trajectories in neurodegenerative diseases such as Alzheimer's disease (AD) are highly variable between individuals (Perneczky et al., 2009; Reed et al., 2010; Valenzuela et al., 2009). Early-life education, good socioeconomic status, work complexity, midlife occupational attainment, and late-life leisure activities have been associated with lower dementia risk (Pettigrew and Soldan, 2019; Scarmeas et al., 2006; Wang et al., 2017). Lifetime experiences may influence individual functional brain processes, potentially moderating between pathology and clinical expression of disease (Perneczky et al., 2019).

The concept of cognitive reserve (CR) was introduced to explain inter-individual differences in cognitive performance related to brain aging or neurodegenerative changes (Stern, 2002). CR encompasses the concepts of neural reserve and neural compensation (Stern, 2017, 2012), referring to the ability of the human brain to maintain cognitive function and recruit compensatory networks in the face of deteriorating network function, respectively (Lee et al., 2019; Perneczky et al., 2019). Socio-behavioral proxies of CR, including education, IQ, occupational complexity, leisure and physical activity, and other protective factors across the lifespan, have been identified in epidemiologic research (Stern et al., 2020) and are reliably captured by the Lifetime of Experiences Questionnaire (LEQ) (Valenzuela and Sachdev, 2007). The LEQ measure can be subdivided into young adulthood, midlife and a late-life score; each period score comprises specific and non-period-specific questions. In younger years, education plays a major role; in midlife, occupation; and social and intellectual activities in later life. The separate analysis of these phases is suitable to reveal different aspects of cognitive reserve, with implications on how effective lifestyle modification for disease prevention could be in different life phases.

Using resting-state fMRI (rs-fMRI), the correlation of blood-oxygen-level-dependent (BOLD) signals between regions of interest (ROIs) can be measured, enabling the detection and analysis of resting-state networks (RSNs) (Biswal et al., 1995, 2010; Damoiseaux et al., 2006). It has been shown repeatedly that the default-mode network (DMN) is affected by disease progression in AD (Greicius et al., 2004), showing remarkable spatial overlap with amyloid pathology (Buckner et al., 2009), hypometabolism and tau pathology in early disease stages (Hoenig et al., 2018; Reiman et al., 2001; Veitch et al., 2019). Functional connectivity (FC) changes in the DMN increase with disease progression (Brier et al., 2012; Chhatwal et al., 2018), even in prodromal and early AD stages (Sheline and Raichle, 2013; Verfaillie et al., 2018). A recent study showed activity disruption in resting-state networks and specific FC changes in patients with AD spectrum in the DELCODE cohort (Amaefule et al., 2021). The anti-correlation between task-negative DMN and task-positive dorsal attention network (DAN) was found to be decreased, i.e. closer to zero, in advanced stages of AD (Brier et al., 2012; Weiler et al., 2017). Intra- and internetwork FC of DMN, especially between the DMN and the DAN, is a major focus of interest in AD research (Elman et al., 2016; Palmqvist et al., 2017).

Early studies on CR proxies were conducted in patients in the dementia stage rather than subjects with prodromal disease (Garibotto et al., 2008). Although more recent studies also included preclinical and prodromal stages of AD (Franzmeier et al., 2017; Franzmeier and Unterauer, 2016; Garibotto et al., 2008; Lee et al., 2019; Mazzeo et al., 2019; Morbelli et al., 2013; Reed et al., 2010; Reijs et al., 2017), where beneficial effects of CR are most pronounced (Scarmeas et al., 2006; Stern, 2012), very few studies included subjects with subjective cognitive decline (SCD) (Du et al., 2021; Jia et al., 2020; Lee et al., 2020; Mazzeo et al., 2019; Reijs et al., 2017; Yang et al., 2020). However, the neural underpinnings of CR are still unclear, especially in the prodromal stage of AD, in which both pharmacologic and non-pharmacologic interventions are likely to be most effective (Morbelli et al., 2013).

Previous studies suggested that CR proxies such as years of education (Arenaza-Urquijo et al., 2013; Bozzali et al., 2015; Franzmeier et al., 2017; Li et al., 2021; Marques et al., 2016; Stern et al., 2020; Weiler et al., 2018), IQ (Franzmeier et al., 2017; Marques et al., 2016) and occupational activities in midlife (Suo et al., 2017) influence rs-fMRI changes due to neurodegeneration. In rs-fMRI studies, CR-associated changes in FC have been reported mainly in regions belonging to the DMN (Arenaza-Urquijo et al., 2013; Bozzali et al., 2015; Perneczky et al., 2006; Weiler et al., 2018) , but also between the DMN and DAN (Franzmeier et al., 2017). It is not clear how individual lifestyle differences influence rs-fMRI changes and cognitive decline in AD.

Here, we aimed to investigate the association between lifestyle at different life-stages and network alterations in patients with patients presenting pathological hallmark of AD and healthy controls (HC), focusing on the DMN. The biological mechanisms underlying CR variables' protective and compensatory effects in AD are still largely unknown; improving our mechanistic understanding of key interactions is crucial for developing effective therapies and preventive strategies (Perneczky et al., 2019).

2. METHODS AND MATERIALS

The dataset analyzed in this study was obtained from the German Center for Neurodegenerative Diseases (DZNE)-Longitudinal Cognitive Impairment and Dementia Study (DELCODE), an observational brain imaging study initiated by the DZNE in 2014 (German Clinical Trials Register: DRKS00007966).

2.1. Standard Protocol Approvals, Registrations, and Patient Consents

At each DELCODE site, the local institutional review boards approved the study protocol and the ethical committees issued local ethical approval. DELCODE is registered at the German Clinical Trials Register (DRKS00007966; 4/05/2015). The study protocol followed the ethical

principles for human experimentation in accordance with the Declaration of Helsinki. All participants in the study provided written informed consent.

2.2. Participants

Eight hundred ninety-three participants were recruited for the DELCODE baseline dataset between May 2014 and August 2018, and 392 participants were eligible for the present analyses because of the availability of CSF biomarkers and appropriate structural and functional MRI data. To ensure that no participants with non-AD neurodegenerative disorders were analyzed, total of 164 individuals either diagnosed as healthy controls but with abnormal amyloid-β (Aβ) CSF concentrations (N=34) or participants with a clinical diagnosis of SCD/MCI/ADD but normal Aβ CSF concentrations (n=117) or participants with increased total-tau (t-tau) and/or phosphorylated-tau (p-tau) 181 but normal Aβ CSF concentrations (N=13) were also excluded. The final cohort consisted of 228 participants, including Aβ negative 76 HC (mean age 68 ± 5, range 60-80, 41 female) and 152 Aβ positive patients with AD (mean age 73 years ± 6, range 61-90 years, 76 female) **(Figure 1)**. The detailed study design, including the inclusion and exclusion criteria and definitions of the diagnostic groups in DELCODE is reported elsewhere (Jessen et al., 2018). Aβ positive participants in the present study were defined as individuals with positive CSF Aβ42 status across the clinical AD spectrum, including individuals with SCD, MCI, and AD dementia (ADD). HC was defined as individuals without Aβ42 in CSF, no memory complaints, and a global score < 0.5 in Clinical Dementia Rating (CDR). Following CSF concentrations were defined in the CSF data of baseline cohort included number of 527 participants (sampling rate: 53%): ≤ 638.7 pg/ml for Aβ42, 510.9 pg/ml for t-tau and 73.65 pg/ml for p-tau, as reported elsewhere (Teipel et al., 2021).

2.3. MR image acquisition and preprocessing

Imaging was performed at nine different DZNE sites on Siemens 3T MRI scanners (three Verio, three TimTrio, one Prisma and two Skyra) using synchronized acquisition parameters. The used MRI machines did not vary within any study site. T1 anatomical imaging was acquired in a 5 min scan (field of view, FOV: 256×256 mm; isotropic voxel size: 1 mm; echo time, TE: 4.37 ms; flip angle, FA: 7; repetition time, TR: 2500 ms; number of slices: 192). Rs-fMRI was acquired in a 7min 54s scan (180 volumes, FOV: 224x224x165mm, isotropic voxel size: 3.5mm, TE: 30ms, TR: 2580ms, FA: 80, parallel imaging acceleration factor 2). Following a visual inspection by an experienced radiologist for completeness, cuts, subject motion, and other artifacts (such as blurring, echoes, and ghosting), images were classified as usable ($N_{structuralMRI}$=208, $N_{functionalMRI}$=185), questionable ($N_{structuralMRI}$=20, $N_{functionalMRI}$=43), or unusable (N=0); only images classified as acceptable were included.

To correct the analyses for inter-individual differences in the degree of cortical atrophy, a meta score of cortical thickness for AD-vulnerable regions was calculated, including the bilateral entorhinal cortices, temporal pole, inferior and middle temporal gyri, inferior and superior parietal cortices, precuneus, and posterior cingulate cortex (Pettigrew et al., 2016). All T1-weighted images were processed in FreeSurfer (version 6.0, http://surfer.nmr.mgh.harvard.edu/) using the recon-all pipeline to derive estimations of cortical thickness in the aforementioned cortical regions (Fischl et al., 2002). Results were checked visually for accuracy and corrected as needed. By adjusting the analyses for cortical thickness levels, we aimed to identify FC changes independent of degree of atrophy, as brain structural characteristics were associated with brain and cognitive resilience before (Ossenkoppele et al., 2020; Perneczky et al., 2010). The mean cortical thickness of vulnerable regions in AD was moderately correlated with the mean global cortical thickness (r=0.32, p<0.001), whereas the correlation differed in study groups (r-ADS=0.31, p-ADS<0.001; r-

HC=0.2, one-tailed-p-HC=0.04). Of note, cortical thickness values of participants were included in all analyses in the present study as the derived mean cortical thickness of the vulnerable regions in AD.

Functional connectivity analysis was performed using the CONN-fMRI Functional Connectivity Toolbox (v17, www.nitrc.org/projects/conn) and SPM12 (www.fil.ion.ucl.ac.uk/spm/) in MATLAB (Release2017b, MATHWORKS). The default preprocessing pipeline for volume-based analyses was used, comprising realignment, slice-time correction, segmentation, and structural and functional normalization. The Artifact Detection Toolbox (ART)-based outlier detection and functional smoothing using a 6 mm kernel (Bastin et al., 2012) was applied. In the denoising step, linear regression of potential confounding effects was performed (Chai et al., 2012): Within each area (white matter and CSF), five potential noise components were estimated, and the blood oxygen level-dependent signal and all other potential confounding effects were averaged across the white matter and CSF. Moreover, residual head motion parameters (3 rotation and 3 translation parameters as well as 6 further parameters representing their first-order temporal derivatives) were regressed out (Chai et al., 2012). A band-pass filter (below 0.008 Hz or above 0.09 Hz) was applied. Consequently, the distribution of correlation between mean motion and FC correlation values were directly compared to an associated null-hypothesis (NH) distribution: 96.8% match with NH (95% or higher match with NH indicate lack of noticeable QC-FC associations) (Ciric et al., 2017).

2.4. Clinical characteristics, cognitive testing, and assessment of CSF biomarkers

Dementia severity was quantified using the CDR-sum of the boxes (CDR-sob). Memory function was assessed using a validated cognitive domain composite score for memory (MEM) (Jessen et al., 2018) derived from the AD Assessment Scale-cognitive subscale word

list, Free and Cued Selective Reminding Test immediate recall, Wechsler Memory Scale Logical Memory 1 and 2, Consortium to Establish a Registry for AD -neuropsychological assessment battery figure savings, Symbol-Digit Modalities Test incidental learning, and Face Name Test. CSF biomarkers were measured using established commercially available analysis kits, including V-PLEX Aβ Peptide Panel 1 (6E10) Kit (K15200E), V-PLEX Human Total Tau Kit (K151LAE) (Meso Scale Diagnostics LLC, Rockville, MD, USA), and Innotest Phospho-Tau (181P) (Fujirebio Germany GmbH, Hannover, Germany) (Jessen et al., 2018). *APOE* ε4 were genotyped using commercially available TaqMan SNP Genotyping Assay (ThermoFisherScientific) (Jessen et al., 2018), and allele carrier status was dichotomized into carriers of one or two alleles vs. non-carriers.

2.5. Assessment of lifestyle parameters

Individual lifestyle differences were assessed using years of formal education and LEQ total and subscores for different stages of life (early adulthood (LEQ-e, age 13 to 30 years), midlife (LEQ-m, age 30 to 65 years), and latelife (LEQ-l, age 65 and older). LEQ was assessed using the validated German version (Roeske et al., 2018). The LEQ scores mirror educational, occupational, and managerial history, social and intellectual activity, and non-specific mental activities (Valenzuela and Sachdev, 2007). The questionnaire was provided to the subjects, who were encouraged to answer to the best of their knowledge and without omissions in the space provided for ticking or in the details of the professions practiced. The latter also enables the so-called motivational reserve to be recorded by using a category system (Forstmeier et al., 2012). We acknowledge that in some patients with dementia, cognitive impairment may have affected the LEQ results. However, the severity of cognitive deficits in this cohort is mild and recall of events from the past should be preserved relatively well.

2.6. Assessment of within- and between- network functional connectivity

Composite scores for intrinsic network connectivity within the DMN (INC-DMN) and for the anti-correlation between DMN and DAN (DMN:DAN) were calculated by averaging fisher-z-transformed bivariate correlation coefficients of FC between pairs of ROI BOLD time-series belonging to the networks, accordingly. Higher levels of ICN indicate higher FC in the corresponding network measured in rs-fMRI. We used definitions of RSNs, obtained as 36 ROIs in DMN and 30 ROIs in DAN (Yeo et al., 2011), defined as anatomical ROIs from the brainnetome atlas (Fan et al., 2016) (**Figure 1** and **Table S1**). The DMN:DAN anti-correlation was calculated as the internetwork connectivity between DMN and DAN, averaging the fisher-z-transformed correlation values between every two nodes from both networks (only inter-network connections).

2.7. Statistical analysis

The statistical analyses were performed using SPSS, version 25.0 (IBM Corp., Armonk, NY), while graphics were made in SPSS or RStudio, v2021.09.1. All tests were two-sided, with $p<0.05$ considered significant. Kruskal-Wallis tests and Chi-square tests were used to compare the baseline sociodemographic, and genetic variables between the study groups. Analysis of covariance (ANCOVA) was conducted to compare differences in clinical and neuropsychological assessments, DMN INC and DMN:DAN anti-correlation between the groups, adjusting for age, sex, years of education, and imaging site, as appropriate. Normal distributions within each group were tested using the Kolmogorov-Smirnov-Test without Lilliefors correction. Variables deviating from the normal distribution were transformed using Rankit's formula (Chambers, 2018).

The multilinear regression models were conducted, testing the CR-proxies separately as the independent and the INC-DMN or DMN:DAN anticorrelation as the

dependent variables. Next, the associations between any two CR-Proxies (years of education, LEQ sub- and total scores) were tested using multilinear regression models. The models were tested in the entire sample and the ADS subgroup and adjusted for age, sex, cortical thickness, MEM, diagnostic group, and study site.

To test our central hypothesis that LEQ moderates the relationship between network deterioration and memory performance, we constructed general linear models (GLMs) with unstructured covariance matrix independently in the entire ADS cohort and the diagnostic subgroups, including interaction terms between continuous CR proxies and FC measures, adjusted for age, sex, cortical thickness, and imaging site. GLMs conducted in the entire AD sample were adjusted for clinical diagnosis. The following two-way interactions were tested in separate models: (1) INC-DMN or DMN:DAN x years of education (2) INC-DMN or DMN:DAN x LEQ-e, (3) INC-DMN or DMN:DAN x LEQ-m, (4) INC-DMN or DMN:DAN x LEQ-l, and (5) INC-DMN or DMN:DAN x LEQ-t. Participants with missing data of LEQ-scores or -subscores (LEQ-e available for N_{HC}=58, N_{SCD}=47, N_{MCI}=43, and N_{ADD}=35; LEQ-m for N_{HC}=60, N_{SCD}=44, N_{MCI}=43, and N_{ADD}=29; LEQ-l for N_{HC}=41, N_{SCD}=41, N_{MCI}=35, and N_{ADD}=31; LEQ-t for N_{HC}=40, N_{SCD}=36, N_{MCI}=34, N_{ADD}=26) were excluded from the analyses in the respective models. The p values from models with LEQ-t and years of education were presented as uncorrected p values given the exploratory character of the study, while the models including LEQ-subscores were corrected for multiple testing using FDR.

General linear models conducted in ROI-level analyses were adjusted for age, sex, cortical thickness, MEM, diagnostic group, and study site. False-discovery-rate (FDR) correction implemented in CONN was applied to adjust p values for multiple ROI-level comparisons.

3. **RESULTS**

Characteristics of the study sample are presented in **Table 1**. As expected, the study groups differed in age, years of education, LEQ-l, *APOE* ε4-status, CDR-sob, MEM, and cortical thickness. HC was the youngest group and had the lowest ratio of *APOE* ε4-carriers and showed the highest LEQ-l subscore. Moreover, MEM and cortical thickness levels were highest in HC, followed by MCI and ADD. The patients with ADD had the highest CDR-sob scores, followed by MCI. Interestingly, LEQ-l subscore was lower in MCI than ADD. The groups within ADS differed from HC in their CSF biomarker profiles. ADD had the highest increase of t-tau and p-tau levels compared to HC and SCD, and t-tau levels compared to MCI.

3.1. The impact of education and LEQ on the association between functional connectivity and memory performance

We explored whether the CR proxies predict the INC composite scores or other CR proxies **(Table 2)**. CR proxies were associated with each other, as expected. LEQ subscores revealed a moderate association with years of education levels, while LEQ-e had the strongest association with educational years among LEQ subscores. However, no significant associations between INC composite scores and CR proxies were found in the regression analyses, neither in the entire sample (including HC) nor in the HC or ADS groups alone (Table 2).

The GLMs revealed a significant attenuating effect of CR proxies on the relationship between MEM and functional network connectivity **(Table 3 and Table S2)**. A median split of the CR proxies was performed to visualize the differences between participants with high and low CR-proxy values (**Figure 2**, only significant interactions are shown). LEQ-t (b=-0.25, $p<0.001$) and LEQ subscores (p-FDR<0.05 for LEQ-e, LEQ-m, and LEQ-l; b=-0.18, b=-0.13 and b=-0.22, respectively) moderated the association between MEM and INC-DMN in SCD (**Figure 2B**), whereas only LEQ-t (b=-0.13, p=0.04) and LEQ-l (b=-0.12, p-FDR=0.03)

showed a moderation in the entire AD group (**Figure 2A**). Participants in ADS and SCD groups with high LEQ scores showed higher MEM scores for low DMN, while participants with low LEQ scores showed higher MEM scores for high DMN **(Figure 2A and 2B)**. In patients with MCI, years of education moderated the relationship between DMN:DAN and MEM (b=0.26, p=0.01), suggesting a closer association between MEM and DMN:DAN in participants with higher years of education **(Figure 2C)**. In contrast, no significant effects of LEQ-t or LEQ subscores on the relationship between INC-DMN or DMN:DAN and MEM score were found.

In contrast to LEQ scores, high education tended to show higher MEM scores for high DMN:DAN, while in the group of patients with AD with low education and MEM were not related to DMN:DAN in MCI **(Figure 2B).** CR proxies did not show significant interactions in ADD. Using a median split may not convey all relevant information on the interaction between continuous variables. Therefore, we also present plots of MEM scores at various levels of CR proxies in supplementary material which show the associations at different levels of the moderators **(Figure S1)**. Of note, the HC group revealed no significant impact of CR proxies on the associations between MEM and INC composite scores (**Table S4**).

3.2. The associations between CR proxies and functional connectivity on ROI analyses

After the moderating effects of LEQ were revealed, we tested the associations between LEQ and ROI analyses, which showed that higher LEQ-t scores were associated with increased connectivity between the left anterior cingulate cortex and right superior temporal gyrus and between the right anterior cingulate cortex (ACC) and bilateral temporal areas in the entire ADS cohort **(Figure 3A)**. SCD revealed more regions with higher connectivity than the entire ADS cohort, mainly between the ACC and temporal areas. More, in patients with SCD, higher LEQ-t levels were associated with an increased FC between temporal areas and inferior frontal gyrus and inferior parietal lobule and between the middle frontal and cingulate cortices

(Figure 3B). In contrast, we found both lower and higher FC between the inferior parietal lobule and both temporal regions and inferior frontal gyrus **(Figure 3C)**. In ADD, LEQ-t was associated with higher FC between the right middle temporal gyrus and the ACC and superior frontal gyrus **(Figure 3D).** We found no significant associations between any CR proxy and ROI-level FC within the DMN in the HC group.

4. DISCUSSION

Years of education and LEQ are socio-behavioral CR proxies, reflecting the degree of mental enrichment during different periods of life. In the present study, we tested their associations with functional network connectivity and their impact on the relationship between functional network connectivity and cognitive performance in individuals across the AD spectrum and HC, focusing on DMN intranetwork connectivity and DMN-DAN internetwork connectivity. We found that a higher level of CR attenuated the association between cognitive function and network deterioration in DMN in the entire ADS cohort, suggesting inter-individual differences in neural reserve that is most prominent in SCD. Interestingly, MCI patients revealed a positive association between DMN:DAN and MEM, suggesting a possible neural compensation. MCI patients with higher CR might display such compensation as the neuropathological changes, i.e. tau pathology, become relevant in this clinical stage. In contrast, the compensation capacity is possibly present. Higher connectivity between inferior parietal and middle frontal regions observed in MCI at a given level of clinical severity might suggests neural compensation. Thus, we provide evidence on potentially modifiable determinants of CR related to active and stimulating lifestyles, going beyond the effects of education and occupation. To the best of our knowledge, this is the first report on the neural underpinning of CR in SCD regarding the rs-fMRI connectivity of DMN.

While the LEQ subscores included in our analyses assess social, academic, occupational, and cognitive lifestyle activities at different stages throughout life (Valenzuela and Sachdev, 2007), we assume that total LEQ-t scores may provide the most comprehensive picture of these lifestyle events, as LEQ scores reflect not only educational and occupational attainment but also leisure activities, associated with CR (Perneczky et al., 2011). Higher levels of LEQ-t attenuated the association between memory and DMN connectivity in ADS. At the same time, only LEQ-l revealed a significant interaction in ADS. This may suggest that LEQ-t is a better overall representation of CR than single subscores, in line with a recent expert consensus suggesting a global nature of socio-behavioral proxies of CR (Stern et al., 2020). Considering the interaction of LEQ-l in ADS, LEQ-l may have a more specific value compared to other LEQ subscores while identifying higher neural reserve. However, reverse causation may interfere with the observations on the LEQ subscore for late life, possibly reflecting early AD symptoms rather than lifestyle choices (Stern et al., 2020); such reverse causation was also be reflected in the lower LEQ-l levels found in ADD. Moreover, participants in the SCD group demonstrated a relatively strong interaction between LEQ, MEM and DMN FC. The SCD group may exhibit the highest neural reserve because of the mild pathological changes present in this particular population allowing reserve mechanisms to occur. In contrast, in later AD stages the effect of CR might be diminished by disease progression.

The LEQ subscore for early adulthood may be a more comprehensive measure of CR compared to years of formal education, most frequently used in research as a CR proxy. Education is likely associated with lifelong activities i.e. intellectual, social and physical activities (Perneczky et al., 2009). The moderate associations between years of education and LEQ subscores or LEQ-t in our results support this notion partly. However, the absence of a moderating effect of education in contrast to LEQ on the association between network connectivity and cognition suggests a closer relationship between LEQ and neural reserve. It

was previously reported that the moderating effect on anti-correlation is inconsistent when comparing years of education tested in different cohorts (Franzmeier et al., 2017). Education, but not LEQ, moderates FC in MCI, suggesting a stronger education-related association between DMN:DAN and MEM, possibly occurring due to neural compensation. This may be explained by a more specific effect of education as CR proxy, while LEQ-e may represent more general aspects of reserve. In line with this notion, LEQ-e shows the same directionality as education in the interaction term (DMN:DAN x LEQ-e).

FC mainly in the ACC and the bilateral superior temporal cortices and multimodal association areas are typically affected by AD pathology (Ingelsson et al., 2004; Maass et al., 2017). Higher connectivity in these areas was associated with higher LEQ-t scores, as a neural correlate of CR in the AD spectrum, pronounced in SCD and possibly sparing the MCI subgroup. Education was suggested to reinforce resting-state FC of the ACC with frontal, temporal, and parietal cortical areas, suggesting mechanisms underlying education-related reserve in healthy older individuals (Arenaza-Urquijo et al., 2013). Similarly, neuropathological and neuroimaging examinations revealed two comparable findings, including (i) higher cortical volume and higher von Economo neuron density in the ACC in individuals with a higher resilience against the effects of age-related cortical atrophy (Gefen et al., 2015; Harrison et al., 2012); and (ii) higher intrinsic connectivity of ACC, maintained by so-called "supernormals", presenting remarkably better memory performance than age-matched peers (Lin et al., 2017), suggesting an involvement in reserve-related mechanisms (Perneczky et al., 2019). Of note, these studies have focused on cognitively normal elderly participants, which might explain the differences compared with our findings. Previous work also reported an interacting effect of FC between CC and left superior temporal gyrus only in Aβ positive amnestic MCI group and suggested a CC-involved neural function as a protective FC alteration against AD pathology (Lin et al., 2017). Furthermore, studies suggested CR-associated higher connectivity assessed via latent CR markers in the right temporal pole (Lee

et al., 2019) and right inferior temporal gyrus (Marques et al., 2016). Differences between the studies can be explained by our focus on the DMN vs. whole-brain analyses, additional analysis methods, i.e., graph theory in these studies and the use of different CR proxy measures.

Another important finding of our study is the asymmetry in FC changes related to CR proxies, namely higher FC in bilateral temporal (right>left) and cingular cortices in AD spectrum, in right superior frontal and left inferior parietal cortices in SCD and the right middle temporal gyrus in AD. Interestingly, lower FC of left inferior parietal FC was associated with higher LEQ-t in MCI. These findings support the observations in patients with prodromal AD, suggesting modifications in FDG-PET due to both neural reserve and neural compensation in prodromal AD (Morbelli et al., 2013). Similar to our findings, the authors concluded that the higher metabolic activity in the left middle temporal and left middle occipital gyri underlie neural reserve. Authors have also suggested higher metabolic activity in the dorsolateral prefrontal cortex, a cortical region not included in the DMN, as neural compensation can explain the difference between studies. A recent systematic review indicated that FC of medial temporal regions and DMN -mainly in the anterior and posterior cingulate cortex- are associated with neural reserve (Anthony and Lin, 2018). The authors also concluded that the FC in frontal and DAN regions are related to neural compensation.

Utilizing a relatively large cohort with rs-fMRI data in different AD stages, including SCD, considering pathological confirmation of AD, and using a comprehensive measure of lifestyle choices across the lifespan are major strengths of our approach. At the same time, we must also acknowledge a few limitations of our study, including the cross-sectional design. Further research is warranted to validate and extend our observations in studies with a longitudinal design. Furthermore, the application of different rs-fMRI analysis methods, such as graph theory, and the further investigation of resting-state networks will help shed light on various neural features of CR. Other relevant future research aims include extending our

approach to potentially modifiable lifestyle factors not reflected with enough detail by LEQ, such as physical activity and nutritional habits, and relevant risk factors, including vascular risk. Other CR proxies, among others latent CR marker approaches, should be tested in association with socio-behavioral CR proxies. These could have fewer limitations considering the indirect and retrospective nature of socio-behavioral CR proxies.

In summary, our results contribute to a better understanding of the brain functional underpinning of CR. They may help to fine-tune future dementia prevention and treatment strategies, for example, by defining specific endophenotypes amenable for disease modification to reduce sample size. Our findings emphasize the possible effectiveness of implementing prevention approaches in AD beginning early in life and demonstrate that healthy lifestyle choices might still be effective in mid- and late-life.

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6. DISCLOSURES

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TABLES AND FIGURE LEGENDS

Table 1. Demographic and clinical characteristics of the study cohort.

[a]Kruskal-Wallis-test, [b]Chi-Square-test, [c]Analysis of Covariance test, adjusted for age, sex and years of education; adjusted mean values are shown. [+]Adjusted additionally for imaging sites. [d]LEQ-e available for N_{HC}=58, N_{SCD}=47, N_{MCI}=43, and N_{ADD}=35; LEQ-m for N_{HC}=60, N_{SCD}=44, N_{MCI}=43, and N_{ADD}=29; LEQ-l for N_{HC}=41, N_{SCD}=41, N_{MCI}=35, and N_{ADD}=31; LEQ-t for N_{HC}=40, N_{SCD}=36, N_{MCI}=34, N_{ADD}=26. Cortical thickness was calculated as the averaged thickness values of the bilateral vulnerable regions in AD (see methods). † Bonferroni-p<0.05 versus HC, ‡ Bonferroni-p<0.05 versus SCD, †† Bonferroni-p<0.05 versus MCI. Abbreviations: SCD, subjective cognitive decline; MCI, mild cognitive impairment; ADD, Alzheimer's disease dementia; CDR-sob, Clinical dementia rating-sum of boxes; LEQ, lifetime experiences questionnaire; LEQ-e, LEQ for early adulthood; LEQ-m, LEQ for midlife LEQ-l, LEQ score for late life; LEQ-t, total LEQ score, Aβ42, Amyloid-β 42; t-tau, total tau; p-tau: phosphorylated-tau.

	Healthy controls (N=76)	**SCD (N=55)**	**MCI (N=52)**	**ADD (N=45)**	**p value**
Age, mean (SD) [a], range	68 (5), 60 - 80	71 (5), 61 - 83†	73 (6), 61 – 84†	75 (6), 64 – 90†,‡	<0.001
Sex, N (% female) [b]	41 (54)	20 (36.4)	27 (51.9)	29 (64.4)	0.04
Years of education, mean (SD) [a], range	14 (3), 9 - 20	15 (3), 10 - 20	14 (3), 8 - 20	13 (3), 8 - 19	0.04
APOE ε4-status, N (% carriers) [b]	13 (17)	30 (54.5) †	31 (59.6) †	28 (62.2) †	<0.001
CDR-SoB, mean (SD) [a]	0.07 (0.17)	0.35 (0.52)	1.81 (1.38) †,‡	4.03 (2.3) †,‡,††	<0.001
Memory composite score, mean (SD) [a+]	0.54 (0.42)	0.32 (0.53)	-0.99 (0.64) †,‡	-1.91 (0.55) †,‡,††	<0.001
Cortical Thickness, mm mean (SD)* [c]	2.7 (0.01)	2.67 (0.11)	2.56 (0.13) †,‡	2.46 (0.15) †,‡,††	<0.001
Binary CSF biomarker profiles					
Aβ42, N (% positive)	0 (0)	55 (100) †	52 (100) †	45 (100) †	<0.001
p-tau, N (% positive)	0 (0)	17 (31) †	27 (52) †	33 (73) †,‡,††	<0.001
t-tau, N (% positive)	0 (0)	15 (27) †	22 (42) †,‡	30 (67) †,‡,††	<0.001
INC composite scores					
DMN, mean [c+] (SD)	0.233 (0.062)	0.228 (0.07)	0.213 (0.071)	0.214 (0.062)	0.54
DMN:DAN, mean [c+] (SD)	-0.036 (0.042)	-0.035 (0.057)	-0.021 (0.051)	-0.031 (0.05)	0.56
LEQ subscores [d]					
LEQ-early adulthood, mean (SD) [a]	37.4 (8.9)	37.2 (7.5)	34.8 (9.7)	33.5 (8.5)	0.13
LEQ-midlife, mean (SD) [a]	44 (11)	45.1 (9.9)	39.1 (13.4)	39.8 (13.2)	0.053
LEQ-late life, mean (SD) [a]	38.2 (9.4)	38.9 (11.1)	36.3 (11.5)	30.7 (7.5) ‡	0.001

LEQ-total, mean (SD) [a]	119.1 (26.8)	122.6 (24.7)	111.7 (30.6)	106.4 (24.1)	0.08

Table 2. Separately tested multilinear regression models with CR proxies as predictors and intrinsic network connectivity composite scores or CR proxies as dependent variables.

Multilinear regression models were adjusted for age, sex, study sites, diagnosis groups, MEM and cortical thickness. Two-tailed p values are shown. *p<0.05, **p<0.001. Abbreviations: CR, cognitive reserve; ADS, Alzheimer's disease spectrum; LEQ-e, LEQ for early adulthood; LEQ-m, LEQ for midlife LEQ-l, LEQ score for late life; LEQ-t, lifetime experiences questionnaire total score; MEM, memory cognitive domain composite score; DMN, intrinsic network connectivity composite score of default mode network; DMN:DAN; anti-correlation between DMN and DAN; b, standardized Beta value; p, p value.

		All (N=228)					HC (N=76)					ADS (N=152)				
Dependent Variables		Predictors					Predictors					Predictors				
		Education	LEQ-e	LEQ-m	LEQ-l	LEQ-t	Education	LEQ-e	LEQ-m	LEQ-l	LEQ-t	Education	LEQ-e	LEQ-m	LEQ-l	LEQ-t
DMN	b	-0.05	-0.02	0.1	0.01	0.08	-0.14	-0.15	0.06	0.15	0.1	0.004	0.06	0.15	-0.05	0.07
	p	0.44	0.81	0.24	0.87	0.34	0.27	0.34	0.69	0.38	0.59	0.97	0.56	0.14	0.65	0.53
DMN:DAN	b	0.08	0.07	0.1	0.05	0.03	0.17	0.23	0.13	0.21	0.27	0.04	0.03	-0.03	0.03	-0.02
	p	0.29	0.39	0.87	0.56	0.77	0.2	0.14	0.37	0.21	0.14	0.68	0.8	0.8	0.75	0.89
Education	b	n.a.					n.a.					n.a.				
	p															
LEQ-e	b	0.66**	n.a.				0.63**	n.a.				0.66**	n.a.			
	p	<0.001					<0.001					<0.001				
LEQ-m	b	0.6**	0.71**	n.a.			0.55**	0.76**	n.a.			0.59**	0.67**	n.a.		
	p	<0.001	<0.001				<0.001	<0.001				<0.001	<0.001			
LEQ-l	b	0.4*	0.51**	0.58**	n.a.		0.29	0.75**	0.74**	n.a.		0.44**	0.42**	0.52**	n.a.	
	p	0.001	<0.001	<0.001			0.09	<0.001	<0.001			<0.001	<0.001	<0.001		
LEQ-t	b	0.64**	0.84**	0.92**	0.8**	n.a.	0.56**	0.92**	0.94**	0.9**	n.a.	0.67**	0.8**	0.9**	0.77**	n.a.
	p	<0.001	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	<0.001	

Table 3. General linear models for testing the interactions between intrinsic network connectivity composite score (intra-network connectivity of DMN or anti-correlation of DMN and DAN) and any given CR proxy on composite memory score. The models with each CR proxy were tested separately.

All models were adjusted for age, sex, imaging sites and cortical thickness. The general linear models conducted in ADS were adjusted additionally for diagnosis groups. The models with significant interaction terms with two-tailed $p<0.05$ values are indicated in bold. The results are presented with all terms included in **Table S2**. Abbreviations: CR, cognitive reserve; ADS, Alzheimer's disease spectrum; SCD, subjective cognitive decline; MCI, mild cognitive impairment; ADD, Alzheimer's disease dementia; b, standardized beta value; SE, standard error; p, p value; p-FDR, false discovery rate corrected p value; LEQ, lifelong experiences questionnaire; LEQ-e, LEQ for early adulthood; LEQ-m, LEQ for midlife LEQ-l, LEQ score for late-life; LEQ-t, total LEQ score; DMN, intrinsic network connectivity composite score of default mode network; DMN:DAN; anti-correlation between DMN and DAN; n.a., not applicable.

	ADS (N=152)					SCD (N=55)					MCI (N=52)					ADD (N=45)				
	Parameter	b	SE	p	p-FDR	Parameter	b	SE	p	p-FDR	Parameter	b	SE	p	p-FDR	Parameter	b	SE	p	p-FDR
DMN	**DMN * LEQ-t**	**-0.13**	**0.06**	**0.04**	n.a.	**DMN * LEQ-t**	**-0.25**	**0.06**	**<0.001**	**n.a.**	DMN * LEQ-t	0.09	0.22	0.68	n.a.	DMN * LEQ-t	0.22	0.14	0.12	n.a.
	DMN * LEQ-e	-0.02	0.06	0.68	0.68	**DMN * LEQ-e**	**-0.18**	**0.06**	**0.01**	**0.01**	DMN * LEQ-e	0.08	0.15	0.59	n.a.	DMN * LEQ-e	0.16	0.09	0.07	n.a.
	DMN * LEQ-m	-0.06	0.05	0.26	0.26	**DMN * LEQ-m**	**-0.13**	**0.05**	**0.01**	**0.01**	DMN * LEQ-m	-0.03	0.14	0.84	n.a.	DMN * LEQ-m	0.13	0.12	0.26	n.a.
	DMN * LEQ-l	**-0.12**	**0.05**	**0.01**	**0.03**	**DMN * LEQ-l**	**-0.22**	**0.06**	**0.001**	**0.003**	DMN * LEQ-l	-0.12	0.20	0.53	n.a.	DMN * LEQ-l	0.06	0.08	0.45	n.a.
	DMN * Education	-0.04	0.04	0.33	n.a.	DMN * Education	-0.14	0.08	0.07	n.a.	DMN * Education	0.01	0.11	0.93	n.a.	DMN * Education	0.01	0.08	0.91	n.a.
DMN:DAN	DMN:DAN * LEQ-t	0.05	0.07	0.45	n.a.	DMN:DAN * LEQ-t	-0.02	0.08	0.79	n.a.	DMN:DAN * LEQ-t	0.13	0.19	0.50	n.a.	DMN:DAN * LEQ-t	0.08	0.10	0.46	n.a.
	DMN:DAN * LEQ-e	0.02	0.06	0.73	n.a.	DMN:DAN * LEQ-e	0.06	0.07	0.41	n.a.	DMN:DAN * LEQ-e	0.01	0.12	0.92	n.a.	DMN:DAN * LEQ-e	0.15	0.08	0.06	n.a.
	DMN:DAN * LEQ-m	0.07	0.05	0.19	n.a.	DMN:DAN * LEQ-m	0.03	0.05	0.54	n.a.	DMN:DAN * LEQ-m	0.08	0.13	0.54	n.a.	DMN:DAN * LEQ-m	0.07	0.08	0.38	n.a.
	DMN:DAN * LEQ-l	0.07	0.06	0.25	n.a.	DMN:DAN * LEQ-l	-0.04	0.10	0.68	n.a.	DMN:DAN * LEQ-l	0.26	0.18	0.16	n.a.	DMN:DAN * LEQ-l	0.11	0.06	0.09	n.a.
	DMN:DAN * Education	0.05	0.05	0.26	n.a.	DMN:DAN * Education	-0.03	0.06	0.60	n.a.	**DMN:DAN * Education**	**0.26**	**0.10**	**0.01**	n.a.	DMN:DAN * Education	-0.01	0.08	0.89	n.a.

Figure 1. Flow diagram of inclusions/exclusions and analyses.

[a]Due to inappropriate ATN-status and/or clinical status (N=164). [b]Regions defined in Brainnetome-Atlas and segmentation of networks were made by using the resting-state networks (54) and resulted in 36 ROI in DMN and 30 ROIs in DAN (**Table S1**). *The CR proxies were tested separately. **Early adulthood corresponds with age 13 to 30 (LEQ-e), mid-life with 30 to 65, and late-life with 65 and above. ***Total LEQ score is calculated as the sum of the three LEQ subscores.

Abbreviations: CR, cognitive reserve; MEM, memory composite cognitive score; ADS, Alzheimer's disease spectrum; SCD, subjective cognitive decline; MCI, mild cognitive impairment; ADD, Alzheimer's disease dementia; INC, intrinsic network connectivity; DMN, default mode network; LEQ, lifelong experiences questionnaire; INC-DMN, intrinsic network connectivity composite score of default mode network; DMN:DAN, inter-network connectivity of default mode network and dorsal attention network. ROI, region of interest.

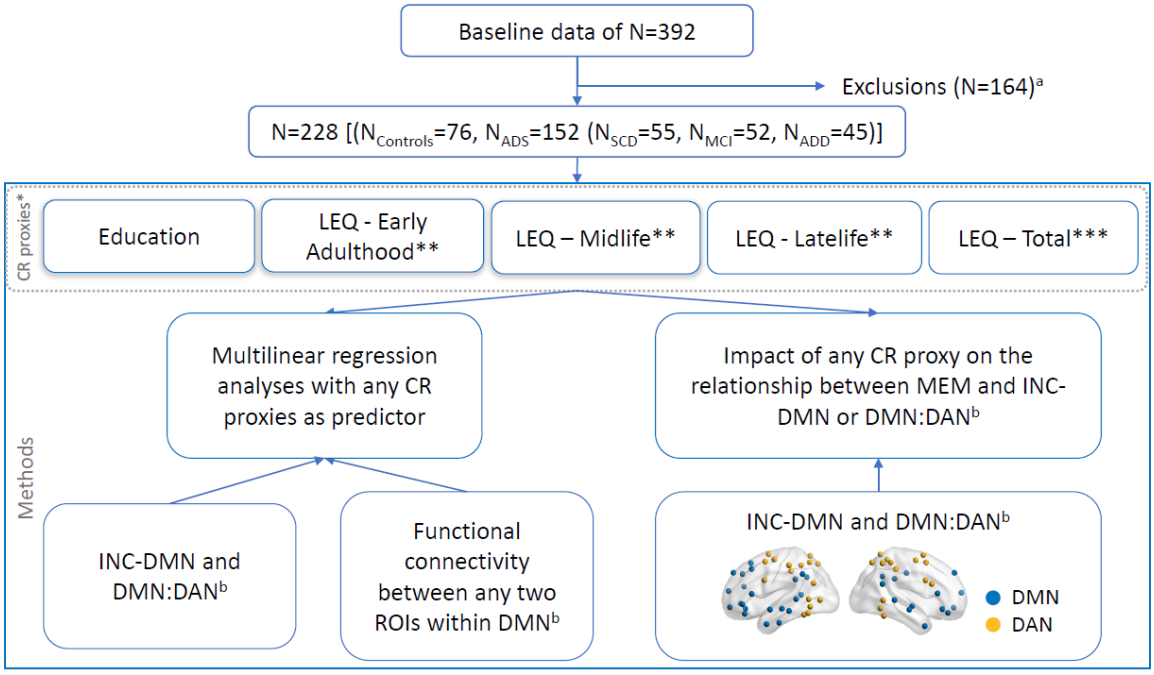


Figure 2. Line plots with 95% confidence interval lines representing the impact of CR proxies, i.e. LEQ scores and years of education, on the association between memory cognitive domain composite score and within- and between-network connectivity scores via median split of CR proxies, separately for A) ADS, B) SCD and C) MCI.

In the models in which statistical tests were conducted with interaction terms, the continuous CR proxy measures were included (see **Table 3**). Binarization of the groups is shown here made for visualization, where significant interactions were found.

Abbreviations: CR, cognitive reserve; ADS, Alzheimer's disease spectrum; SCD, subjective cognitive decline; MCI, mild cognitive impairment; LEQ, lifelong experiences questionnaire; LEQ-e, LEQ for early adulthood; LEQ-m, LEQ for mid-life LEQ-l, LEQ score for late-life; LEQ-t, total LEQ score; MEM, memory composite score; DMN, intrinsic network connectivity composite score of the default mode network; DMN:DAN, inter-network connectivity of default mode network and dorsal attention network.

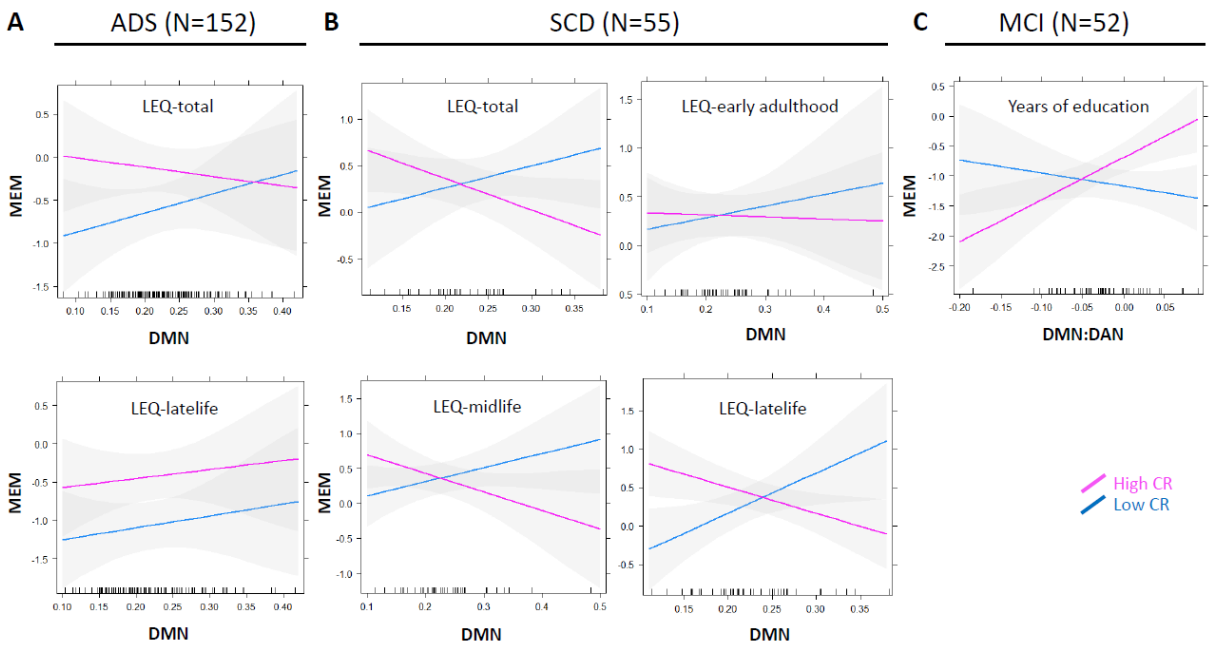
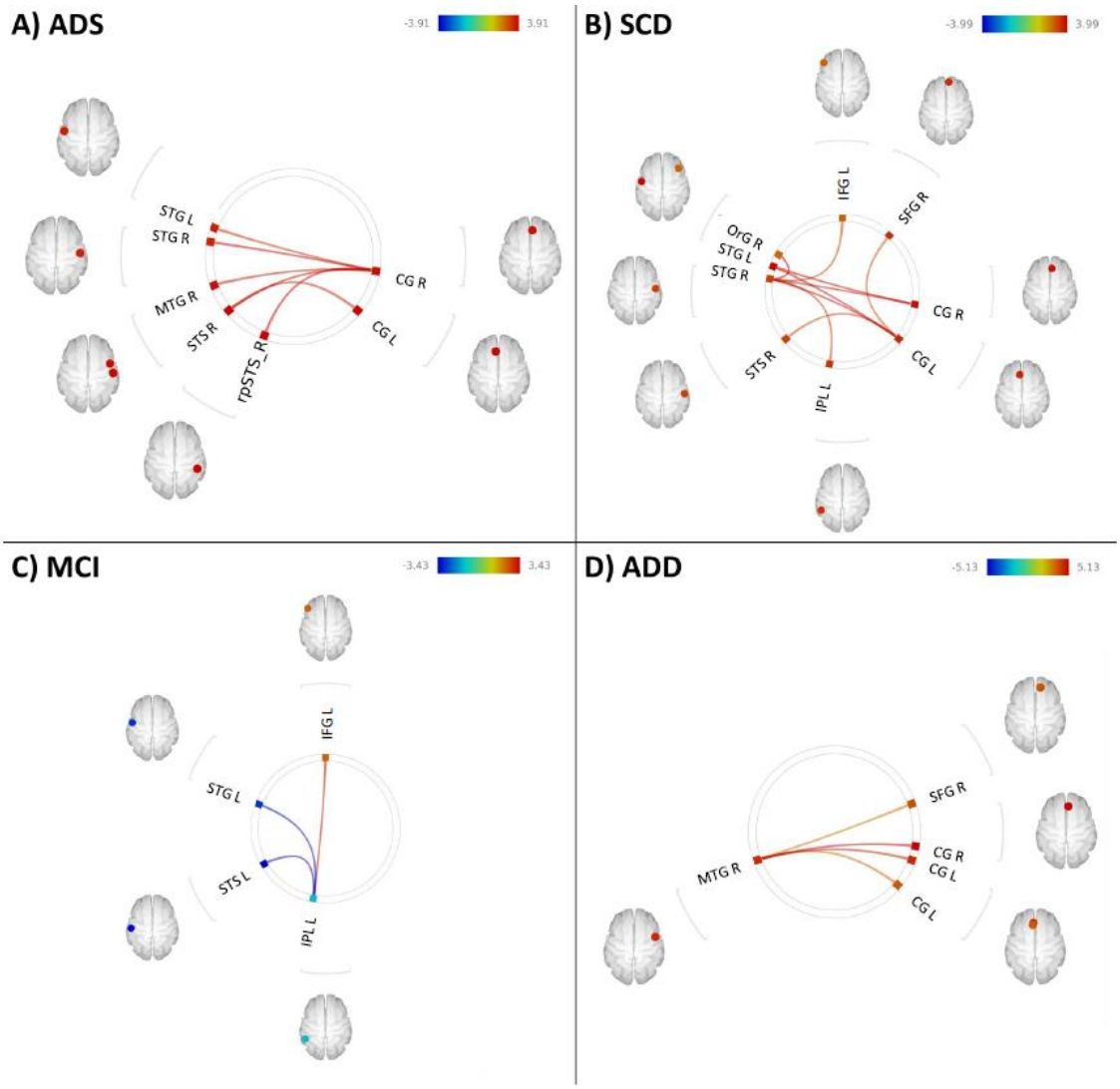


Figure 3. Functional connectivity between ROIs belonging to the DMN showing significant associations with the LEQ-t in ADS (A), SCD (B), MCI (C), and ADD (D).

Edges are represented as a connectivity ring when two-tailed-$p<0.05$, adjusted for age, sex, cortical thickness, imaging sites, and MEM. The general linear model conducted in ADS was adjusted additionally for diagnosis groups. The regions with two-tailed $p<0.05$ are shown in the connectivity ring with T values presented in the color bar. Regions are shown in an axial view with standardized beta values and FDR-corrected p values. Exact Atlas-ROI definitions are shown in supplementary material (**Figure S2**).

Abbreviations: ADS, Alzheimer's disease spectrum; SCD, subjective cognitive decline; MCI, mild cognitive impairment; ADD, Alzheimer's disease dementia; MEM, memory composite score; LEQ, lifelong experiences questionnaire; LEQ-t, total LEQ score; STG, Superior Temporal Gyrus; MTG, Middle Temporal Gyrus; STS, Superior Temporal Sulcus; CG, Cingulate GyrusOrG, Orbital Gyrus; IFG, Inferior Frontal Gyrus; SFG, Superior Frontal Gyrus; IPL, Inferior Parietal Lobule; SFG, Superior Frontal Gyrus; L, left, R, right.


A) ADS
-3.91
3.91
STG L
STG R
MTG R
STS R
rpSTS_R
CG R
CG L
B) SCD
-3.99
3.99
IFG L
SFG R
OrG R
STG L
STG R
CG R
CG L
STS R
IPL L
C) MCI
-3.43
3.43
IFG L
STG L
STS L
IPL L
D) ADD
-5.13
5.13
SFG R
MTG R
CG R
CG L
CG L

Supplementary material: Lifelong experiences as a proxy of cognitive reserve moderate the association between connectivity and cognition in Alzheimer's disease

Table S1. Detailed description of the cortical regions defined in Brainnetome-Atlas derived from (http://atlas.brainnetome.org/download.html). For ROI definitions, please refer http://atlas.brainnetome.org/bnatlas.html. Abbreviations: MNI, Montreal Neurosciences Institute coordinates; RSN, resting-state network; ROI, region of interest; DMN, Default Mode Network; DAT, Dorsal Attention Network.

RSN	ROI	MNI (X, Y, Z)
DAN	A8m_R	7, 16, 54
DAN	A9/46d_L	-27, 43, 31
DAN	A44op_L	-39, 23, 4
DAN	A44op_R	42, 22, 3
DAN	A44v_L	-52, 13, 6
DAN	A44v_R	54, 14, 11
DAN	A4tl_L	-52, 0, 8
DAN	A4tl_R	54, 4, 9
DAN	A1/2/3ll_L	-8, -38, 58
DAN	cpSTS_L	-52, -50, 11
DAN	cpSTS_R	57, -40, 12
DAN	dIa_L	-34, 18, 1
DAN	dIa_R	36, 18, 1
DAN	vId/vIg_L	-38, -4, -9
DAN	vId/vIg_R	39, -2, -9
DAN	dId_L	-38, 5, 5
DAN	dId_R	38, 5, 5
DAN	A32p_R	5, 28, 27
DAN	A24cd_L	-5, 7, 37
DAN	A24cd_R	4, 6, 38
DAN	A23c_L	-7, -23, 41
DAN	A23c_R	6, -20, 40
DMN	A8dl_L	-18, 24, 53
DMN	A9l_L	-11, 49, 40
DMN	A9l_R	13, 48, 40
DMN	A9m_L	-5, 36, 38
DMN	A10m_L	-8, 56, 15
DMN	A10m_R	8, 58, 13
DMN	A8vl_L	-33, 23, 45
DMN	A45c_L	-53, 23, 11
DMN	A45c_R	54, 24, 12
DMN	A45r_L	-49, 36, -3
DMN	A14m_L	-7, 54, -7

DMN	A14m_R	6, 47, -7
DMN	A12/47o_L	-36, 33, -16
DMN	A12/47o_R	40, 39, -14
DMN	A12/47l_L	-41, 32, -9
DMN	A12/47l_R	42, 31, -9
DMN	A22r_L	-55, -3, -10
DMN	A22r_R	56, -12, -5
DMN	A21c_L	-65, -30, -12
DMN	A21r_L	-53, 2, -30
DMN	A21r_R	51, 6, -32
DMN	aSTS_L	-58, -20, -9
DMN	aSTS_R	58, -16, -10
DMN	A20il_L	-56, -16, -28
DMN	rpSTS_L	-54, -40, 4
DMN	rpSTS_R	53, -37, 3
DMN	A40c_L	-56, -49, 38
DMN	A39rv_R	53, -54, 25
DMN	A31_L	-6, -55, 34
DMN	A31_R	6, -54, 35
DMN	A23d_L	-4, -39, 31
DMN	A23d_R	4, -37, 32
DMN	A32p_L	-6, 34, 21
DMN	A23v_L	-8, -47, 10
DMN	A32sg_L	-4, 39, -2
DMN	A32sg_R	5, 41, 6

Table S2. General linear models for testing the interaction between intrinsic network connectivity composite score (intra-network connectivity of DMN or anticorrelation of DMN and DAN and any given CR proxy on composite memory score. The models with each CR proxy were tested separately. All models were adjusted for age, sex, imaging sites, mean cortical thickness of the vulnerable regions. Models that were tested in ADS were additionally adjusted for diagnosis. Abbreviations: CR, cognitive reserve; ADS, Alzheimer's disease spectrum; SCD, subjective cognitive decline; MCI, mild cognitive impairment; ADD, Alzheimer's disease dementia; b, standardized beta value; SE, standard error; p, p-value; LEQ, lifelong experiences questionnaire; LEQ-e, LEQ for early Adulthood; LEQ-m, LEQ for midlife LEQ-l, LEQ score for late-life; LEQ-t, total LEQ score; DMN, intrinsic network connectivity composite score of default mode network; DMN:DAN; anticorrelation between DMN and DAN.

		ADS				SCD				MCI				ADD			
		Parameter	b	SE	p.	Parameter	b	SE	p.	Parameter	b	SE	p.	Parameter	b	SE	p.
DMN	LEQ-t	Intercept	-1.94	0.36	<0.001	Intercept	0.21	0.11	0.05	Intercept	-0.64	0.53	0.22	Intercept	-1.83	0.53	0.001
		DMN	-0.05	0.06	0.38	DMN	-0.01	0.07	0.83	DMN	-0.01	0.14	0.92	DMN	-0.01	0.08	0.88
		LEQ-t	0.08	0.06	0.20	LEQ-t	0.04	0.07	0.54	**LEQ-t**	**0.29**	**0.13**	**0.03**	LEQ-t	-0.02	0.11	0.84
		DMN * LEQ-t	**-0.13**	**0.06**	**0.04**	**DMN * LEQ-t**	**-0.25**	**0.06**	**<0.001**	DMN * LEQ-t	0.09	0.22	0.68	DMN * LEQ-t	0.22	0.14	0.12
	LEQ-e	Intercept	-2.06	0.33	<0.001	Intercept	0.02	0.09	0.86	Intercept	-0.65	0.43	0.13	Intercept	-2.53	0.43	<0.001
		DMN	-0.04	0.05	0.45	DMN	0.02	0.06	0.73	DMN	0.07	0.10	0.51	DMN	-0.15	0.08	0.05
		LEQ-e	0.08	0.05	0.11	LEQ-e	0.06	0.06	0.28	**LEQ-e**	**0.26**	**0.09**	**0.003**	LEQ-e	0.02	0.08	0.77
		DMN * LEQ-e	-0.02	0.06	0.68	**DMN * LEQ-e**	**-0.18**	**0.06**	**0.01**	DMN * LEQ-e	0.08	0.15	0.59	DMN * LEQ-e	0.16	0.09	0.07
	LEQ-m	Intercept	-1.98	0.35	<0.001	Intercept	0.15	0.10	0.14	Intercept	-0.74	0.51	0.15	Intercept	-2.03	0.44	<0.001
		DMN	-0.06	0.05	0.24	DMN	-0.09	0.06	0.13	DMN	-0.05	0.12	0.69	DMN	-0.04	0.09	0.68
		LEQ-m	0	0.06	0.98	LEQ-m	0.04	0.07	0.55	LEQ-m	0.10	0.11	0.36	LEQ-m	-0.13	0.12	0.26
		DMN * LEQ-m	-0.06	0.05	0.26	**DMN * LEQ-m**	**-0.13**	**0.05**	**0.01**	DMN * LEQ-m	-0.03	0.14	0.84	DMN * LEQ-m	0.13	0.12	0.26
	LEQ-l	Intercept	-2.01	0.34	<0.001	Intercept	0.14	0.10	0.18	Intercept	-0.65	0.53	0.22	Intercept	-2.51	0.47	<0.001
		DMN	-0.06	0.06	0.31	DMN	0	0.07	1.00	DMN	-0.02	0.16	0.89	DMN	-0.07	0.08	0.40
		LEQ-l	0.09	0.05	0.11	**LEQ-l**	**0.13**	**0.07**	**0.06**	LEQ-l	0.12	0.13	0.34	LEQ-l	-0.08	0.09	0.36
		DMN * LEQ-l	**-0.12**	**0.05**	**0.01**	**DMN * LEQ-l**	**-0.22**	**0.06**	**0.001**	DMN * LEQ-l	-0.12	0.20	0.53	DMN * LEQ-l	0.06	0.08	0.45
	Education	Intercept	-2.03	0.28	<0.001	Intercept	0.08	0.09	0.34	Intercept	-0.78	0.45	0.09	Intercept	-2.35	0.34	<0.001
		DMN	-0.03	0.04	0.47	DMN	0.01	0.06	0.92	DMN	0.08	0.09	0.38	DMN	-0.11	0.08	0.15
		Education	**0.16**	**0.05**	**0.001**	**Education**	**0.12**	**0.06**	**0.048**	**Education**	**0.21**	**0.09**	**0.02**	Education	-0.04	0.08	0.66
		DMN * Education	-0.04	0.04	0.33	DMN * Education	-0.14	0.08	0.07	DMN * Education	0.01	0.11	0.93	DMN * Education	0.01	0.08	0.91
DMN:DAN	LEQ-t	Intercept	-2.00	0.34	<0.001	Intercept	0.25	0.13	0.05	Intercept	-0.58	0.46	0.21	Intercept	-2.33	0.51	<0.001
		DMN:DAN	0.19	0.06	0.001	DMN:DAN	0.15	0.08	0.06	DMN:DAN	0.34	0.13	0.01	DMN:DAN	0.10	0.11	0.36
		LEQ-t	0.06	0.06	0.29	LEQ-t	-0.11	0.08	0.17	LEQ-t	0.27	0.11	0.01	LEQ-t	-0.08	0.11	0.45
		DMN:DAN * LEQ-e	0.05	0.07	0.45	DMN:DAN * LEQ-t	-0.02	0.08	0.79	DMN:DAN * LEQ-t	0.13	0.19	0.50	DMN:DAN * LEQ-t	0.08	0.10	0.46

LEQ-e	Intercept	-2.00	0.33	<0.001	Intercept	0.05	0.09	0.60	Intercept	-0.53	0.43	0.22	Intercept	-2.28	0.42	<0.001
	DMN:DAN	0.09	0.05	0.06	DMN:DAN	0.08	0.06	0.17	**DMN:DAN**	**0.22**	**0.10**	**0.02**	DMN:DAN	0.02	0.08	0.84
	LEQ-e	0.07	0.05	0.14	LEQ-e	0.01	0.07	0.82	**LEQ-e**	**0.21**	**0.08**	**0.01**	LEQ-e	-0.05	0.07	0.45
	DMN:DAN * LEQ-e	0.02	0.06	0.73	DMN:DAN * LEQ-e	0.06	0.07	0.41	DMN:DAN * LEQ-e	0.01	0.12	0.92	DMN:DAN * LEQ-e	0.15	0.08	0.06
LEQ-m	Intercept	-1.96	0.34	<0.001	Intercept	0.16	0.10	0.11	Intercept	-0.63	0.50	0.21	Intercept	-2.12	0.43	<0.001
	DMN:DAN	**0.14**	**0.05**	**0.002**	**DMN:DAN**	**0.14**	**0.06**	**0.02**	**DMN:DAN**	**0.29**	**0.11**	**0.01**	DMN:DAN	0.03	0.08	0.70
	LEQ-m	-0.01	0.05	0.84	LEQ-m	-0.07	0.06	0.29	LEQ-m	0.08	0.10	0.41	LEQ-m	-0.18	0.10	0.08
	DMN:DAN * LEQ-m	0.07	0.05	0.19	DMN:DAN * LEQ-m	0.03	0.05	0.54	DMN:DAN * LEQ-m	0.08	0.13	0.54	DMN:DAN * LEQ-m	0.07	0.08	0.38
LEQ-l	Intercept	-2.05	0.33	<0.001	Intercept	0.10	0.11	0.37	Intercept	-0.44	0.48	0.36	Intercept	-2.80	0.45	<0.001
	DMN:DAN	**0.16**	**0.05**	**0.002**	DMN:DAN	0.12	0.07	0.09	DMN:DAN	0.27	0.15	0.06	DMN:DAN	0.14	0.08	0.09
	LEQ-l	0.04	0.05	0.44	LEQ-l	-0.01	0.07	0.90	LEQ-l	0.10	0.11	0.35	LEQ-l	-0.07	0.08	0.36
	DMN:DAN * LEQ-l	0.07	0.06	0.25	DMN:DAN * LEQ-l	-0.04	0.10	0.68	DMN:DAN * LEQ-l	0.26	0.18	0.16	DMN:DAN * LEQ-l	0.11	0.06	0.09
Education	Intercept	-2.00	0.28	<0.001	Intercept	0.08	0.09	0.37	Intercept	-0.92	0.41	0.03	Intercept	-2.32	0.34	<0.001
	DMN:DAN	0.08	0.04	0.055	DMN:DAN	0.05	0.05	0.30	**DMN:DAN**	**0.28**	**0.09**	**0.001**	DMN:DAN	0.02	0.08	0.77
	Education	**0.15**	**0.05**	**0.001**	**Education**	**0.18**	**0.06**	**0.004**	**Education**	**0.21**	**0.08**	**0.01**	Education	-0.03	0.08	0.68
	DMN:DAN * Education	0.05	0.05	0.26	DMN:DAN * Education	-0.03	0.06	0.60	**DMN:DAN * Education**	**0.26**	**0.10**	**0.01**	DMN:DAN * Education	-0.01	0.08	0.89

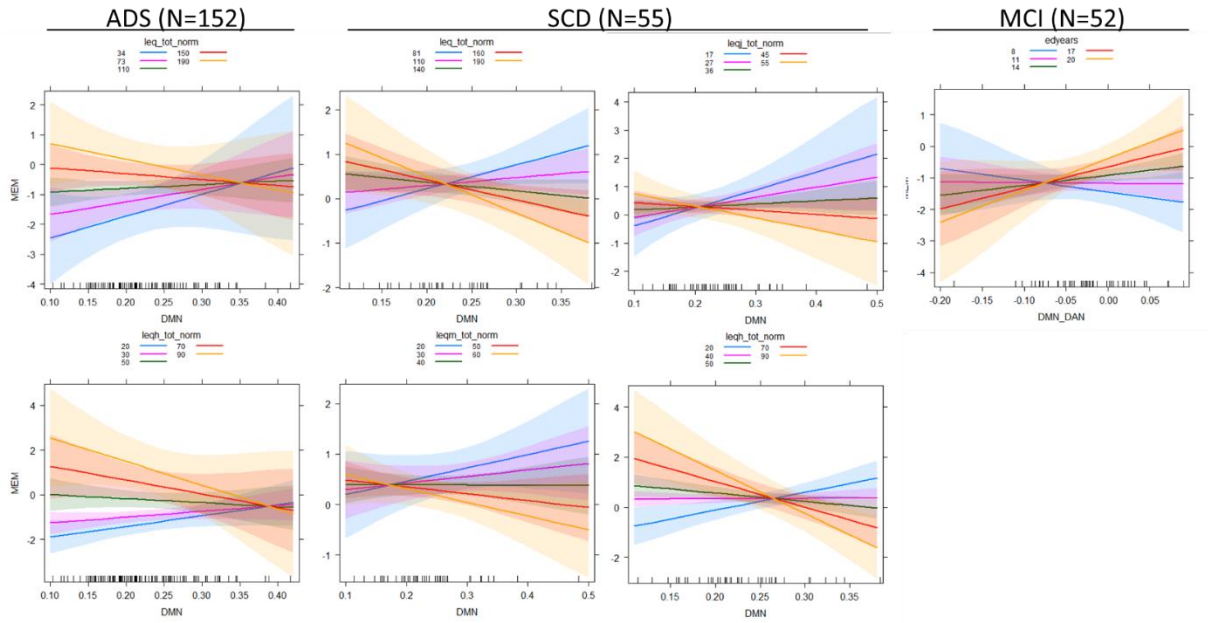
Table S3. General linear models in healthy controls for testing the interaction between intrinsic network connectivity composite score (intra-network connectivity of DMN or anticorrelation of DMN and DAN and any given CR proxy on composite memory score. All models were adjusted for age, sex, imaging sites, mean cortical thickness of the vulnerable regions. The models with each CR proxy were tested separately.

Abbreviations: CR, cognitive reserve; SE, standard error; p, p-value; LEQ, lifelong experiences questionnaire; LEQ-e, LEQ for early Adulthood; LEQ-m, LEQ for midlife LEQ-l, LEQ score for late-life; LEQ-t, total LEQ score; DMN, intrinsic network connectivity composite score of default mode network; DMN:DAN; anticorrelation between DMN and DAN.

		Parameter	b	SE	p
DMN	**Education**	Intercept	0.31	0.12	0.01
		Education	0.11	0.05	0.04
		DMN	-0.06	0.05	0.20
		Education * DMN	0.01	0.05	0.87
	LEQ-e	Intercept	0.34	0.15	0.02
		LEQ-e	0.09	0.06	0.17
		DMN	-0.10	0.06	0.10
		LEQ-e * DMN	-0.03	0.06	0.61
	LEQ-m	Intercept	0.34	0.14	0.01
		LEQ-m	0.14	0.06	0.03
		DMN	-0.11	0.06	0.06
		LEQ-m * DMN	-0.08	0.07	0.24
	LEQ-l	Intercept	0.08	0.18	0.64
		LEQ-l	-0.12	0.08	0.14
		DMN	-0.06	0.07	0.40
		LEQ-l * DMN	0.09	0.07	0.22
	LEQ-t	Intercept	0.12	0.19	0.54
		LEQ-t	-0.02	0.09	0.78
		DMN	-0.07	0.08	0.36
		LEQ-t * DMN	0.02	0.08	0.78
DMN:DAN	**Education**	Intercept	0.33	0.12	0.004
		Education	0.12	0.05	0.02
		DMN:DAN	0.00	0.06	0.99
		Education * DMN:DAN	-0.04	0.06	0.42
	LEQ-e	Intercept	0.35	0.15	0.02
		LEQ-e	0.09	0.07	0.15
		DMN:DAN	0.03	0.07	0.62
		LEQ-e * DMN:DAN	0.03	0.07	0.63
	LEQ-m	Intercept	0.33	0.14	0.02
		LEQ-m	0.11	0.07	0.09
		DMN:DAN	0.03	0.06	0.60
		LEQ-m * DMN:DAN	-0.03	0.07	0.62
	LEQ-l	Intercept	0.13	0.18	0.45
		LEQ-l	-0.09	0.08	0.26
		DMN:DAN	0.09	0.08	0.30

	LEQ-l * DMN:DAN	0.04	0.08	0.59
LEQ-t	Intercept	0.15	0.18	0.39
	LEQ-t	-0.04	0.08	0.68
	DMN:DAN	0.09	0.09	0.28
	LEQ-t * DMN:DAN	0.10	0.09	0.28

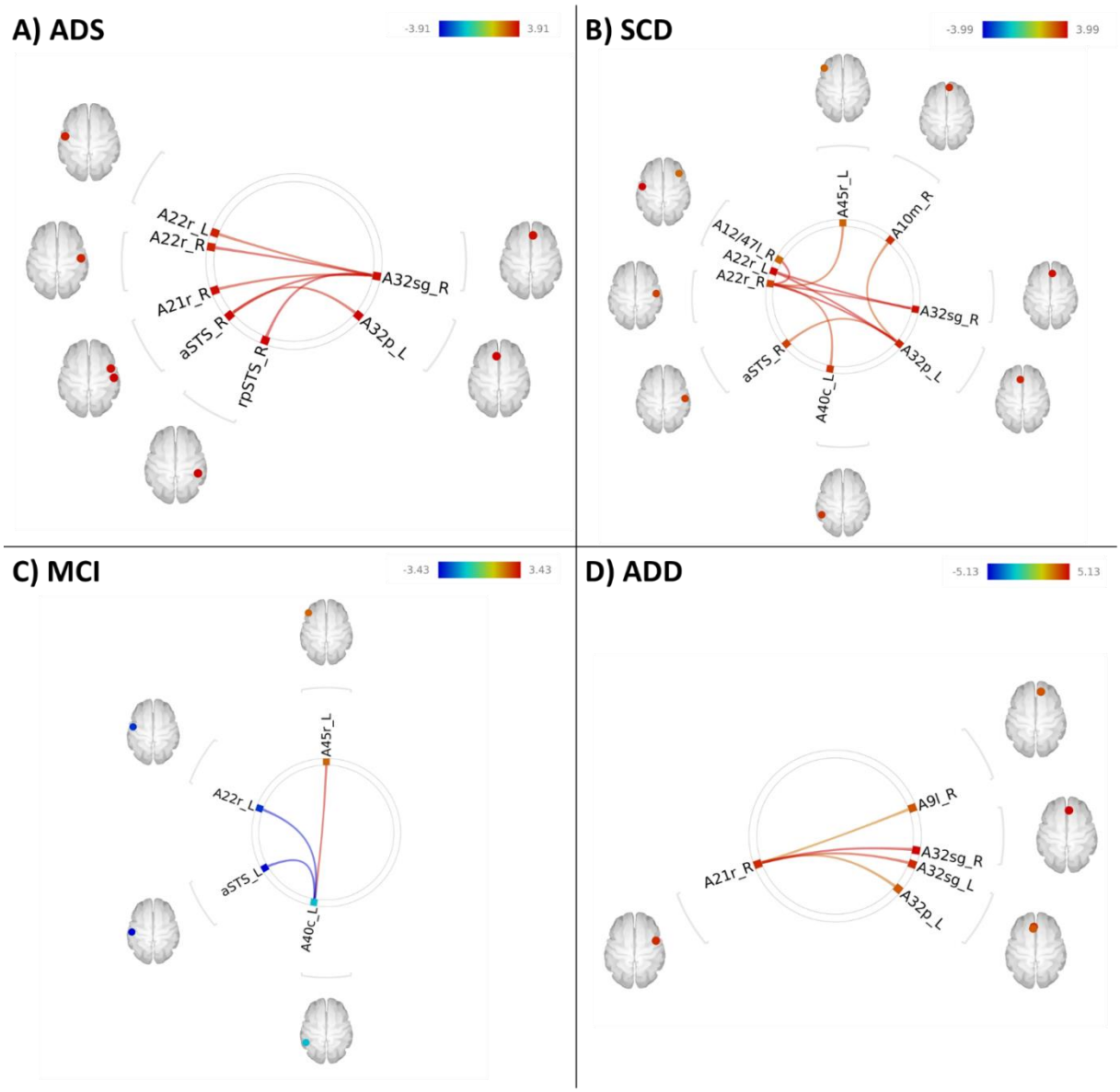
Figure S1. Line plots with 95% confidence interval lines representing the impact of CR proxies, i.e. LEQ scores and education, on the association between memory cognitive domain composite score and within- and between-network connectivity scores, separately for ADS, SCD and MCI.



Abbreviations: ADS, Alzheimer's disease spectrum; SCD, subjective cognitive decline; MCI, mild cognitive impairment; LEQ, lifelong experiences questionnaire; leq_tot_norm, LEQ-total; leqj_tot_norm, LEQ for early adulthood; leqm_tot_norm, LEQ for mid-life leqh_tot_norm, LEQ score for late-life; MEM, memory composite score; DMN, intrinsic network connectivity composite score of the default mode network; DMN:DAN, inter-network connectivity of default mode network and dorsal attention network.

Figure S2. Functional connectivity between ROIs belonging to the DMN showing significant associations with the LEQ-t in ADS (A), SCD (B), MCI (C), and ADD (D).

Edges are represented as a connectivity ring when two-tailed-p<0.05, adjusted for age, sex, cortical thickness, imaging sites, and MEM. The general linear model conducted in ADS was adjusted additionally for diagnosis groups. The regions with two-tailed p<0.05 are shown in the connectivity ring with T values presented in the color bar. Regions are shown in an axial view with standardized beta values and FDR-corrected p values.



Abbreviations: ADS, Alzheimer's disease spectrum; SCD, subjective cognitive decline; MCI, mild cognitive impairment; ADD, Alzheimer's disease dementia; MEM, memory composite score; LEQ, lifelong experiences questionnaire; LEQ-t, total LEQ score; A22r, Superior Temporal Gyrus rostral area 22; A21r, Middle Temporal Gyrus rostral area 21; aSTS, Anterior Superior Temporal Sulcus; A32sg, Cingulate Gyrus Subgenual Area 32; A32p, Cingulate Gyrus Pregenual Area 32; A12/47l, Orbital Gyrus Lateral Area 12/47; A45r, Inferior Frontal Gyrus Rostral Area 45; A10m, Superior Frontal Gyrus Medial Area 10; A40c, Inferior Parietal Lobule Caudal Area 40; A9l, Superior Frontal Gyrus Lateral Area 9; L, left, R, right.