



Increased functional homotopy of the prefrontal cortex is associated with corpus callosum degeneration and working memory decline



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ABSTRACT

Functional homotopy reflects the link between spontaneous activity in a voxel and its counterpart in the opposite hemisphere. Alterations in homotopic functional connectivity (FC) are seen in normal aging, with highest and lowest homotopy being present in sensory-motor and higher-order regions, respectively. Homotopic FC relates to underlying structural connections, but its neurobiological underpinnings remain unclear. The genu of the corpus callosum joins symmetrical parts of the prefrontal cortex (PFC) and is susceptible to age-related degeneration, suggesting that PFC homotopic connectivity is linked to changes in white-matter integrity. We investigated homotopic connectivity changes and whether these were associated with white-matter integrity in 338 individuals. In addition, we examined whether PFC homotopic FC was related to changes in the genu over 10 years and working memory over 5 years. There were increases and decreases in functional homotopy, with the former being prevalent in subcortical and frontal regions. Increased PFC homotopic FC was partially driven by structural degeneration and negatively associated with working memory, suggesting that it reflects detrimental age-related changes.

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1. Introduction

Functional homotopy refers to the level of functional synchrony in spontaneous activity between any given voxel and its mirrored equivalent in the opposite hemisphere (Stark et al., 2008; Zuo et al., 2010). Interhemispheric coordination, a fundamental characteristic of the brain, is largely attributable to homotopic connections (Messé et al., 2014; Shen et al., 2015b). Although functional connectivity (FC), in general, may vary across cognitive states (Geerligs et al., 2015; Hellyer et al., 2014; Spreng et al., 2016; Tavor et al., 2016; Vidaurre et al., 2018), homotopic FC is temporally stable (Gonzalez-Castillo et al., 2014; Shen et al., 2015a,b; Zalesky et al., 2014) and considerably stronger than connectivity between heterotopic regions (Jo et al., 2012; Shen et al., 2015b). Importantly, functional homotopy is disturbed in a variety of neurological and psychiatric conditions, including Alzheimer's disease, mild

cognitive impairment, schizophrenia, depression, and sleep disorders, suggesting that homotopic activity might serve as a marker of healthy brain functioning (Guo et al., 2013; Qiu et al., 2016; Woodward et al., 2011; Zhang et al., 2014; Zhu et al., 2016).

Alterations in homotopic connectivity are also present in normal aging. Zuo et al. (2010) reported that older individuals showed higher connectivity in areas such as the premotor and somatosensory cortex, and lower connectivity in areas such as the anterior cingulate and inferior parietal cortex. Previous studies have also reported a general gradient, where the highest and lowest levels of homotopic FC are found in sensory-motor and higher order regions, such as the prefrontal cortex (PFC), respectively (Stark et al., 2008; Zuo et al., 2010). Importantly, Zuo et al. (2010) showed that global homotopic FC was best described with a quadratic fit, suggesting that, although connectivity decreases during development, it increases again during middle age. Such age-related increases in bilateral connectivity are thought to reflect a decline in specialization but it is unclear whether they indicate brain deterioration or compensation (Zuo et al., 2010). Still, it is well established that cross-sectional estimates of age-related

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cognitive decline can deviate markedly from those found in longitudinal studies (Nyberg et al., 2010; Rönnlund et al., 2005), which emphasizes the importance of comparing results from cross-sectional and longitudinal designs. Accordingly, a key aim of this study is to, for the first time, investigate longitudinal changes in homotopic FC in a healthy sample across the adult life span.

Previous research supports the notion that FC reflects underlying structural connections (Damoiseaux and Greicius, 2009; Honey et al., 2009; Skudlarski et al., 2008; Uddin, 2013; Van Den Heuvel et al., 2009), with various degrees of structural-functional correspondence across the brain (Vázquez-Rodríguez et al., 2019; Baum et al., 2020). However, the neurobiological underpinnings of age-related changes in FC are unclear. On the one hand, it is well established that FC is associated with structural connectivity strength but, on the other, there is evidence of FC between brain regions that do not share a direct structural path (Hermundstad et al., 2013; Honey et al., 2009). The corpus callosum (CC), the largest and most highly organized commissure in the human brain, illustrates this point. This structure is primarily responsible for connecting analogous regions in each hemisphere (Aboitiz, 1992; Hofer and Frahm, 2006; Innocenti, 2009; Jarbo et al., 2012); however, studies with patients who suffer from callosal agenesis or for whom the CC was removed have provided mixed findings, with some reporting decreased homotopic FC (Johnston et al., 2008; Lowe et al., 2008; Quigley et al., 2003; Roland et al., 2017), and others normal or nearly normal homotopic FC (Khanna et al., 2012; Owen et al., 2013; Tovar-Moll et al., 2014; Tyszka et al., 2011; Uddin et al., 2008).

Post-mortem and in vivo studies of the CC indicate that the genu might be more susceptible to age-related white-matter degeneration, whereas the splenium remains relatively intact (Aboitiz et al., 1996; Bartzokis, 2004; Head et al., 2004; Madden et al., 2004; Nyberg and Salami, 2014; O'Sullivan et al., 2001; Salami et al., 2012; Salat et al., 2005). This pattern is consistent with the notion that the human frontal cortex is disproportionately affected by aging, and that age-related alterations in the brain follow an anterior-to-posterior gradient (Greenwood, 2000; Pfefferbaum et al., 2005). Our second aim is to investigate the link between structural connectivity and FC. Although a one-to-one mapping between structural and functional homotopy is unlikely, it is reasonable to expect that changes in homotopic FC are associated with changes in white-matter integrity of the genu, which is responsible for joining symmetrical parts of the PFC.

Finally, there have been few cross-sectional studies combining functional homotopy and cognition (Kelly et al., 2011). This precludes conclusions regarding the influence of differences in homotopic FC on age-related cognitive changes. Most commonly, stronger and weaker homotopic connectivity, respectively, are interpreted as higher coordination between regions and more independent processing (Zuo et al., 2010). However, there is also evidence from animal work that homotopic connectivity is responsible for transferring redundant neural information from one hemisphere to the other. This redundancy is crucial for neural circuitry robustness, so that modules can function autonomously and/or correct each other when needed (Li et al., 2016). Accordingly, both too low and too high functional homotopy could be detrimental for cognition. A third aim of this study is to investigate changes in homotopic connectivity in relation to changes in cognition. Given previous work showing both under- and over-recruitment of the PFC in old age (Bäckman et al., 1997; Cabeza et al., 2002; Davis et al., 2008, 2012; Persson et al., 2006; Rajah and Esposito, 2005; Rieckmann et al., 2011) as well as its prominent role in working memory (Kane and Engle, 2002; Rottschy et al., 2012), we focused on changes in homotopic connectivity of the PFC and its association to working memory changes.

2. Materials and methods

2.1. Participants

Participants in this study are from the Betula project on memory, health, and aging (Nilsson et al., 1997, 2004), a longitudinal population-based study with data collected in Umeå, Sweden. To date, there have been 7 main data collection waves at different time (T) points, with MRI examinations starting at T5: (T1) 1988–1990, (T2) 1993–1995, (T3) 1998–2000, (T4) 2003–2005, (T5) 2008–2010, (T6) 2013–2014, and (T7) 2017–2019. The interval between T's is approximately 5 years. The sample included a total of 338 participants who underwent MRI at T5 (mean age: 61.6 ± 13.5 , range 25–95 years, 179 women). At T6, a total of 209 participants (mean age: 64.5 ± 13.2 , range 30–85, 98 women) were included, of whom 206 had attended data collection at T5 and 1 was new. Finally, at T7 only individuals who were 65 years and older were called for additional imaging, leaving a sample of 101 participants (mean age: 72.3 ± 6.5 , range 65–90, 44 women). Exclusion criteria included depression, stroke, Parkinson's disease, and dementia. All were native Swedish-speakers, had normal or corrected to normal vision, and no history of neurological illness (for additional details on the sample, recruitment, imaging, and other methodological procedures see Nyberg et al., 2019; Pudas et al., 2018). The Regional Ethical Vetting Board approved the protocol and informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

All participants underwent 6 minutes of resting-state functional magnetic resonance imaging (fMRI), during which they were instructed to keep their eyes open and look at a fixation cross (for details see Salami et al., 2014, 2016). Participants also underwent diffusion tensor imaging (DTI). From the total sample of individuals who completed resting-state fMRI and DTI, we further excluded those who did not pass data quality checks. These checks included visual inspection, severe motion (mean total displacement), inaccurate registration of DTI images, and exclusion of outliers (defined as 2.5 standard deviations from the mean). This left a total sample of 197 participants to investigate voxelwise changes in connectivity over a 5-year period and 92 participants over a 10-year period. Of these, 148 had longitudinal working memory data from baseline (T5) to the first follow-up (T6). For details on other characteristics of interest, see Table 1.

2.2. Data acquisition

2.2.1. Imaging data

Brain imaging data were acquired with a 3T General Electric scanner equipped with a 32-channel head coil. Functional data were obtained with a gradient-echo planar imaging sequence as follows: repetition time (TR) = 2000 ms, 37 transaxial slices (3.4 mm thick), gap = 0.5 mm, field of view = 25×25 cm, flip angle = 80° , echo time (TE) = 30 ms, 170 volumes. Ten dummy scans were obtained to allow for equilibration of the fMRI signal. Structural high-resolution T1-weighted images (TR = 8.2 ms, 180 slices [1 mm thick], field of view = 25×25 cm, flip angle = 12° , TE = 3.2 ms) were collected after the functional images. Diffusion-

Table 1
Participants' characteristics

	T5	T6	T7
Years of education	13.4 ± 4.0		
Systolic blood pressure (baseline)	134.4 ± 17.5		
Diastolic blood pressure (baseline)	80.8 ± 9.2		
Global cognition (MMSE >24)			
	28.2 ± 1.5	28.2 ± 1.4	27.2 ± 1.8

Key: MMSE, Mini-Mental State Exam.

weighted data were acquired with a spin-echo-planar T2-weighted sequence as follows: TR = 8000 ms, 64 slices, field of view = 25×25 cm, flip angle = 90° , TE = 84.4 ms, 3 repetitions and 32 independent directions, $b = 1000$ s/mm 2 and 6 $b = 0$ images. The experimental design was identical during T5, T6, and T7 (i.e., same acquisition time using the same scanner and head coil), with the exception that the last follow-up did not include 3 repetitions of the diffusion-weighted sequence. To allow for consistency, when combining data from the 3 time points, only the first repetition was used for T5 and T6.

2.2.2. Cognitive data

Working memory was assessed outside the scanner, with an n -back task where a list of 40 words was presented visually with an interval of 3 seconds between each word. Participants responded “yes” if the current word was the same as the one presented 2 words back in the list, and “no” if the word was different. The sum of correct responses (i.e., correct hits and correct rejections) was used as the outcome measure.

2.3. Data analysis

2.3.1. Preprocessing

Resting-state fMRI data for both baseline and follow-up(s) were preprocessed using Statistical Parametric Mapping Software (SPM12; Wellcome Department of Cognitive Neurology, University College London). Preprocessing details can be found elsewhere (Salami et al., 2016). In summary, images were corrected for differences in slice-time acquisition within each volume. The resulting slice-timing corrected images were rigidly aligned to the first volume to correct for head motion. This was followed by a within-subject rigid registration in order to align functional and structural images. T1-weighted images were then segmented into gray matter (GM) and white matter (WM), and a subject-specific template was created with Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra (DARTEL; Ashburner, 2007). First, GM and WM images were imported into DARTEL space following a 6-step iterative procedure. This results in a baseline and follow-up representative template for each participant. A group-specific template was then created from all subject-specific templates. Finally, co-registered fMRI images were nonlinearly normalized to the group-specific template, affine aligned to the Montreal Neurological Institute (MNI) template, and smoothed using an 8-mm full-width at half-maximum Gaussian filter. Given that non-neuronal activity, such as motion, can create confounds in FC data (Buckner et al., 2013; Power et al., 2011), additional preprocessing steps were taken before conducting voxel-mirrored homotopic connectivity analyses. Specifically, the time series of all voxels were high-pass filtered (cut-off 130s) and residualized according to a set of nuisance parameters: mean WM, CSF, global signal, and the Friston 24-parameters model (Yan et al., 2013).

Diffusion-weighted data were preprocessed using the University of Oxford's Center for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) package (<http://www.fmrib.ox.ac.uk/fsl>). The protocol included 3 subject-specific diffusion acquisitions, which were concatenated in time, followed by eddy current correction to correct for eddy-current-induced distortions and head motion. When combining data from the 3 time points, only the first repetition was used for T5 and T6, and, thus, concatenation was not necessary. The b -matrix was also reoriented based on the transformation matrix (Leemans and Jones, 2009). Next, brain extraction was performed using the Brain Extraction

Tool (BET; Smith, 2002) by thresholding the first volume ($b = 0$), followed by tensor fitting using DTIfit (Jenkinson and Smith, 2001). This step fits a diffusion tensor to each voxel in the brain mask created in the previous step. Importantly, we also compared the standard FSL pipeline with the longitudinal one suggested by Engvig et al. (2012), and found that results across the skeleton were highly correlated (fractional anisotropy in the entire skeleton: $r = 0.96$, $p < 0.001$).

2.3.2. Statistical analyses

2.3.2.1. Changes in homotopic functional connectivity. Voxel-mirrored homotopic connectivity at rest was calculated by computing the temporal correlation coefficients between 2 voxels with left-right equivalent coordinates. This operation was performed for every voxel pair across the brain at each time point, and the values were Fisher z-transformed. A symmetrical template in MNI space was not used, but the hemispheres were still largely symmetrical (i.e., we created masks for GM in the left and right hemisphere and calculated an averaged degree of correlation between the 2 hemispheres, $r = 0.99$, $p < 0.001$). We then performed a second-level repeated-measures analysis of variance across the brain for complete cases ($N = 92$) to investigate the effect of time using F -tests (see Supplementary A). However, given that the results of this analysis are unspecific with regard to the direction of the effect, changes in homotopic FC between time points were computed as well. Those are shown as the main results in the section below. First, we created difference image maps (T5–T6; T6–T7) using the IMCALC toolbox in SPM and ran one-sample t -tests (threshold: $p < 0.01$, false discovery rate, FDR, corrected, $k > 100$). At locations close to the midline, correlation values between corresponding voxels approach 1. Thus, a GM mask excluding edge voxels was used. Although findings from T5 to T6 and T6 to T7 concurred in relation to which brain regions showed increases and decreases in functional homotopy, we had a smaller sample in the latter subset of analyses ($N = 197$ vs. $N = 92$) and the effects were also somewhat weaker.

When running voxelwise analyses in relation to WM, we used a larger sample with complete cases from T5 to T6 ($N = 197$) and investigated change over 5 years. In addition to the voxelwise analyses of complete cases (i.e., excluding individuals with 1 or more missing measurements), we used linear-mixed effects (LME) models, which are able to handle missing data (Fitzmaurice et al., 2008), to characterize individual trajectories of change in relation to age. Here, we were able to account for change across the entire 10-year interval. The dependent variables were homotopic connectivity and WM across the genu of the CC. Importantly, although the PFC exhibited significant increases in connectivity over time, our voxelwise findings also showed that there were several portions of this region which were not age sensitive. Results for the whole PFC can be seen in Supplementary B. We carried on by analyzing the dorsolateral PFC (dlPFC) specifically (Cappell et al., 2010; Lamar and Resnick, 2004; MacPherson et al., 2002; Phillips et al., 1998). For this analysis, we created an anatomical mask corresponding to the dlPFC (specifically, BA9 and 46) and extracted homotopic FC values from this region for each participant and time point. Age was used as a continuous variable and the model included a random intercept and a random slope to allow for both between- and within-subject variability. The fixed effect was mean-centered baseline age and random effects were added for participants, in order to control for differences in intercept, and time, in order to control for differences in slope. To further explore the trajectory of age-related changes in connectivity, generalized additive mixed models (GAMM; Wood, 2017) were carried out

using the gamm4 package in R (Wood and Scheipl, 2014), which fits the association between homotopic connectivity and age semi-parametrically. Finally, we also performed a flexible factorial second-level analysis to further investigate the effect of time point, age group, and a possible time point \times age group interaction (for details see [Supplementary C](#)).

Subsequent voxelwise analyses in relation to homotopic FC were masked with clusters showing significant increases or decreases in the right hemisphere only. This was done to avoid problems when correcting for multiple comparisons, given that findings in the right and left hemisphere were identical. Moreover, although we had specific a priori hypotheses in regard to the relation of homotopic FC in prefrontal areas and WM and cognition, we still masked the results with regions showing longitudinal increases or decreases as this process would serve as a sanity check and rule out spurious findings (e.g., it is unlikely that there would be associations between homotopic FC and the genu in more posterior regions of the brain). We also did not know whether a change-change association between homotopic connectivity and WM would be unique to the dIPFC or be present in other parts of the PFC as well.

2.3.2.2. Changes in homotopic functional connectivity in relation to changes in white-matter and working memory. After exploring voxelwise changes in homotopic FC across the brain and in the dIPFC, we focused on the association between functional and structural connectivity. Because we were specifically interested in the PFC, we extracted fractional anisotropy (FA) and mean diffusivity (MD) for the genu of the CC by applying Tract-Based Spatial Statistics (Smith et al., 2006). Participants' FA data were aligned into common space using the Nonlinear Image Registration Tool in FSL. This is done by first identifying a registration target among the available FA images and then nonlinearly normalizing them to this target, followed by affine-aligning them into a $1 \times 1 \times 1$ mm MNI152 standard space. The second step included both generating a mean of the aligned images and creating a skeletonized mean FA by thinning the mean images (threshold = 0.2). The default threshold worked well in excluding CSF and GM voxels from the mean skeleton image. This skeleton is a representation of the center of all tracts common to all participants. After this, each participant's aligned FA data were projected onto the skeleton and the resulting data were fed into voxelwise cross-subject statistics. The nonlinear transformation and skeleton projection were repeated using the MD maps. Images were also checked using tbss_deproject, which deprojects skeletonized images into the space of each nonlinearly registered participant. Finally, the John Hopkins University Institute for Computational Medicine DTI (JHU ICM-DTI-81) WM labels, which are part of the FSL atlas tools, were used to compute average FA and MD along the genu of the CC.

Given the abovementioned concerns in relation to sample size at T7, we ran voxelwise analyses in relation to WM on the complete sample at T5 and T6. Change in the genu (T5–T6) for both measures was calculated, and paired *t*-tests for FA and MD were computed. We also illustrated individual trajectories in WM using GAMM. Next, we conducted separate multiple regressions with change in WM (i.e., FA or MD) and change in homotopic FC, controlling for age. In brief, this meant that 2 multiple regressions were ran for each variable of interest to examine the association between change in WM and (1) increased homotopic connectivity or (2) decreased homotopic connectivity in the regions identified in the previous section. FA and MD were analyzed separately due to possible multicollinearity issues. In our sample, FA and MD along the genu were correlated at both baseline ($r = -0.698$, $p < 0.001$) and follow-up ($r = -0.703$, $p < 0.001$), and were also significantly

associated with baseline age (FA: $r = -0.463$, $p < 0.001$; MD: $r = 0.515$, $p < 0.001$).

We were still interested in the relationship between homotopic connectivity and WM over the 10-year period, as such, we ran LME models for FA in a similar fashion to what is described above for the dIPFC. In summary, mean-centered baseline age was added as a fixed effect and a random effect was added for participants and time, to control for both differences in intercept and slope respectively. We then calculated the intercept and slope for the dIPFC connectivity and FA models and correlated them. In our LME analyses, participants showing normalized residuals >0.975 were considered outliers.

Finally, to examine longitudinal changes in homotopic FC in relation to cognition, we again ran a multiple regression with change in working memory (i.e., *n*-back sum of correct responses at T5–*n*-back sum of correct responses at T6) and homotopic connectivity while controlling for age. All second-level analyses were thresholded at $p < 0.005$, uncorrected, $k > 20$. We performed additional analyses where minimal smoothing was applied to the data and where we further controlled for framewise displacement (for details see [Supplementary D](#)).

3. Results

3.1. Cognitive data

We used paired *t*-tests to investigate performance on the *n*-back task. Our results show that the sum of correct responses on the *n*-back task did not differ significantly between T5 and T6 ($t(147) = -1.545$, $p = 0.124$). Still, there were individual differences in change. Older participants performed worse than younger people at both T5 ($r = -0.484$, $p < 0.001$) and T6 ($r = -0.485$, $p < 0.001$). Additionally, older participants had longer reaction times in all trials at baseline ($r = 0.184$, $p = 0.026$) and follow-up ($r = 0.309$, $p < 0.001$). They also had significantly longer reaction times for correct trials at follow-up ($r = 0.297$, $p < 0.001$), and these were marginally significant at baseline ($r = 0.148$, $p = 0.073$).

3.2. Changes in homotopic functional connectivity

Whole-brain voxelwise analyses revealed both increases and decreases in homotopic FC across the 10-year follow-up interval. For additional details on overall results for complete cases ($N = 92$), see [Supplementary A](#). However, given that these are nonspecific in regard to the direction of the effect, our main findings, displayed below, show change in connectivity separately for each follow-up. Increases were present in frontal and subcortical regions ([Fig. 1A](#)), whereas decreases were observed in the primary and premotor cortex, supplementary motor area, and visual association regions ([Fig. 1B](#)). Of note, although there are regions in the PFC showing increased connectivity over time, this is not the case for the entire PFC (i.e., there are also age-invariant areas). As such, we focused on the dIPFC, which has previously been shown to have a larger age effect compared to other prefrontal regions (Cappell et al., 2010; Lamar and Resnick, 2004; MacPherson et al., 2002; Phillips et al., 1998).

Critically, changes in homotopic FC were more widespread from T5 to T6 compared to T6 to T7 as can be seen in [Fig. 1](#). Increases in dIPFC connectivity were also larger from baseline to the first follow-up ([Fig. 2](#)). Thus, when carrying out voxelwise analyses, we focused on the larger sample with 197 individuals over 5 years for whom cognitive data were also available.

In addition to the voxelwise results, we also used LME models to investigate change in dIPFC homotopic connectivity by using a region-of-interest approach ([Fig. 3](#)). This method allowed us to

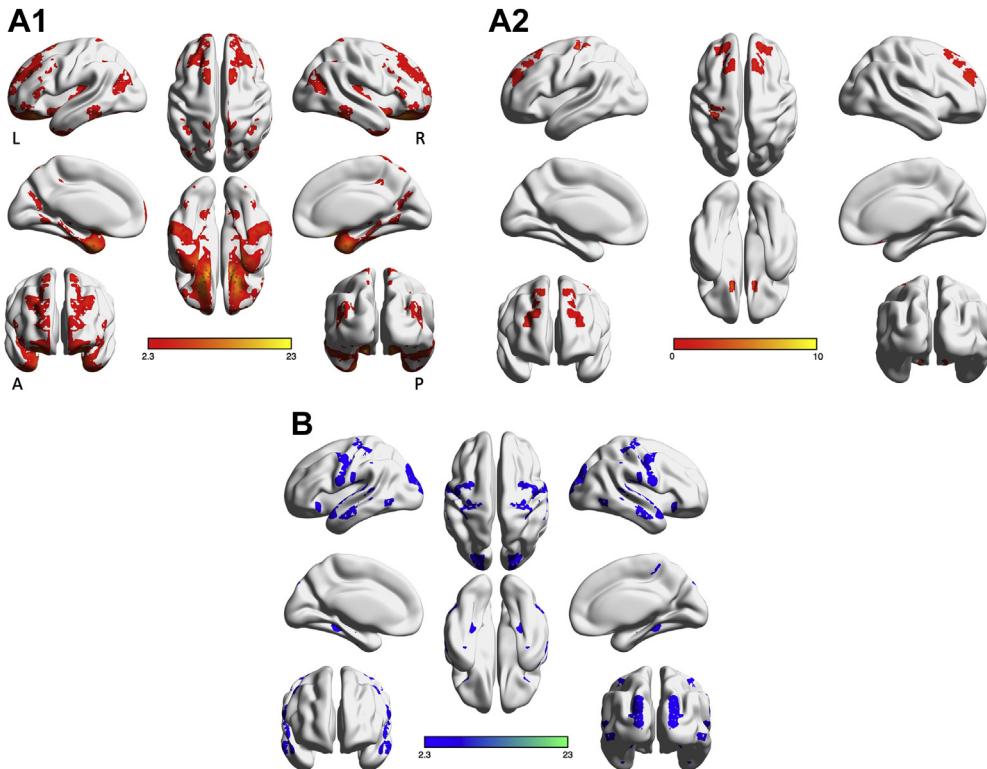


Fig. 1. (A) Brain regions showing increases in homotopic functional connectivity from (A1) T5 to T6 ($N = 197$) and (A2) T6 to T7 ($N = 92$); and (B) brain regions showing decreases in homotopic functional connectivity from T5 to T6. No brain regions showing decreases from T6 to T7 survived the threshold ($p < 0.01$, FDR corrected, $k > 100$). Note that the scale reflects different functional homotopy patterns in A (increases) and B (decreases). Abbreviations: A, anterior; FDR, false discovery rate; L, left; P, posterior; R, right.

account for change across the entire 10-year period and, given that it can handle missing data, we used the entire sample ($N = 338$). We used a model with a random intercept and slope, which showed an effect of time ($\beta = 0.04674$, confidence interval [CI]: 0.0354–0.0580) and age ($\beta = 0.00252$, CI: 0.0009–0.00252), and an interaction between the 2 ($\beta = -0.00155$, CI: -0.0009 to -0.000526). There was no effect of sex ($\beta = 0.017946993$, CI: -0.00498 to 0.040877).

3.3. Changes in PFC homotopic functional connectivity are associated with changes in white-matter integrity of the genu

The voxelwise analyses on homotopic FC change revealed more widespread increases from T5 to T6. Thus, we first explored whether degeneration in the CC could, at least partly, account for elevated homotopic FC over the same time period. We found that FA

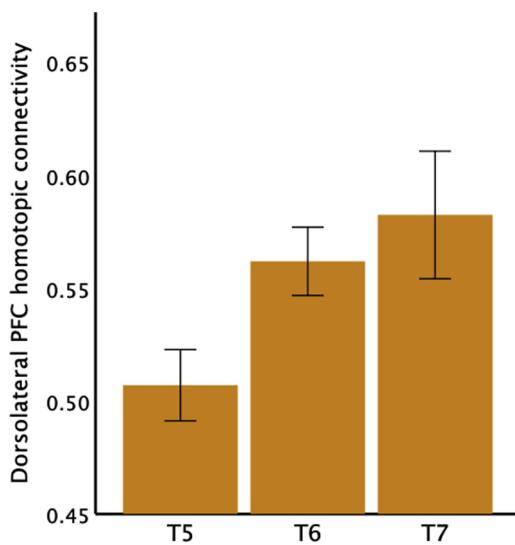


Fig. 2. Dorsolateral prefrontal homotopic functional connectivity. Error bars show standard errors of the mean. Values represent Fisher's z-transformed scores. PFC, prefrontal cortex.

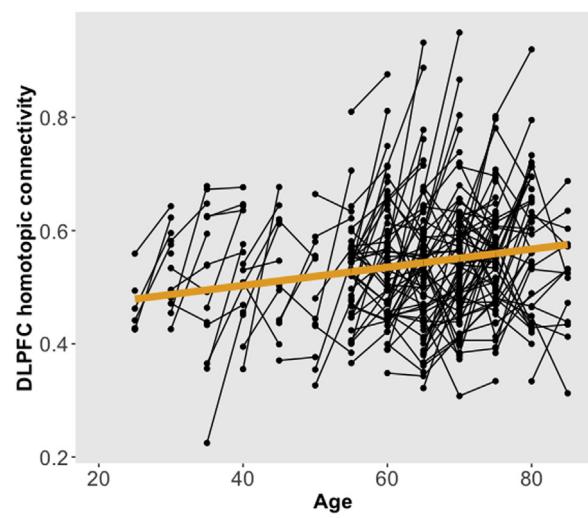


Fig. 3. Individual trajectories for change in dlPFC homotopic connectivity, with the bold line indicating mean change estimated with GAMM. Abbreviations: dlPFC, dorsolateral prefrontal cortex; GAMM, generalized additive mixed models.

significantly decreased ($t(162) = 11.99, p < 0.001$) and MD significantly increased ($t(162) = -2.092, p = 0.038$) in the genu of the CC over 5 years (Fig. 4A). Importantly, change in homotopic FC in 2 PFC clusters was negatively associated with change in FA of the genu (Fig. 4B), indicating that increases in functional homotopy were associated with decreased WM integrity in the anterior parts of the CC. No change-change associations were found for homotopic FC and MD.

The relationship between functional homotopy in the dIPFC and FA over 10 years was then investigated using LME models. We found no association between the intercepts ($r = 0.113, p = 0.114$) and slopes ($r = 0.043, p = 0.655$) across the entire sample. However, when analyzing older participants (>55 years of age at baseline) separately, there was a positive association between the intercepts ($r = 0.228, p = 0.012$) but not slopes ($r = 0.066, p = 0.472$). No significant associations were found between connectivity in the entire PFC and WM integrity of the genu over 10 years.

3.4. Changes in PFC homotopic connectivity are associated with changes in working memory

Functional integrity of the PFC has been associated with working memory (Kane and Engle, 2002; Rottschy et al., 2012), so it is reasonable to expect that changes in homotopic FC of the PFC would be associated with changes in working memory performance. Voxelwise analyses revealed that change in homotopic connectivity in the PFC (i.e., specifically, 3 clusters mainly located within dorsolateral prefrontal regions) was negatively associated with change in working memory (Fig. 5). This indicates that individuals showing the smallest increases in homotopic connectivity (i.e., showed relatively intact functional homotopy) were also those who

kept their working memory intact over 5 years. No positive change-change associations between connectivity and working memory were observed.

4. Discussion

We investigated 10-year changes in resting-state homotopic FC in relation to changes in WM integrity of the genu over the same time period and working memory performance over 5 years. The findings can be summarized in 3 main points. First, we found regional variability in homotopic connectivity change, with motor and visual regions showing decreases and the PFC and subcortical regions showing increases. Moreover, increased homotopic FC was associated with (1) decreased FA in the genu and (2) worse working memory over 5 years. To the best of our knowledge, our results are the first to show longitudinal changes in functional homotopy in a healthy sample covering the adult lifespan. These findings fit with reports showing that aging is associated with increases in bilateral FC in subcortical regions (Salami et al., 2014; Ystad et al., 2010) and the PFC (Davis et al., 2012; Rieckmann et al., 2011). Likewise, there is evidence that connectivity between sensory motor and other resting-state networks increases with aging (Betzel et al., 2014; Geerligs et al., 2014), which, in turn, may lead to lower homotopic connectivity.

Previous work indicates that global homotopic connectivity increases after middle age (Zuo et al., 2010). However, the authors also report a complex pattern of positive and negative linear, cubic, and quadratic trajectories in homotopic FC for different brain areas, with adjacent regions sometimes showing opposite connectivity patterns. Additionally, the age distribution in Zuo et al. (2010) is heavily biased toward younger age cohorts with few participants

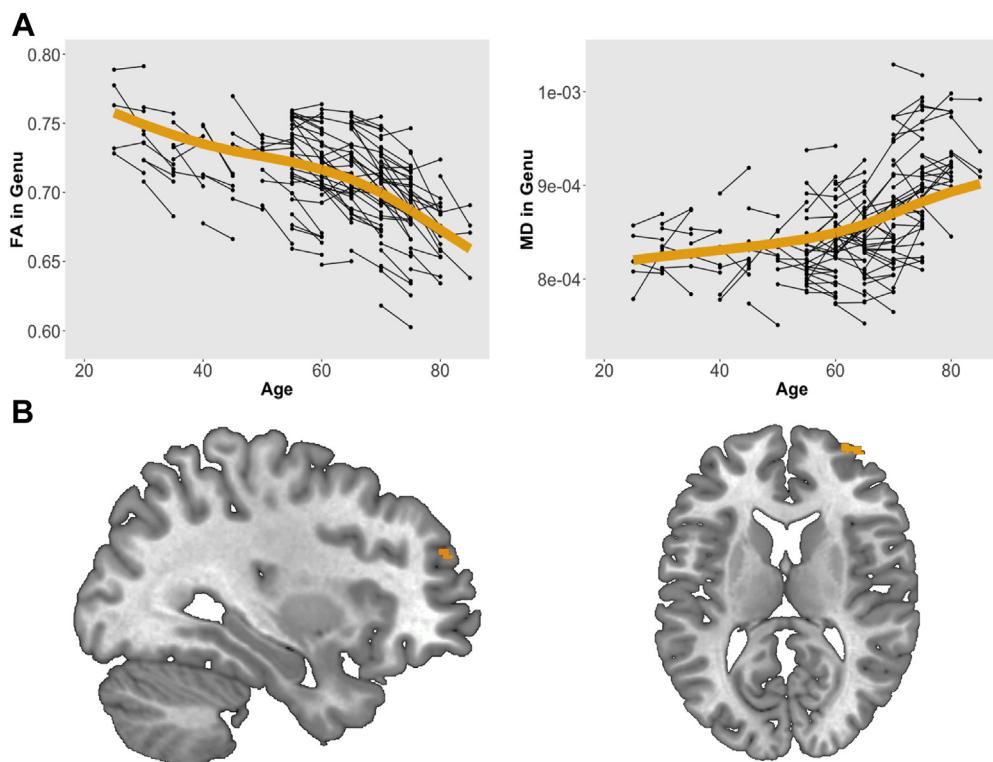


Fig. 4. (A) Individual trajectories for change in FA and MD in the genu of the corpus callosum, with the bold line indicating mean change estimated with GAMM; and (B) brain regions showing an association between change in homotopic connectivity and change in FA (BA46: peak cluster XYZ = 32 52 24, $k = 22$, $t = 3.21$; BA10: peak cluster XYZ = 36 60 12, $k = 32$, $t = 3.95$). Note that analyses were masked with only 1 of the hemispheres to avoid problems when correcting for multiple comparisons. Results for the left hemisphere were identical. Abbreviations: FA, fractional anisotropy; GAMM, generalized additive mixed models; MD, mean diffusivity.

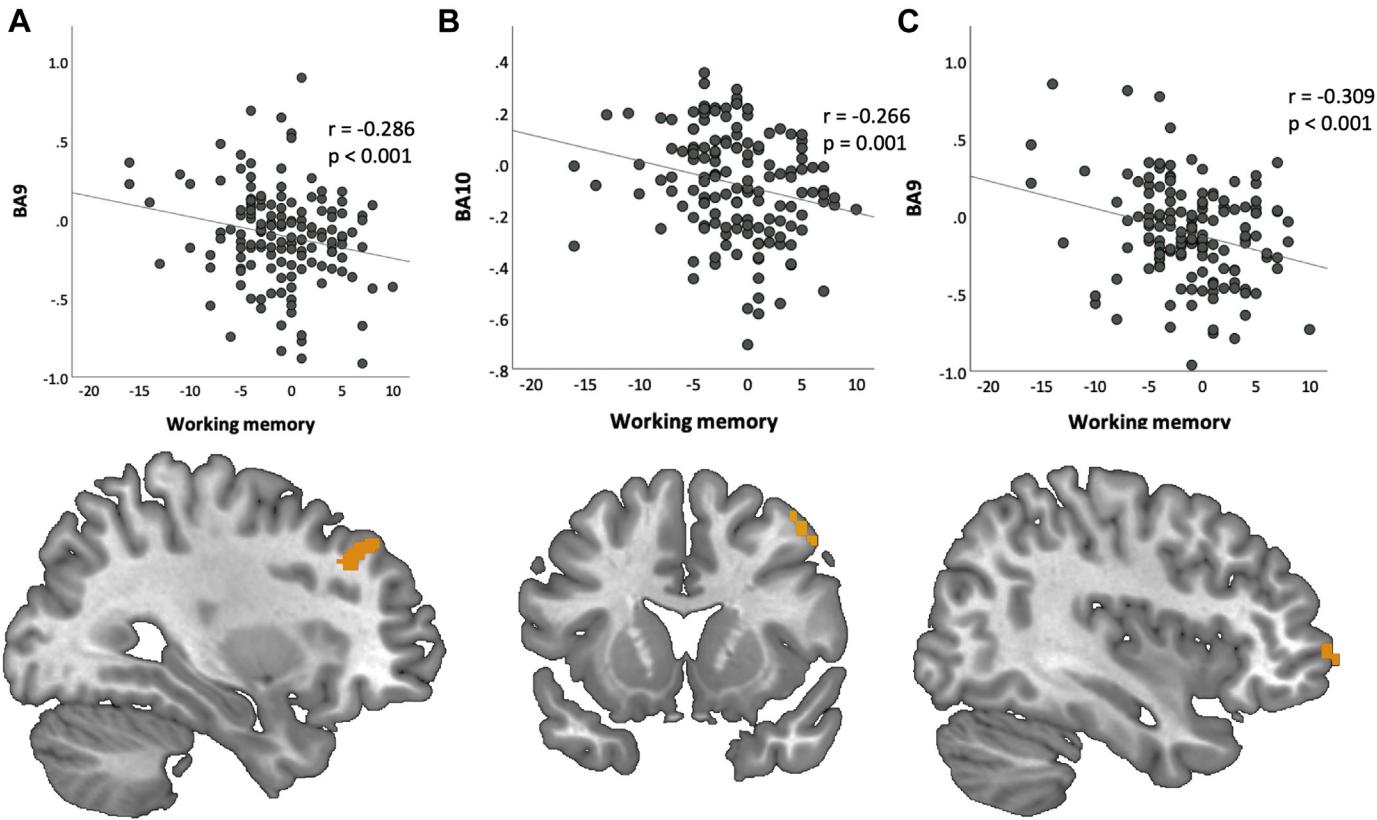


Fig. 5. Scatterplots and brain regions showing an association between change in homotopic connectivity and change in working memory: (A) BA9: peak cluster XYZ = 36 40 44, $k = 65$, $t = 3.49$; (B) BA9: peak cluster XYZ = 46 16 52, $k = 25$, $t = 4.62$; and (C) BA10: peak cluster XYZ = 36 62 2, $k = 28$, $t = 3.49$.

over the age of 60. This, together with the cross-sectional design of the study, makes it difficult to adequately separate brain-related development from degeneration. It is of note, however, that in our study, the increases in overall prefrontal homotopic FC were not greatly affected by age at baseline. Across the entire PFC there was an effect of time, but only a marginally significant effect of age. However, alterations in homotopic FC were observed within the dlPFC, suggesting an heterogenous effect of age across different prefrontal subregions. Additionally, the results indicate that homotopic connectivity of the dlPFC increased over 10 years. Homotopic connectivity may arguably show little change over 5 years as it appears to be more stable compared to other types of FC. Still, our results show an interaction between time point and age for the dlPFC over 10 years, suggesting that connectivity in this region increases with time and accelerates with advancing age. It is also possible that similar increases in homotopic connectivity reflect different underlying process(es) across different age cohorts. During development, a decrease in functional homotopy likely reflects functional specialization, which is part of the natural developmental process (Kelly et al., 2009; Supekar et al., 2009). After the age of 25, however, this process should be complete. This could lead to a natural increase in functional homotopy as the brain ages, given that the maximum peak for specialization has already been reached. On the other side of the spectrum, bilateral recruitment of given brain regions has been associated with both compensatory processes (Grady et al., 2010; Rieckmann et al., 2011) as well as lack of neural specificity and dedifferentiation (Li and Lindenberger, 1991; Park and Reuter-Lorenz, 2009) in older ages. With aging, increased functional homotopy might reflect a level of specialization that is suboptimal, perhaps similar to those seen in young children, and, thus, detrimental to cognition.

Age-related WM changes measured by DTI are thought to reflect a variety of structural alterations, including loss of myelin, decreased axonal diameter and density, and loss of axons (Burzynska et al., 2010; Hugenschmidt et al., 2008; Minati et al., 2007). Consistent with past work, we found decreased FA and increased MD in the genu of the CC, with the former being associated with elevated homotopic connectivity of the PFC. Decline in FA is present in disorders where fiber integrity is lost, such as in Alzheimer's disease (Medina et al., 2006), whereas increases in MD are often present in conditions where membrane density is reduced (Beaulieu, 2002; Concha et al., 2006; Sen and Basser, 2005). It is plausible that subtle changes in WM microstructure, such as minor fiber or myelin loss, may first result in changes for FA and only later affect parameters such as MD (Burzynska et al., 2010; Ciccarelli et al., 2006; Lowe et al., 2008; Sen and Basser, 2005). Still, one should be cautious when interpreting either of the 2 measures as reflecting particular brain parameters, as the link between DTI variables and specific neurobiological substrates is not yet clear (Jones, 2010; Madden et al., 2012). Changes in FA and MD are frequently, but not always, reported concurrently in the literature. However, the 2 measures are not necessarily correlated and their association might be region-specific. Note that our results show that neither FA nor MD were associated with decreases in functional homotopy, suggesting that only elevation in homotopic FC can be linked to neurodegeneration of the genu.

Reports on the relation of structural and functional homotopy often rely on patient studies. Although valuable, these studies suffer from a severe limitation due to the large heterogeneity of the study populations involved. Indeed, many of the individuals included cannot be classified as neurologically normal (e.g., epileptic) even at baseline (O'Reilly et al., 2013). This precludes definite conclusions

on the association between WM and homotopic FC in normal aging. The negative change-change association between WM and connectivity may seem contradictory, but a study with rhesus monkeys showed that normal homotopic FC can be sustained even after complete removal of the CC (O'Reilly et al., 2013). Notably, this occurred only when the anterior commissure was retained, implying that the neural circuitry on which functional homotopy relies can be preserved with just a few indirect noncallosal connections (O'Reilly et al., 2013; Risso et al., 1978; Tovar-Moll et al., 2014; Tyszka et al., 2011; Uddin et al., 2008; Vincent et al., 2007). Our sample consists of healthy younger and older individuals, and thus, compared to complete or partial removal of the CC, the damage to WM microstructure is minimal. Consequently, it is more likely that the brain will adapt to these changes and allow for secondary pathways to take over transfer of information. However, it is also possible that increased homotopic connectivity in the PFC was achieved at the expense of lower connectivity in other regions of the brain (e.g., visual cortex). Still, it is important to note that the animal work described above, together with the spatially selective associations between WM and homotopic FC reported in this study, suggest that homotopic connectivity can be surprisingly robust in the presence of damage to the CC.

When focusing on individuals 60 years and older, we found that the intercept for FA and dIPFC homotopic connectivity were positively correlated. In view of the negative change-change association found longitudinally using a voxelwise approach, this suggests that greater WM coherence is linked to higher homotopic connectivity regardless of age. Although speculative, this elevation may be optimal in younger age. However, as one grows old, age-related decreases in WM integrity may lead to excessive elevation in homotopic connectivity, which is deleterious for cognitive processing.

Finally, our findings show that working memory was associated with elevated homotopic FC in working memory relevant brain regions. These results are in line with previous work showing that contralateral activity was linked to worse episodic memory and reduced WM integrity (Persson et al., 2006). The brain encodes relevant representations in multiple brain regions and at different levels of abstraction, often bilaterally, so that information is redundantly stored (Christophel et al., 2017; Li et al., 2016). This serves the purpose of enabling autonomous processing but also rectifying the contralateral module when necessary. For such a process to be efficient, restrictions must be in place so that there is no overload of representations simultaneously stored as this would likely cause interference. Prefrontal increases in homotopic connectivity might reflect decline in the number or effectiveness of these restrictions. This overload could already be present at rest and exacerbated during task performance, especially in tasks containing representational loops such as in the case of working memory (Christophel et al., 2017). Although the specificity of changes in dIPFC in relation to working memory remains to be further explored, we know that working memory is strongly dependent on dorsolateral prefrontal activity (Bäckman and Nyberg, 2013; Salami et al., 2018), so it is possible that this cognitive domain is particularly susceptible to detrimental connectivity increases in frontal brain regions. On the other hand, there is also evidence suggesting that the CC might be responsible for inhibiting the nondominant hemisphere (Davis et al., 2012; Langan et al., 2010). If this is the case, its degeneration could lead to lower inhibition of the contralateral hemisphere and consequently increase homotopic connectivity and network dysfunction.

There is reason to believe that the CC might be relevant for memory processing, given work showing that individuals with agenesis of the CC display worse memory performance than controls (Cabeza and Nyberg, 2000; Christman et al., 2003; Erickson

et al., 2014; Paul et al., 2016). However, in our study, we did not find a link between cognition and WM microstructure. This is partly in contrast with the literature (Gorbach et al., 2017; Hedden et al., 2016; Laukka et al., 2013; Madden et al., 2004; Persson et al., 2006; Salami et al., 2012; Turken et al., 2008). However, many of the cognitive domains described in these studies implicate (or are perhaps confounded by) processing speed. It is far less common to find associations between WM and higher order cognitive processes, but given that this study was exclusively focused on the most anterior part of the CC, we cannot rule out that other parts of the CC or other tracts might be associated with working memory.

This work is not without limitations. We applied spatial smoothing to the data, which allows for better correspondence between regions in the left and right hemisphere. Given evidence that smoothing has a non-negligible effect on homotopic connectivity (Zhu et al., 2016; Zuo et al., 2010), we ran control analyses accounting for this. Importantly, by applying a longitudinal pre-processing pipeline to our resting-state data, we could not investigate the effects of zero smoothing, but we applied 1 mm smoothing instead. The results demonstrated that homotopic connectivity strength was markedly lower, which was to be expected given that the similarity between hemispheres was decreased. Still, the pattern of regional variability initially reported remained, which suggests that our findings were not driven by the spatial smoothing applied in the main analyses. Finally, given that there was no significant association between WM and working memory in our sample, we could not test whether FC mediates this relationship. We hope future longitudinal work will continue to investigate these links and delve into the issue of causality.

In sum, our findings show altered interhemispheric communication over 10 years. We report differential patterns across the brain, but also specific change-change relationships of PFC homotopic connectivity to WM and working memory performance. We found no significant associations between decreased homotopic FC in the PFC and WM degeneration, or performance. Our results suggest that (1) only elevated functional homotopy of the PFC can be linked to WM degeneration of the CC and (2) increased homotopic connectivity of the PFC is functionally relevant and deleterious for prefrontally based memory functions.

Disclosure statement

The authors have no current or potential conflicts of interest.

Data availability statement

The data that support the findings of this study are not publicly available due to privacy or ethical restrictions, but are available upon reasonable request.

CRediT authorship contribution statement

Bárbara Avelar-Pereira: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Lars Bäckman:** Conceptualization, Methodology, Investigation, Resources, Writing - review & editing, Supervision, Funding acquisition. **Anders Wåhlin:** Software, Formal analysis, Investigation, Writing - review & editing. **Lars Nyberg:** Conceptualization, Methodology, Investigation, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition. **Alireza Salami:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.neurobiolaging.2020.08.008>.

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