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Functional connectivity change across multiple cortical networks relates to episodic memory changes in aging

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ABSTRACT

A major task of contemporary cognitive neuroscience of aging is to explain why episodic memory declines. Change in resting-state functional connectivity (rsFC) could be a mechanism accounting for reduced function. We addressed this through 3 studies. In study 1, 119 healthy participants (20–83 years) were followed for 3.5 years with verbal recall testing and magnetic resonance imaging. Independent of atrophy, recall change was related to change in rsFC in anatomically widespread areas. Striking age-effects were observed in that a positive relationship between rsFC and memory characterized older participants while a negative relationship was seen among the younger and middle-aged. This suggests that cognitive consequences of rsFC change are not stable across age. In study 2 and 3, the age-dependent differences in rsFC-memory relationship were replicated by use of a simulation model (study 2) and by a cross-sectional experimental recognition memory task (study 3). In conclusion, memory changes were related to altered rsFC in an age-dependent manner, and future research needs to detail the mechanisms behind age-varying relationships.

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1. Introduction

A major task of contemporary cognitive neuroscience is to understand why the efficiency in forming and consolidating new long-term episodic memories is reduced with aging (Nyberg et al., 2012; Reuter-Lorenz and Park, 2010). Through the concept of resting-state functional connectivity (rsFC), we now have a tool to study cognitive processes likely relevant for memory function (Albert et al., 2009; Durrant and Lewis, 2009; Hasson et al., 2009; Stevens et al., 2010; Takashima et al., 2009; Tambini et al., 2010; Wang et al., 2010a, 2010b; Wig et al., 2008): rsFC is altered after encoding (Albert et al., 2009; Daselaar et al., 2010; Hasson et al., 2009; Stevens et al., 2010; Takashima et al., 2009), with the magnitude of alterations related to memory performance (Albert et al., 2009; Stevens et al., 2010; Takashima et al., 2009; Tambini et al., 2010; Wig et al., 2008).

For instance, using probabilistic independent component analysis of rsFC data, Albert et al. (2009) found a frontoparietal and a cerebellar component that increased in strength after motor learning. Tambini et al. (2010) found enhanced functional connectivity (FC) between the hippocampus and a portion of the lateral occipital complex during rest following a task with high subsequent memory, an effect that was not seen during a task with poor subsequent memory. Additionally, the magnitude of the hippocampal-occipital correlation during post-task rest predicted later associative memory. However, the direction of reported rsFC-memory relationships vary between studies and as a function of the networks in question and likely the analysis methods chosen. For instance, Hasson et al. (2009) found 6 regions where rsFC varied as a function of the immediately preceding language content of the task and the direction of effects varied across regions. Wig et al. (2008) showed that participants with greater task-induced deactivations in medial temporal lobe performed superiorly on an offline memory test. Takashima et al. (2009) observed weaker connectivity with consolidation between the posterior hippocampus and the early visual areas bilaterally, extending to the fusiform face area and the posterior parietal cortex. A positive correlation was seen between memory performance and FC in the left middle and/or inferior occipital cortex and a negative correlation in the right precuneus.

It must be added that the direction of effects is not always easy to interpret due to differences with regard to, for example, whether global signal is regressed out (Murphy et al., 2009). One study instead focused on relative differences in correlation values

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between rest conditions and found that magnitude of one such interaction predicted subsequent recognition (Stevens et al., 2010). Finally, in a very recent study, Tompary et al. (2015) demonstrated that the strength of post-encoding FC between the ventral tegmental area (VTA) and CA1 of the hippocampus, during a non-related task, selectively correlated with long-term associative memory. In contrast, VTA-perirhinal cortex FC during the same period correlated with long-term item memory. Interestingly, connectivity between VTA and the medial temporal lobe regions were only related to memory tested after a delay of 24 hours.

These previous studies used young and healthy participants, with fewer aging-studies actively manipulating protocols to study rsFC and memory consolidation. However, reduced FC in elderly [for a comprehensive review, see (Sala-Llonch et al., 2015)] has been related to declining cognitive function, including memory [(Andrews-Hanna et al., 2007; Geerligs et al., 2014; He et al., 2012; Mevel et al., 2013; Onoda et al., 2012; Wang et al., 2010a), but see Ystad et al., 2010]. It has been suggested that higher intranetwork connections, that is, efficiency of communications within networks, and lower inter-network connections, reflecting specificity and selectivity of the network, may be beneficial for cognitive function in aging (Antonenko and Floel, 2014; Salami et al., 2012; Spreng and Schacter, 2012). These findings support the dedifferentiation theory of aging, according to which decreased selectivity results in more diffuse patterns of FC (Antonenko and Floel, 2014). However, findings are not fully coherent. In one study, it was found that older participants showed lower connectivity of long-range connections together with higher functional segregation of these same connections, indicating a more local clustering of information processing (Sala-Llonch et al., 2014). Interestingly, higher local clustering in older participants was negatively related to memory performance. Also, elevated FC between left and right hippocampus has been associated with declining memory >20 years in middle-aged and older adults (Salami et al., 2014).

In sum, the studies reviewed previously indicate a positive relationship between rsFC and memory performance, but with great variations across studies and networks, probably at least partly as a result of the analysis strategy used. On this background of previous research, tracking of cortical rsFC over time may provide insights into the neural foundation for decline of long-term memory in aging. Regrettably, such studies are as of yet lacking, except for one study reporting that relative increase in rsFC >6 years within the default mode network (DMN) was related to better memory outcome in middle-aged and older adults (Persson et al., 2014). Additionally, we recently found that although changes in corticostriatal rsFC were positively related to memory change in older adults, hippocampal-cortical rsFC changes were negatively related to memory in younger and middle-aged adults (Fjell et al., 2015). We now need to address whether rsFC change across different cortical networks relates to altered episodic memory function over time in older adults and whether the pattern of change differs from that of younger and middle-aged.

We hypothesized that, better preservation of rsFC over time would yield more favorable memory outcome at follow-up testing. Furthermore, based on the phenomenon of over-activation or less specific activation patterns in aging (Grady, 2012; Reuter-Lorenz and Park, 2010), we hypothesized that changes in multiple networks would impact memory, and more so in older than younger and middle-aged adults. In aging, compensatory processing (Cabeza et al., 2002), for example, as formulated in the compensation-related utilization of neural circuits model (Reuter-Lorenz and Park, 2010), or dedifferentiation and breakdown of functional specialization (Lindenberger and Baltes, 1994), is expected to resulting in a more "global" connectivity pattern with less clearly separated functional networks. Accordingly, more networks are expected to impact memory in older adults. Finally, we hypothesized that changes in regions with high connectivity to other cortical areas would impact memory more than changes in more isolated regions. This is related to the idea that certain brain areas interconnect distinct, functionally specialized systems (Buckner et al., 2009), and these seem to be especially vulnerable to effects of aging (Lustig et al., 2003; Sala-Llonch et al., 2015). As these are critical for integration of information, they were envisioned to have substantial impact on memory. Within the established resting-state DMN, the most clearly defined hub-regions are the posterior cingulate cortex and the anterior medial prefrontal cortex (Andrews-Hanna et al., 2010), and we expect age-related changes in these regions to be of special importance. Additionally, we hypothesize that the medial temporal lobe subsystem of the DMN, consisting of the medial temporal cortex, retrosplenial cortex, the ventral medial prefrontal cortex, and the posterior inferior parietal lobe (Andrews-Hanna et al., 2010), will be related to episodic memory function.

Three studies were run: in study 1, we tested the relationship between rsFC change >3.5 years and changes in verbal episodic recall in older (60–86 years) and younger and middle-aged adults (20–52 years). In study 2, we constructed a simulation model, allowing explication of all model parameters, and compared the output to the empirical results from study 1. In study 3, we ran replication analyses based on a completely different cross-sectional visual recognition memory task.

2. Study 1: longitudinal neuroimaging and memory

2.1. Materials and methods

2.1.1. MRI acquisition and analysis

Imaging data were collected using a 12-channel head coil on a 1.5 T Siemens Avanto scanner (Siemens Medical Solutions; Erlagen, Germany) at Rikshospitalet, Oslo University Hospital. The same scanner and sequences were used at both time points. The pulse sequences used had the following parameters:

For morphometric analyses: the pulse sequence used included 2 repetitions of a 160 slices sagittal T_1-weighted magnetization prepared rapid gradient echo sequences with the following parameters: repetition time/echo time/time to inversion/flip angle = 2400 ms/3.61 ms/1000 ms/8°, matrix = 192 × 192, field of view = 240, voxel size = 1.25 × 1.25 × 1.20 mm, scan time 4 minutes 42 seconds.

For FC: the resting-state blood-oxygen-level dependent (BOLD) sequence included 28 transversally oriented slices (no gap), measured using a BOLD-sensitive T2*-weighted echo planar imaging sequence (repetition time = 3000 msec, echo time = 70 msec, flip angle = 90°, voxel size = 3.44 × 3.44 × 4 mm, field of view = 220, descending acquisition, generalized autocalibrating partially parallel acquisition acceleration factor = 2), producing 100 volumes and lasting for ~5 minutes. Three dummy volumes were collected at the start to avoid T1 saturation effects.

Surface reconstruction and subcortical labeling were performed at the Neuroimaging Analysis Laboratory, Research Group for Lifespan Changes in Brain and Cognition, Department of Psychology, University of Oslo. Morphometry analyses were performed by use of FreeSurfer v. 5.1 (http://surfer.nmr.mgh.harvard.edu/) (Dale et al., 1999; Fischl et al., 1999; Fischl and Dale, 2000; Fischl et al., 2002), please see a detailed account elsewhere (Storsve et al., 2014; Walhovd et al., 2014). All volumes were inspected for accuracy, and minor manual edits were performed when needed by a trained operator on the baseline images, usually restricted to removal of nonbrain tissue included within the cortical boundary.

Resting-state functional imaging data were preprocessed following Lifespan Changes in Brain and Cognition's custom analysis stream. Images were motion- and slice-timing corrected and

smoothed (5 mm full-width at half maximum) in volume space using FSL's FMRI Expert Analysis Tool (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki). Five millimeter smoothing was chosen as we wanted to be as anatomically precise as possible in our analyses due to the use of regions of interest derived from structural 1 mm volumes, while at the same time benefitting from the increased signal-to-noise ratio following from even moderate spatial smoothing. Then, FSL's Multivariate Exploratory Linear Optimized Decomposition into Independent Components was used in combination with FMRIB's independent component analysis-based Xnoiseifier (FIX) to autoclassify independent components into signal and noise components and remove the noise components from the 4D functional magnetic resonance imaging (fMRI) data (Salimi-Khorshidi et al., 2014). A prerequisite for FIX-classification is a hand-labeled training set of typical signal and noise components. After manually inspecting and validating that it fitted to our data, we used the default classification template provided with the FIX-toolbox. FreeSurfer-defined individually estimated anatomical masks of cerebral white matter (WM) and cerebrospinal fluid (CSF) and/or lateral ventricles were resampled to each individual's functional space. All anatomical voxels that "constituted" a functional voxel had to be labeled as WM or CSF for that functional voxel to be considered a functional representation of noncortical tissue. Average time series were then extracted from functional WM and CSF voxels and were regressed out of the FIX-cleaned 4D volume together with a set of estimated motion parameters (rotation and/or translation) and their derivatives. Following recent recommendations about noise removal from resting-state data (Hallquist et al., 2013), we also band-pass filtered the data (0.009–0.08 Hz) after regression of confound variables. In-scanner head motion may substantially impact measures of FC (Satterthwaite et al., 2012; Van Dijk et al., 2012), with the risk of causing spurious correlations, especially when comparing groups of participants where differences in head movement may exist. Such artifacts could lead to an underestimation of long-range correlations and an overestimation of short-range correlations, and such motion-induced artifacts could occur even after motion parameters are regressed out (Power et al., 2012). Thus, in addition to regressing out estimated motion parameters from the time series before they were entered into further analyses and band-pass filtering the data according to current recommendations, motion was also included as a covariate in all statistical analyses (see Section 2.1.3). It must also be noted that independent component analysis-based procedures for denoising of fMRI-data used in the present study have been shown to effectively reduce adverse effects of motion on FC estimates, showing similar results to methods such as spike regression and motion scrubbing (Pruim et al., 2015a, 2015b).

To calculate rsFC within established cortical functional networks, we took advantage of Yeo et al. (2011) cortical parcellation estimated by intrinsic FC from 1000 participants and made available in FreeSurfer's average surface space (http://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation_Yeo2011) (see Fig. 1). This is among the best validated delineations of cortical resting-state networks. The parcellation scheme consists of 17 networks in each hemisphere as well as values representing the estimated confidence of each surface vertex belonging to its assigned network. Spheres (6 dilations around center vertex; 127 vertices) were drawn on the average surface around each network's highest

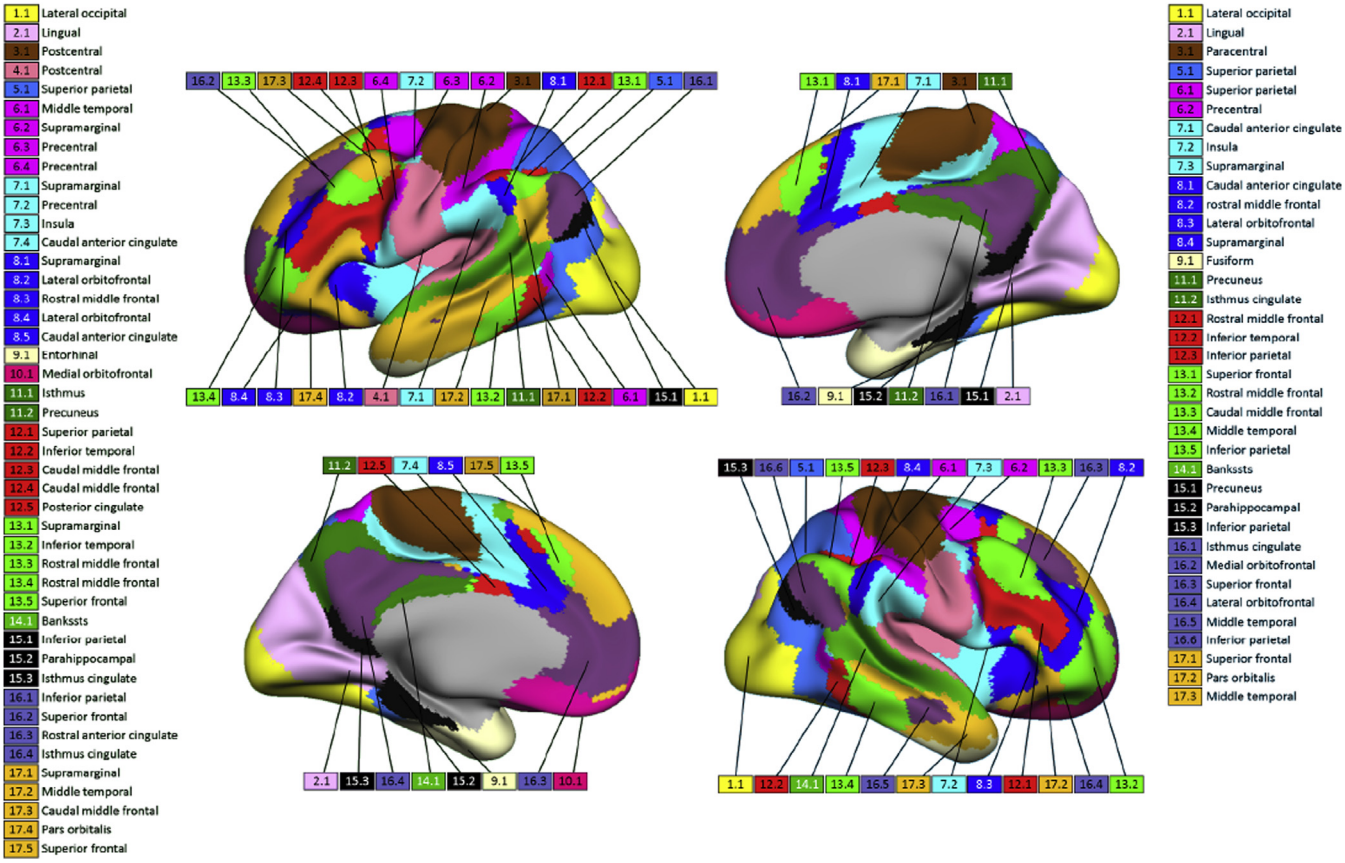

Fig. 1. Functional connectivity–based parcellation of the cerebral cortex. The cerebral cortex was parcellated according to a 17-network scheme (15 in the right hemisphere) (Yeo et al., 2011). For each parcellation, a point was placed in the area with the highest degree of confidence and dilated to cover 127 vertices. Resting-state functional connectivity was calculated between each of these seed regions and the rest of the cortex.

confidence vertex (vertices if a network consisted of several disconnected segments), resampled into individual subject space, and correlated with all other vertices. This resulted in rsFC estimates for each of the 17 networks (collapsed over hemispheres) for each participant ("intranetwork" rsFC). In addition, rsFC was calculated between each network and all other networks, yielding an "internetwork" rsFC measure.

2.1.2. Sample

The longitudinal sample was drawn from the ongoing project Cognition and Plasticity through the Lifespan at the Research Group for Lifespan Changes in Brain and Cognition, Department of Psychology, University of Oslo (Storsve et al., 2014; Walhovd et al., 2014; Westlye et al., 2010a, 2010b). All procedures were approved by the Regional Ethical Committee of Southern Norway, and written consent was obtained from all participants. For the first wave of data collection, participants were recruited through newspaper advertisement. Recruitment for the second wave was by written invitation to the original participants. At both time points, participants were screened with a health interview. Participants were required to be right handed (self-report), fluent Norwegian speakers, and have normal or corrected to normal vision and hearing. At both time points, exclusion criteria were history of injury or disease known to affect central nervous system function, including neurological or psychiatric illness or serious head trauma, being under psychiatric treatment, use of psychoactive drugs known to affect central nervous system functioning, and magnetic resonance imaging (MRI) contraindications. Moreover, participants were required to score $\geq$26 on the Mini-Mental State Examination [MMSE; (Folstein et al., 1975)], have a Beck Depression Inventory (Beck and Steer, 1987) score $\leq$16, and obtain a normal IQ or above (IQ $\geq$ 85) on the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). The MMSE cutoff was used as an initial screening. We did not follow the norm cutoff value of 24 (Tombaugh and McIntyre, 1992) but chose 26 because we have experience from several previous longitudinal studies that this generally is a reasonable criterion for cognitively healthy elderly. For instance, Kukull et al. (1994) showed a sensitivity of 0.80 and a specificity of 0.87 for Alzheimer's disease with a cutoff of 26. At both time points all scans were evaluated by a neuroradiologist and were required to be deemed free of significant injuries or conditions. At follow-up, an additional set of inclusion criteria was used: MMSE change from time point 1 to time point 2 <10%; California Verbal Learning Test II—alternative version [CVLT II; (Delis et al., 2000)] immediate delay and long delay T-score >30; CVLT II immediate delay and long delay change from time point 1 to time point 2 <60%. The CVLT cutoff criterion was based on the established neuropsychological criterion of 2 standard deviations below the estimated population mean (Lezak et al., 2012), whereas the criterion for functional change was based on pragmatic considerations as there are no established conventions. In addition to the above mentioned, other neuropsychological domains tested included executive function including tests from the Miyake battery (plus-minus; number-letter; local-global; keep track; letter memory; antisaccade; Stroop) (Miyake et al., 2000) and attention and working memory (the Attention Network Test; n-back; digit span) (Fan et al., 2002). Tests were administered at baseline and follow-up. Additionally, ≈100 participants underwent a visual recognition memory task at baseline while electrophysiological activity was recorded.

Two hundred eighty-one participants completed time point 1 (Tp1) assessment. For the follow-up study, 42 opted out, 18 could not be located, 3 did not participate due to health reasons (the nature of these were not disclosed), and 3 had MRI contraindications, yielding a total of 66 dropouts (35 females, mean [standard deviation] age = 47.3 [20.0] years). Detailed dropout characteristics are published elsewhere (Storsve et al., 2014). Of the 215 participants that completed MRI and neuropsychological testing at both time points, 8 failed to meet one or more of the additional inclusion criteria for the follow-up study described previously, 4 did not have adequately processed diffusion MRI data, and 2 were outliers (4 or more tracts showing change values >6 standard deviation from mean). This resulted in a follow-up sample of 201 participants (118 females) aged 20–84 years at Tp1 (see Storsve et al., 2014; Walhovd et al., 2014). Of these, resting-state fMRI was not acquired for the first 81 and valid memory data were lacking for 1 additional, yielding a sample of 119 with quality checked functional and anatomical MRI data as well as cognitive scores for both time points. Tp1 rsBOLD data was lacking for all participants between 52 and 63 years, and we therefore formed 2 age groups: a younger and middle-aged group of 23–52 years and 1 group of older adults of 63–86 years. Sample descriptives are provided in Table 1. As can be seen, follow-up interval differed statistically between the group of young and middle-aged adults and the group of older adults (3.1 vs. 3.4 years). To ensure that this did not affect the results, follow-up interval was included as covariate in all statistical analysis. One participant scored 26 on Mini Mental Status exam for the second time point. This participant was 82.7 years and showed no signs of dementia on the neuropsychological evaluation, including a CVLT learning total score of 40 words and a 30-minute free recall score of 9 words, the former representing an improvement from the baseline score. Thus, we chose to include this participant in all further analyses.

Mean MMSE score was different between age groups, indicating that general cognitive function is higher in the young and middle-aged participants. This is to be expected in aging studies, and equal MMSE scores would thus indicate age-varying sampling bias. Inherently challenging in all aging-studies that do not have

Table 1
Sample characteristics

Variable	Study 1		Study 3			
	Younger and middle-aged	Older adults	Sig, $p <$	Younger and middle-aged	Older adults	Sig, $p <$
N	64	56[a]		59[b]	52	
Age	32.9 (23–52)	71.6 (63–86)	10^{-61}	29.4 (20–49)	68.1 (60–83)	10^{-56}
Sex (females/males)	40/24	29/27		38/21	27/25	
Education	15.9 (12–23)	16.5 (8–26)		15.7 (12–22)	16.6 (8–26)	
IQ	119 (101–133)	120 (90–146)		120 (101–133)	120 (90–146)	
MMSE	29.6 (27–30)	29.0 (26–30)	10^{-3}	29.6 (27–30)	29.0 (27–30)	10^{-3}
Follow-up interval	3.4 (2.7–4.0)	3.1 (2.8–3.8)	10^{-9}	3.4 (2.7–4.0)	3.1 (2.8–3.8)	10^{-7}

Age, IQ, and MMSE values from Tp2, education from Tp1. Mean (range) values are provided. Follow-up interval given in years.
Difference between age groups was tested by independent samples *t* tests, and *p*-values are provided when $p < 0.05$.
Key: MMSE, Mini-Mental State Examination; Tp1, time point 1; Tp2, time point 2.
[a] One participant lacked valid memory scores.
[b] One participant lacked valid MMSE and IQ scores.

information about youth cognitive function for all participants is to balance the risk of age-varying sampling bias by using too strict inclusion criteria versus the risk of including participants with early cognitive decline. In the present study, the thorough screening makes it less likely that participants have abnormal cognitive or cerebral deficits, but the same screening may have caused a certain bias in that the older participants on average are possibly better functioning cognitively compared to the population mean than the young and middle-aged participants.

2.1.3. Statistical analyses

Statistical analyses were done in FreeSurfer 5.3 and SPSS 22. Movement at each time point, sex, and interval between scans were used as covariates of no interest, as well as age for all within-group analyses. Surface results were tested against an empirical null distribution of maximum cluster size across 10,000 iterations using Z Monte Carlo simulations, synthesized with a cluster-forming threshold of $p < 0.05$ (2-sided), yielding results corrected for multiple comparisons across space.

Pearson correlation was used to test the relationship between rsFC and age, both cross-sectionally and longitudinally. Also, rsFC between all nodes within a network ("intranetwork"), as well as between the nodes in each network and the nodes of the rest of the brain ("internetwork"), was calculated, yielding a global (mean) rsFC measure. Note that, for the networks consisting of only one region or node, intranetwork FC could not be calculated. Change in global rsFC (ΔrsFC) was calculated as the difference between time points (Tp2−Tp1) in mean z-transformed correlations across all nodes. Next, the relationship between memory and age was tested both cross-sectionally and longitudinally with partial correlations, and change in memory performance from Tp1 to Tp2 was tested with *t* tests.

For analyses of the relationship between rsFC and memory, the sum of CVLT 1–5 was used as "learning score" and the mean of 5 and 30 minutes CVLT recall was used as a total "recall score" (see the following section). Performance change was expressed as score at Tp2 as a function of score on Tp1 (Tp2 score/Tp1 score), denoted as Δlearning and Δrecall, and correlated with age and global rsFC change. A preliminary repeated measures general linear model showed that interval (5 vs. 30 minutes) from CVLT learning to test did not significantly affect the relationship with ΔrsFC. Thus, because the relationship between CVLT-score change and change in rsFC was not significantly different for 5 minutes versus 30 minutes recall, it should not matter whether the relationship between recall and rsFC was tested by use of separate CVLT scores for 5 and 30 minutes recall or rather an average of the 2. Because using the average would yield higher reliability due to the inclusion of 2 rather than 1 indicator of the construct recall, as well as reducing the number of tests to be done and reported by 50%, we chose to use the mean score for all statistical analyses. In a separate analysis, total cortical atrophy was included as an additional covariate. After establishing a relationship between Δrecall and global ΔrsFC, post hoc tests were performed where Δrecall was correlated with ΔrsFC within and between each of the 17 predefined networks. Differences in correlation strength between the younger and middle-aged group and the group of older adults were tested by t-tests of Fisher z-transformed correlations.

To test whether common regions could be responsible for the relationship between Δrecall and ΔrsFC, we computed "network overlap maps", through the following steps: (1) for each of the 92 seed regions, ΔrsFC was calculated between that regions and the rest of the cortex, yielding 92 surface maps. (2) For all seed regions belonging to a given network, these maps were averaged, yielding rsFC change maps for 17 networks in the left hemisphere and 15 in the right. (3) Each of these ΔrsFC maps were then correlated with Δrecall, yielding maps of *p*-values for the relationship between rsFC change in that network and Δrecall. (4) The results were corrected for multiple comparisons by permutation testing (see previously mentioned), and binarized so that each vertex was classified as "significant" or "not significant". (5) All maps were stacked on top of each other, and the number of times each vertex was significant was counted, yielding a value of minimum 0 and maximum 17 (left) or 15 (right). A high number would mean that Δrecall and ΔrsFC was significant for many networks at that location. The same procedure was also done for age-interactions, that is, the number of times vertices where ΔrsFC was differentially related to Δrecall in the old versus the younger and middle-aged group. Local cortical atrophy was also calculated from the vertices most heavily involved across multiple networks, and the Δrecall and ΔrsFC correlations re-run with atrophy as an additional covariate.

Finally, rsFC maps for all nodes were averaged across time points and participants to yield a map of mean connectivity for each vertex. This connectivity surface map was then correlated with the age-interaction network overlap maps described previously. A positive correlation would mean that vertices showing different ΔrsFC-Δrecall relationships across age groups across many networks had relatively higher mean connectivity to the rest of the cortex. To test this further, vertices were also grouped according to number of networks showing age-interactions: 0 networks, 1–5 networks, 6–10 networks or ≥11 networks.

2.2. Study 1 results

The relationships between age and rsFC are presented in Table 2. Cross-sectionally, a negative age-relationship was seen across networks, whereas the global ΔrsFC–age-correlation was 0.23 ($p < 0.05$). Adding a quadratic age-term did not explain additional variance, showing that the longitudinal age-effect was not different in different parts of the age-range. The age-relationships did not vary much between the specific networks. Scatterplots are presented in Figs. 2 and 3.

Table 2
Correlations between age, rsFC, and memory

Network number	Age-relationships				Correlations ΔrsFC with Δrecall			
	Cross-sectional		Longitudinal		Younger and middle-aged		Older	
	Inter	Intra	Inter	Intra	Inter	Intra	Inter	Intra
N1	−0.14		0.14		**−0.26**		**0.29**	
N2	**−0.24**		0.11		**−0.37**		**0.29**	
N3	**−0.24**		**0.20**		−0.13		**0.31**	
N4	**−0.27**		**0.22**		**−0.28**		**0.32**	
N5	−0.15		**0.29**		**−0.30**		0.27	
N6	−0.18	**−0.30**	0.17	0.12	−0.21	−0.18	**0.31**	**0.30**
N7	−0.17	**−0.24**	**0.21**	0.17	−0.25	−0.18	**0.29**	**0.28**
N8	**−0.20**	**−0.22**	**0.23**	**0.25**	−0.21	−0.13	0.27	0.10
N9	**−0.22**		0.07		**−0.39**		**0.29**	
N10	0.14		0.04		**−0.28**		0.02	
N11	−0.14	**−0.23**	**0.23**	**0.20**	−0.10	0.10	0.27	0.23
N12	**−0.18**	**−0.23**	**0.23**	**0.21**	−0.22	−0.12	0.24	0.18
N13	**−0.19**	**−0.23**	**0.30**	**0.22**	−0.23	−0.18	0.21	−0.03
N14	**−0.20**		0.17		**−0.31**		**0.28**	
N15	**−0.20**	−0.16	0.13	0.10	**−0.35**	−0.24	**0.31**	**0.31**
N16	**−0.19**	**−0.21**	**0.21**	0.18	**−0.33**	−0.21	**0.30**	0.16
N17	**−0.25**	**−0.35**	**0.22**	0.09	−0.25	−0.00	**0.29**	0.19

N: Network (Yeo et al., 2011). Inter denotes rsFC between each node in a network and all nodes outside that network. Intra denotes rsFC between all nodes within a network. Cross-sectional analyses are based on the mean of time points, while longitudinal are based on the difference (Tp2−Tp1). Bold indicates $p < 0.05$. Numbers are partial correlations with controlling for movement, sex, and interval between scans, as well as age for the memory analyses. Connectivity is calculated as the mean of hemispheres. Intranetwork correlations could not be calculated for networks consisting of only 1 region.
Key: rsFC, resting-state functional connectivity.

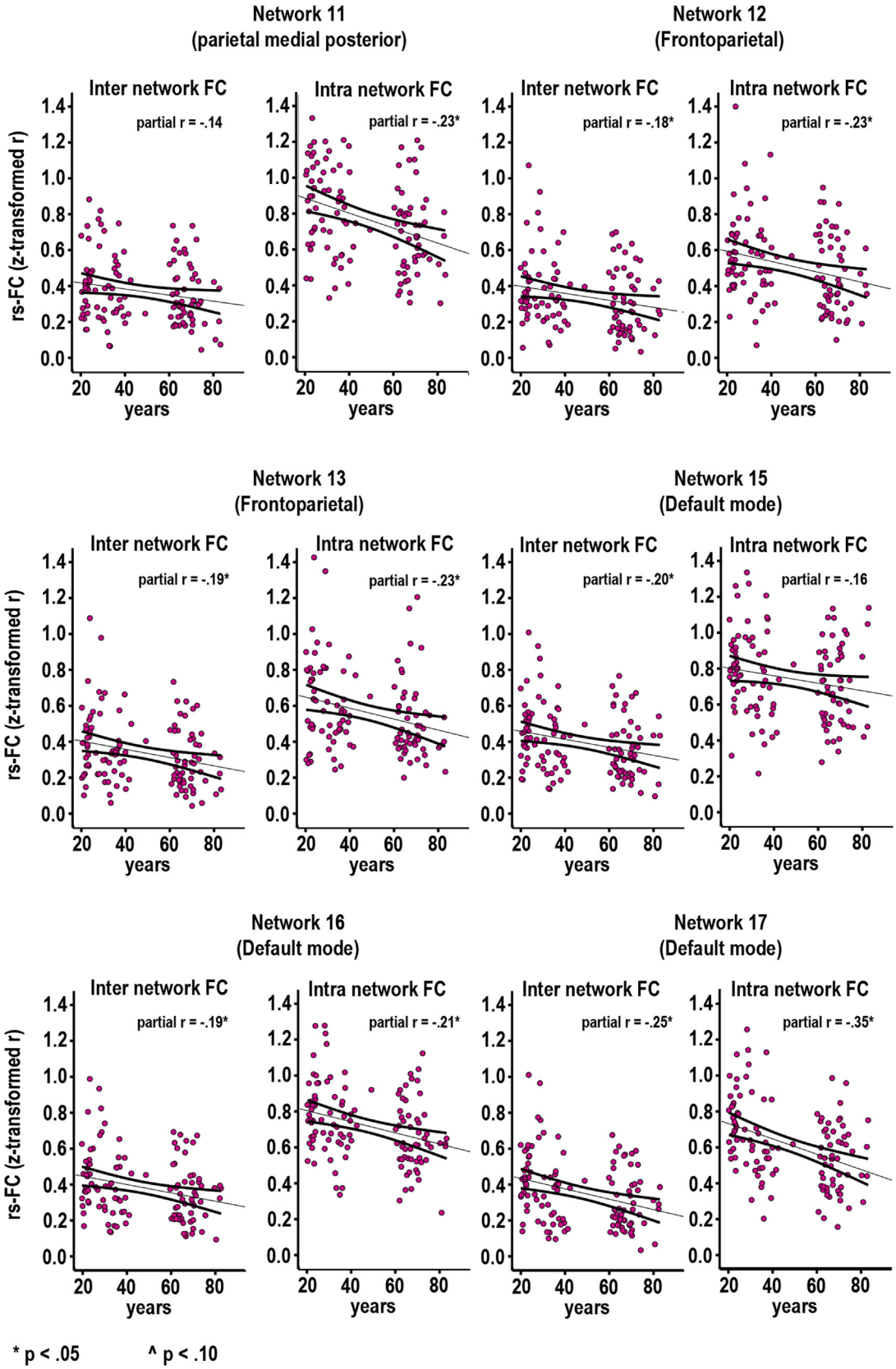

Fig. 2. Cross-sectional age–functional connectivity relationships. Intra network rsFC is the mean connectivity (z-transformed correlations) between all seeds within a network, whereas internetwork rsFC is the mean connectivity between the seeds within a network and all seeds outside the network. All data points are the mean value of Tp1 and Tp2. Selected networks are shown. Abbreviation: rsFC, resting-state functional connectivity.

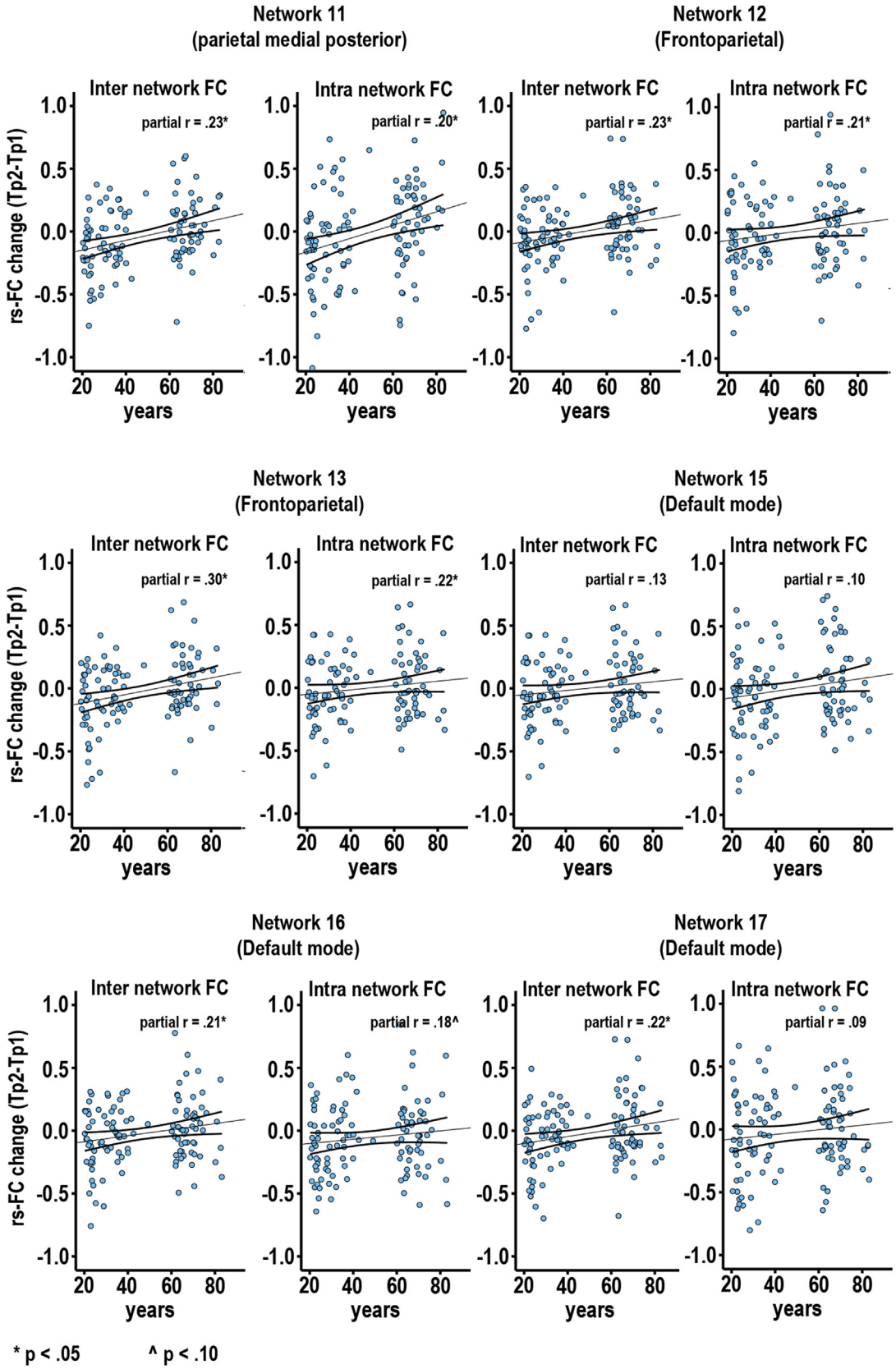

Fig. 3. Longitudinal age–functional connectivity relationships. The relationship between age and change in rsFC for selected networks. Change in rsFC is the difference between Tp2 and Tp1 in z-transformed correlations. Abbreviations: rsFC, resting-state functional connectivity; Tp1, time point 1; Tp2, time point 2.

2.2.1. Age-changes in memory function

Cross-sectional age correlated negatively with CVLT scores at both time points (CVLT learning r = −0.63/−0.57 at Tp1 and Tp2, respectively; CVLT 5 minutes recall r = −0.61 and −0.49 at Tp1 and Tp2; CVLT 30 minutes recall r = −0.60 and −0.44 at Tp1 and Tp2, all $ps < 10^{-6}$). Although alternative test versions were used at Tp1 and Tp2, net change from Tp1 to Tp2 was not observed (learning 57.9 vs. 58.6 at Tp1 vs. Tp2, t [118] = −0.85, not significant (ns)/recall 12.8 vs. 13.1 at Tp1 vs Tp2, t [118] = 1.52, ns). Age did not correlate with Δlearning (r = −0.10, ns), while a tendency was observed for less positive Δrecall with higher age (r = −0.18, $p = 0.057$). A follow-up test of Δrecall in each age-group separately showed that the younger and middle-aged participants had a significant practice effect (14.0 vs. 14.7 at Tp1 vs Tp2, t [62] = 3.31, $p < 0.005$), whereas the older group did not show a significant change (11.4 vs. 11.2 at Tp1 vs Tp2, t [55] = 0.55, ns).

2.2.2. Relationship between ΔrsFC and change in memory function

Cross-sectionally, learning and recall at baseline did not correlate with changes in rsFC in either age group. For the longitudinal analyses, we first run a general linear model with global rsFC change as dependent variable; age group as fixed factor; and CVLT recall, sex, and movement at each time point as covariates. A main effect of age group (F [1,119] = 5.05, $p < 0.05$) and an interaction effect of age group × recall (F [1,119] = 7.60, $p < 0.01$) was found. No effects were found for learning. Testing the relationship separately in each age group, in the older group, increased rsFC was related to better memory outcome (partial r = 0.29, $p < 0.05$), whereas a negative correlation was seen for the younger and middle-aged (partial r = −0.28, $p < 0.05$, difference between correlations z = 2.91, $p < 0.005$, by tests of Fisher z-transformed correlations) (Fig. 4). Including total cortical atrophy as an additional covariate did not affect the correlations (young: partial r = −0.31, old: partial r = 0.30). To test whether the negative relationship was uniform across the age-range in the young group, a regression was run with global rsFC change as dependent and CVLT recall and the square of CVLT recall as predictors and movement, age and sex as covariates of no interest. The quadratic term was marginally significant ($p = 0.089$). We then did follow-up partial correlation analyses for those <30 and those in the young and middle-aged group from 30 years and up. In the young-young group, CVLT recall change correlated −0.39 ($p < 0.05$, degrees of freedom = 27) with global rsFC change while in the old-young group the correlation was 0.17 (ns, degrees of freedom = 22). These correlations were marginally significantly different (Z = 1.9, $p = 0.057$). Change in the CVLT learning condition did not correlate with ΔrsFC (young: partial r = −0.15; old: partial r = 0.15, ns), and so, further analyses were done for Δrecall only.

Post hoc correlations between ΔrsFC and Δrecall in all networks were calculated, yielding 17 internetwork and 9 intranetwork correlations. Fourteen positive correlations in the old group ($p < 0.05$) and 9 negative in the younger and middle-aged ($p < 0.05$) were found (Table 2). Twenty of 26 correlations were significantly different between the age groups, with no significant differences for between versus within network correlations.

To test whether the relationship between global ΔrsFC and age was dependent on longitudinal change in recall, we divided each age group in 2, based on whether they showed relatively higher versus relatively lower preservation of recall function (median split). The results are shown in Fig. 5. In the high-preservation group, a positive age-correlation (r = 0.36, $p < 0.05$) was seen, whereas no relationships were observed in the low preservation group (r = 0.07, ns). The difference between the correlations was marginally significant ($p = 0.10$, z = 1.64).

2.2.3. Network overlap

The similarities in correlations across networks indicated that common regions could be responsible for the relationship with Δrecall, and thus, network overlap maps were computed as described previously (Fig. 6). Significant age-interactions were seen for at least 5 networks for 63% of the total number of vertices and at least 10 networks for 25%. Lateral, medial, and inferior temporal cortex, especially in the left hemisphere, showed age-interactions in >10 networks. Other regions of known relevance for normal memory function, such as posterior medial parietal and medial prefrontal cortex, also showed effects across >10 networks. However, some regions not traditionally regarded as important for memory, for example, posterior cortical and areas around the central sulcus, still showed age effects across multiple networks.

Extent of network overlap was higher for older than younger and middle-aged. In the older, ΔrsFC was significantly related to Δrecall in >10 networks in widespread regions, including left parahippocampal and parts of the superior temporal cortex bilaterally and portions of the lateral and medial parietal and prefrontal cortex. For the young, fewer regions showed extensive network overlap, especially in the right hemisphere. Regions of highest overlap included the medial and lateral temporal cortex and the precuneus, which are prime memory regions. Here, overlapping effects were seen for 7–8 networks in the left hemisphere and 4 in the right.

Volume change was then extracted from the vertices most heavily involved across multiple networks. For the older group, volume change was calculated for vertices where rsFC change in at

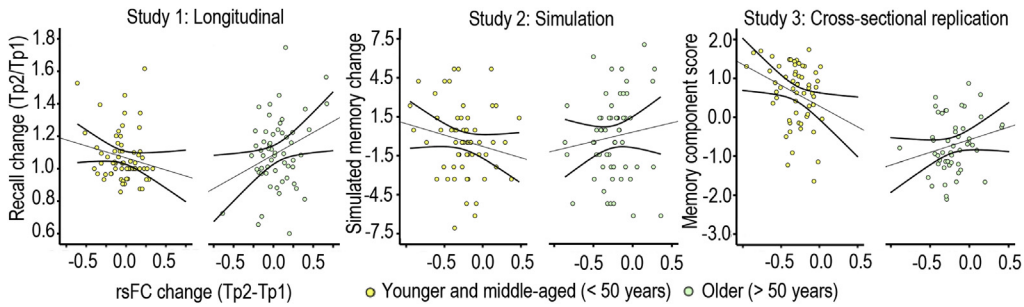

Fig. 4. Longitudinal recall–global functional connectivity relationship. Left panel: the relationship between change in global rsFC and recall change from study 1. Recall change is the recall scores at Tp2 divided by Tp1. Middle panel: simulation results. A simulation study was run, where all terms were explicated and model parameters drawn from the actual data. The simulation results replicated the cross-sectional results and the inverse rsFC-memory change relationship from the real data, without any assumption of increased rsFC in the older group. Right panel: cross-sectional recognition memory replication. Relationship between change in rsFC and cross-sectional recognition memory performance, expressed as a principal component of accuracy, reaction time (RT), and RT stability. Abbreviations: rsFC, resting-state functional connectivity; Tp1, time point 1; Tp2, time point 2.

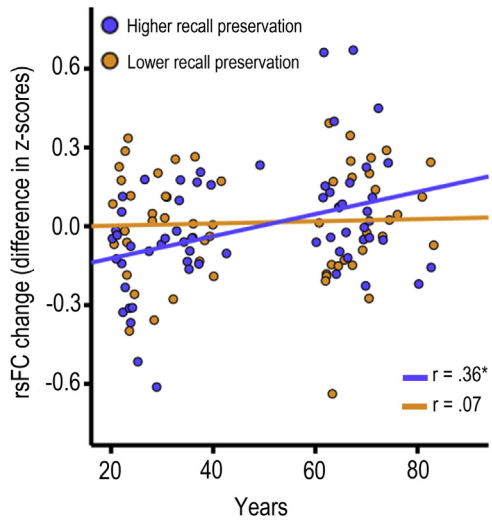

Fig. 5. Relationship between rsFC change and age as a function of memory preservation. The sample was split into those with high degree of preservation of recall scores and those with lower degree of preservation by a median split in each age-group separately. A positive relationship between age and global rsFC change was seen in the high preservation group, and no relationship was observed in the low preservation group. *$p < 0.05$. Abbreviation: rsFC, resting-state functional connectivity.

least 9 networks was related to recall change, whereas the threshold was set to 3 in the younger and middle-aged to avoid including a too small portion of the cortex. Rerunning the ΔrsFC-Δrecall correlations in Table 2 with local cortical atrophy as additional covariate, 1 network correlation (NW 5) changed from 0.27 ($p < 0.10$) to 0.30 ($p < 0.05$) and 1 (NW 8 internetwork) from 0.27 ($p < 0.10$) to 0.28 ($p < 0.05$) for the old group. The other networks showed only minor changes after inclusion of atrophy as an additional covariate.

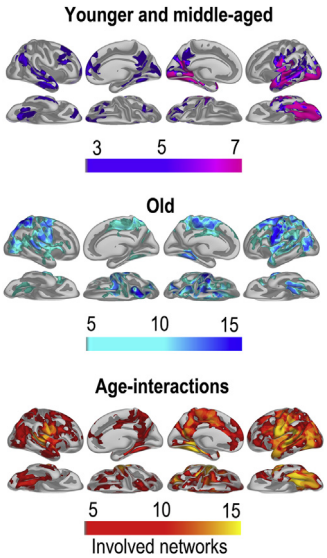

Fig. 6. Anatomical distribution of recall change—functional connectivity change relationships. resting-state functional connectivity (rsFC) change maps were computed for all networks, and each map was correlated with recall change. The results were corrected for multiple comparisons by permutation testing. The figure shows the number of networks for which recall change correlated with rsFC change, yielding a minimum of 0 and a maximum of 17 (left hemisphere) or 15 (right hemisphere) networks. In the older group (middle row), rsFC-memory change relationships involved many networks and covered large parts of the cortex. For the younger and middle-aged (top row), number of networks involved was lower. Age-interactions (bottom row) were found for large parts of the cerebral cortex.

2.2.4. Memory-rsFC change and overlap with regions of high rsFC

Mean connectivity maps for all nodes are shown across time points and participants in Fig. 7. This connectivity surface map was correlated with the surface map in the last row in Fig. 6. A significant positive correlation was found in both hemispheres (left r = 0.48, right r = 0.53, $p < 0.05$ by permutation testing), meaning that high mean connectivity was associated with more age effects on ΔrsFC-Δrecall relationships. To test this further, vertices were grouped according to number of networks showing age interactions: 0 networks (left hemisphere: 7.5% of vertices/right hemisphere: 17%), 1–5 networks (left: 24.7%/right: 50.1%), 6–10 networks (left: 35.1%/right: 28.9%), or ≥11 networks (left: 32.7%/right: 4.0%). Connectivity was very low in the vertices not showing age-interactions for any network. As long as age-interactions with at least 1 network were found, connectivity did not vary as a function of the number of networks showing age-interactions.

3. Study 2: simulation model

3.1. Materials and methods

The purpose of running a simulation study was to examine whether a hypothesized model would be expected to generate a set of observed patterns in the data similar to those actually observed. Especially, this was motivated by the observation of opposite change in rsFC in the 2 age groups, in both cases being correlated with memory change. Importantly, the purpose of study 2 was not to propose a realistic model for causes of age-related memory change. Thus, simulation data were generated by a model of age, connectivity, and memory. The full R-code for the simulation is presented as Supplemental Information. The model contained the following variables (see Fig. 8):

3.1.1. Connectivity

Measured connectivity is equal to exp(actual connectivity plus measurement error). The model is formulated in terms of logged measurement units because connectivity measurements in the real sample appear skewed relative to a normal distribution.

Actual connectivity is generated from a discretized Brownian motion with drift and mean reversion. A Brownian motion models a process where units are exposed to a normally distributed shock or influence each instant in time. This causes the units in a pure

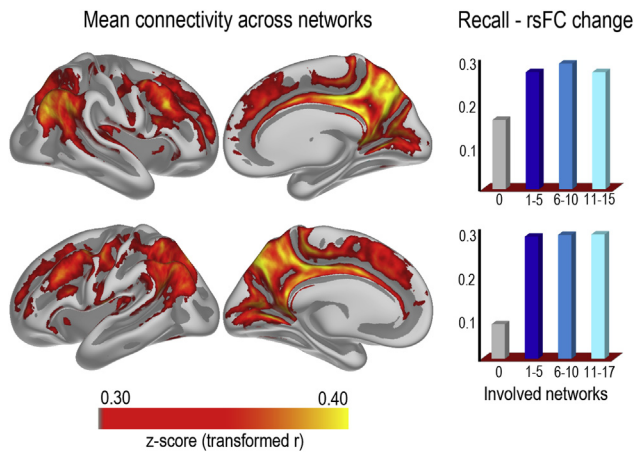

Fig. 7. Mean connectivity as a function of age-interactions. The surface maps (left) show vertexwise mean rsFC, thresholded at $z > 0.30$. The bar plots (right) shows mean rsFC as a function of number of age-interactions in the bottom row of Fig. 6. Vertices not showing age-interactions in rsFC-memory change had lower rsFC with the rest of the cortex. Abbreviation: rsFC, resting-state functional connectivity.

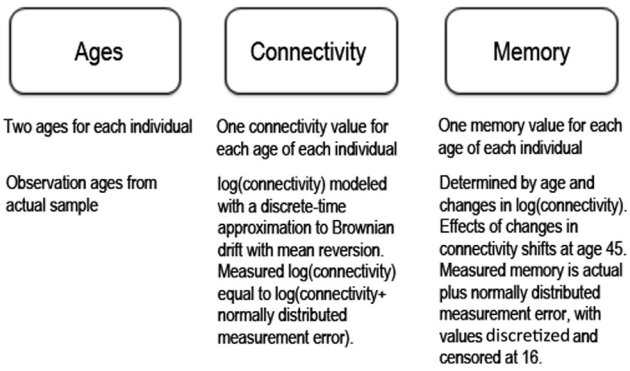

Fig. 8. Schematic outline of the variables included in the simulation model.

Brownian motion process to diffuse across the outcome space over time, spreading further and further "away" from each other. For simplicity, the code uses a discrete time approximation, where the shocks only happen once a year.

The drift in the Brownian process represents a common influence that shifts all the units in the same direction. In our case, this is an aging effect: a linear annual change in a cohort's average log(-connectivity). The simulation code allows the trend to shift at age 45 years. In the real data, the connectivity distribution does not seem to increase over time in the way a Brownian motion would imply. We therefore impose mean reversion, a "force" that pulls the particles some portion of the way back to the population average. In sum, we get a process where everyone's connectivity has a common tendency over time (an aging effect), but with individual developmental differences around this average trend.

Measurement error seems probable, as well as plausible in light of the measured changes in connectivity: Some individuals see their connectivity doubled or halved after 3 years, and there is very strong regression to the mean.

3.1.2. Memory

Observed memory is "actual memory" observed with a measurement error and converted to a discretized scale with 16 as the maximum observation to match the range of the empirical measure, which had pronounced ceiling effects.

"Actual memory" is modeled as a linear function of age and changes in log(connectivity): an initial memory value at age 15 years is drawn from a normal distribution, the same linear memory decline occurs for each year of aging, and changes in log(connectivity) affect memory (with different parameters for the effect before and after age 45 years).

In addition, there is a test-learning effect that shifts the entire distribution of the memory values observed at the second observation ages by a common value.

Actual memory is then converted to a scale similar to the one used on the actual sample: discretized, in that the latent memory value is rounded to the closest integer value, and with a ceiling effect, whereby any value >16 is set equal to 16.

3.1.3. Parameter values

The purpose of this part of the study was to see whether a hypothesized "structural" model could be made consistent with observed patterns in empirical data. To examine this, we created a simulation model and calibrated this to reproduce observed patterns. The calibration was based on the empirical data, which contained 2 memory measures (both measured on a scale from 0 to 16) and 1 connectivity measure, all taken at 2 ages for each of 119 participants. These data were used to run regressions of age on log(connectivity), age on memory, (we used only one of the memory measures for this exercise), of log(connectivity) on memory, and of age and log(connectivity) on memory. Parameters within the observed coefficient and residual standard error ranges were chosen and adjusted manually using trial-and-error to make visually assessed patterns in the data similar to those in the observed data. These adjustments required multiple, often interconnected changes to the parameter values used. For instance, if the measurement error assumed for connectivity was increased, this meant that the assumed standard deviation of the connectivity process as an individual aged needed to be reduced to make the total variation in the simulated measurements of connectivity similar to the empirical.

3.2. Study 2 results

Simulated data were generated by a model of age, global rsFC, and recall. For full results, please see Supplemental Information. The real and the simulated data showed a similar cross-sectional reduction of rsFC and memory with age, and a positive, cross-sectional relationship between rsFC and memory, that is, the simulation model reproduced the relationships observed in the real cross-sectional data. Furthermore, the negative ΔrsFC-Δmemory relationship in the younger and middle-aged and the positive relationship in the older participants were replicated (Fig. 4). Although the changes in rsFC in the real data were $\Delta z = 0.05$ (old) versus $\Delta z = -0.04$ (young), in the simulated data these were more similar and had the same sign $\Delta z = -0.015$ (old) versus $\Delta z = -0.012$ (young), demonstrating that increase in rsFC over time in the older age group was not necessary to observe the age-dependent memory relationship.

4. Study 3: cross-sectional replication

The purpose of study 3 was to test whether the effect of age on the rsFC-memory relationship could be replicated with cross-sectional data and a different type of memory task. If so, this would demonstrate that the observed relationship was not due to aspects of the CVLT per se. The rational for this is that the level of performance on baseline is assumed related to ongoing brain changes that can be measured with rsFC. Furthermore, using a cross-sectional task from Tp1 also insured that practice effect did not unduly bias the results in any way. Previous research has demonstrated that sensitive tasks at baseline can predict future changes in certain brain properties (Raz et al., 2008). Thus, cross-sectional memory performance from a visual recognition task was correlated with longitudinal change in rsFC in the same participants as in study 1. Although no cross-sectional relationship between baseline memory score and rsFC change was identified in study 1, we reasoned that a more demanding memory task would be better able to differentiate participants than the 16-point CVLT memory scale when not taking the presumably more sensitive longitudinal changes into account.

4.1. Materials and methods

4.1.1. Sample

One hundred nine participants from study 1 (younger and middle-aged $n = 59$, older $n = 52$) underwent a visual recognition memory task at Tp1 and were included in study 3 (see sample characteristics in Table 1). For recruitment and screening, please see description of Sample in study 1. The sample was representative of the study 1 sample, with almost identical education, IQ, and MMSE scores.

4.1.2. Memory task

The task visual recognition memory was a modified version of one used by Duarte et al. (2006). E-prime (Psychology Software Tools Inc, www.pstnet.com) was used for presentation of stimuli and registration of responses. The total duration of the task was ~30 minutes, including 10 minutes encoding and 20 minutes recognition test. These were separated by 45 minutes of nonrelated cognitive tasks.

The participants were seated in a comfortable chair, ~60 cm from a monitor used to present the stimuli. Responses were given by button press with the right hand on a response box. Stimuli were line drawings of common objects or animals in black on a white background made by a professional illustrator. The encoding phase consisted of 2 blocks, each containing 75 stimuli. The participants were informed that they would later be asked to perform a memory task, where they would be required to remember each drawing as well as in which block each drawing was presented. Each stimulus was presented for 1000 ms, followed by a 1000 ms window within which they were required to give a response. After the response, a jittered interstimulus interval of 700–3600 ms followed.

The 2 encoding blocks were separated by 60 seconds. In the first block, the participants were asked to make a judgment of whether they would be able to lift what the drawing represented with one hand. In the second block, they were asked to make a judgment of whether they would be able to fit what the drawing represented within a car. The response alternatives were "yes" or "no".

After 45 minutes of performing nonrelated cognitive tasks, a recognition test was given, where the encoded stimuli were presented intermingled an equal number of new line-drawings. The recognition block consisted of 100 drawings presented during encoding and 100 new drawings presented in a pseudorandomized sequence. During this part of the experiment, each drawing was shown for 1000 ms, followed by a 1500 ms window within which the participant was required to give a response. After the response, a jittered interstimulus interval of 700–3600 ms followed. The participants first made a decision about whether they had seen the drawing during encoding. If they responded "no", the task moved on to the next stimuli. If they responses "yes", they got a follow-up question on in which of the 2 blocks the drawing was first presented. They got 3 response alternatives: The "lift block," the "car block," or "don't remember". The presentation of the instruction terminated when the response was given.

4.1.3. Statistical analyses

Twelve memory-related parameters were extracted: hits, correct rejections, misses, false alarms, hits reaction time (RT), correct rejections RT, misses RT, false alarms RT, hits standard deviation of the RT (sdRT), correct rejections sdRT, misses sdRT, false alarms sdRT. These were all entered into a principal component analysis to extract a higher-order memory component representing the optimal linear combination of the 12 memory-related parameters. This component was saved and inverted, to ensure that higher scores represented better memory function. The relationship between this memory component and global rsFC change was tested in each age group separately with partial correlations, and the same covariates as in study 1 (age, movement, sex, and interval between scans) and the correlations were compared by *t* tests of Fisher z-transformed correlation coefficients.

4.2. Study 3 results

One component explained 54.6% of the variance in memory score, with Eigenvalue = 6.56. The component matrix is shown in Table 3. The pattern of reverse relationships to global rsFC change in younger and middle-aged versus older adults from study 1 was replicated, with a significantly different memory-ΔrsFC relationship in the 2 groups (younger and middle-aged $r = -0.27$ $p < 0.05$, old $r = 0.23$, $p = 0.11$, difference between correlations $z = 2.61$, $p < 0.01$), Scatterplots are shown in Fig. 4. Regressing out performance on 2 other speeded tests, the Stroop word reading condition and the "Plus" condition in the plus/minus test, did not affect the results (younger and middle-aged $r = -0.25$, old $r = 0.24$, difference between correlations $z = 2.56$, $p = 0.01$). This indicates that processing speed is less likely to be the main contributor to the memory component.

Table 3
Component matrix

Variable	Loading
RT correct rejection	0.91
RT hit	0.91
RT miss	0.88
sdRT correct rejection	0.87
sdRT hit	0.84
RT false alarm	0.84
sdRT miss	0.75
Correct rejection	−0.68
Hits	−0.59
sdRT false alarm	0.49
False alarm	0.46
Miss	0.37

For the statistical analyses, the component loadings were inversed so that higher scores would indicate higher performance.
Key: RT, reaction time; sdRT, the intraindividual standard deviation of the reaction time.

5. Discussion

We have reported the results from 3 closely related studies. In study 1, longitudinal changes in rsFC were related to changes in recall abilities, independently of ongoing brain atrophy. Striking age-effects were seen, with increased rsFC predicting improved recall performance in older adults whereas reduced rsFC predicted improved recall in younger. This could mean that there are age-related differences in rsFC that are relevant for understanding age-decline in memory function. In study 2, we constructed a simulation model that was able to reproduce the main age-effects on memory and rsFC reported in study 1. In study 3, visual recognition memory performance at baseline predicted longitudinal change in rsFC, with negative relationships in the group of young and middle-aged adults and positive relationships in the older adults. Thus, the main findings were replicated across 3 variants of the study, demonstrating that the results cannot be attributed to aspects of the specific memory task used or practice effects inherent in most longitudinal studies.

5.1. Functional connectivity change and memory function over time

rsFC measured post encoding may partly reflect consolidation of memory (Albert et al., 2009; Daselaar et al., 2010; Hasson et al., 2009; Stevens et al., 2010; Takashima et al., 2009). In the present study, rsFC changes were measured independently of the encoding task, and may index ongoing, trait-like functional characteristic of the individual, rather than specific consolidation of the encoded material per se. Interestingly, we found a positive relationship between rsFC change and recall change in the group of older adults and a negative relationship in the group of younger and middle-aged adults. The positive rsFC-recall change relationship in the older group is in accordance with one previous study of longitudinal changes within the DMN in elderly (Persson et al., 2014) and a

longitudinal drug intervention study where increased FC between left posterior hippocampus and the medial prefrontal cortex correlated with increases in retention scores (Witte et al., 2014). Several cross-sectional studies have also observed positive rsFC-memory relationships (Andrews-Hanna et al., 2007; Fjell et al., 2014; Geerligs et al., 2014; Mevel et al., 2013; Onoda et al., 2012; Wang et al., 2010a; Ward et al., 2015), but not uniformly, as both higher and lower functional couplings have been associated with decreased cognitive functions (Antonenko and Floel, 2014). Ferreira and Busatto (2013) proposed that greater rsFC represents more efficient brain networks in a number of conditions, but that both functional specialization and functional segregation are important for cognition, sometimes yielding negative relationships between rsFC and cognition. Similarly, it has been suggested that higher efficiency of communications within networks and lower internetwork connections, reflecting specificity and selectivity of the networks, impact cognition positively (Antonenko and Floel, 2014). Geerligs et al. (2014) found less distinct functional networks and lower local efficiency in older adults, and age-related increases in the recruitment of more general instead of specific functional networks, that is, higher internetwork FC and lower intranetwork FC, have been associated with lower function in specific cognitive domains (Antonenko and Floel, 2014; Salami et al., 2012; Spreng and Schacter, 2012). This can be interpreted within the dedifferentiation theory of aging (Lindenberger and Baltes, 1994), according to which segregation of cognitive abilities, and hence, functional specialization between networks, is reduced with aging. Our longitudinal results did not show differential effects of within versus between-network changes on memory, indicating that this distinction may be less important for within-subject change. However, the finding that rsFC change in large regions and across multiple networks was associated with memory change in older adults could be caused by breakdown of functional specificity resulting in more diffuse patterns of FC with age, possibly related to compensatory activity (Reuter-Lorenz and Park, 2010). This conclusion must not be overstated, however, because widespread effects were not exclusively seen in the older participants, with longitudinal change in 9 different networks being associated with recall change in the younger and middle-aged group.

Although rsFC-recall relationships were found for networks assumed to be of importance for memory, such as the DMN (Andrews-Hanna et al., 2014; Spreng et al., 2009; Vincent et al., 2006), additional involvement from other networks were also seen. Interestingly, the regions where age did not influence the relationship between rsFC change and recall change were more weakly connected to other networks of the cortex. Regions with strong connections to many other cortical regions play a key role in information integration in the cortex and are likely critical in a range of conditions (Buckner et al., 2009), including memory. However, it was not only changes in the most highly interconnected cortical areas that drove the rsFC-memory relationships because all regions showing at least one age interaction had high connectivity.

The most striking age-effect was the inverse rsFC-memory change relationship in the older versus the younger and middle-aged participants. This was replicated across the longitudinal data, the simulated data, and in the cross-sectional recognition memory task and match what we have previously seen with subcortical-cortical connectivity change (Fjell et al., 2015). To understand the conditions for the effect, we need to look at the longitudinal changes in rsFC in combination with the simulation results. Age correlated negatively with absolute rsFC and positively with change in rsFC, the latter caused by longitudinal decrease in the younger and middle-aged and increase in the older participants. Increased rsFC could potentially reflect compensatory activity in response to reduced efficiency of neurocognitive processing (for a review, see Grady, 2012). Agosta et al. (2012) found higher executive network connectivity in Alzheimer's disease patients than controls, and a positive correlation with neuropsychological performance, interpreted as functional compensation. The same conclusion was drawn in a study that found increased connectivity between inferior parietal and medial prefrontal cortex was associated with better episodic memory performance for older adults with small gray matter volumes, whereas this relationship was not seen for those with larger gray matter volumes (He et al., 2012). Similarly, Lim et al. (2014) observed higher rsFC in DMN in Pittsburgh compound B-positive cognitively normal older adults compared to Pittsburgh compound B negative, with a positive relationship to episodic memory scores. Thus, in cross-sectional studies, the seemingly paradoxical pattern of higher rsFC in disease or risk groups, with positive correlations with cognitive function, has been observed previously. Still, this does not explain the discrepancy between the cross-sectional and the longitudinal observations in the present data. Thus, we turned to the simulation results. The purpose of the simulation study was to decide which terms and parameters that needed to be included in a model that could reproduce the observed rsFC-memory change relationship. In the simulation model, connectivity changed according to a common, age-related reduction and an individual shock. Importantly, no terms specified rsFC increases or age-dependent differences in connectivity change. The results clearly showed that the age-effect on the rsFC-memory relationship was not conditioned on increased rsFC in the older age group. Another point that can be considered is the not perfect test-retest reliability of rsFC (Honey et al., 2009), which makes the probability of surprising observations larger due to increased noise. Still, several studies have suggested that the reliability is acceptable (Guo et al., 2012; Thomason et al., 2011) and rsFC has consistently been able to distinguish between different brain states and conditions (Barkhof et al., 2014). In sum, because we lack a convincing explanation for the observed increase in rsFC, we advise that this is interpreted with caution and replicated in an independent sample.

6. Conclusion

Longitudinal changes in rsFC impact recall function in a highly age-dependent manner. Of importance, the effect on memory was not restricted to specific networks but was seen across large regions of the cortex. This phenomenon was even more evident in the older than the younger and middle-aged adults, in line with theoretical views on neurocognitive aging involving compensatory activity and reduced specificity of functional networks. The results suggest that off-line cortical processes are relevant for understanding the reduced efficiency in forming and consolidating new episodic memories commonly seen in normal aging.

Disclosure statement

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2015.08.020.

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