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Recollection-related increases in functional connectivity across the healthy adult lifespan

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Abstract

In young adults, recollection-sensitive brain regions exhibit enhanced connectivity with a widely distributed set of other regions during successful versus unsuccessful recollection, and the magnitude of connectivity change correlates with individual differences in recollection accuracy. Here, we examined whether recollection-related changes in connectivity and their relationship with performance varied across samples of young, middle-aged, and older adults. Psychophysiological interactions (PPI) analyses identified recollection-related increases in connectivity both with recollection-sensitive seed regions and among regions distributed throughout the whole brain. The seed-based approach failed to identify age-related differences in recollection-related connectivity change. However, the whole-brain analysis revealed a number of age-related effects. Numerous pairs of regions exhibited a main effect of age on connectivity change, mostly due to decreased change with increasing age. After controlling for recollection accuracy, however, these effects of age were for the most part no longer significant, and those effects that were detected now reflected age-related increases in connectivity change. A subset of pairs of regions also exhibited an age by performance interaction, driven mostly by a weaker relationship between connectivity change and recollection accuracy with increasing age. We conjecture that these effects reflect age-related differences in neuromodulation.

Keywords

recollection; aging; functional connectivity; episodic memory; psychophysiological interactions; associative recognition

Healthy aging is marked by memory decline, and recollection - memory for specific contextual details about a prior event (Mandler, 1980; Yonelinas, 2002) - is particularly affected (Nilsson, 2003; Old and Naveh-Benjamin, 2008). Age-related decline in recollection has been attributed to deficits in the ability to associate or 'bind' different aspects of an event into a single, cohesive representation (Naveh-Benjamin, 2000; Naveh-Benjamin and Craik, 1995), as well as to impairments in retrieval processes that are

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necessary for successful recollection; processes such as goal-directed processing of retrieval cues (Jacoby et al., 2005; Morcom and Rugg, 2004) and the monitoring and evaluation of retrieved information (Gallo et al., 2006; McDonough et al., 2013; Mitchell et al., 2013).

Functional neuroimaging studies have demonstrated in both younger and older adults that recollection is associated with enhanced activity in a set of brain regions that have been referred to as ‘the core recollection network’ (Kim, 2010; Rugg and Vilberg, 2013; Spaniol et al., 2009). These regions include left angular gyrus (AnG), medial prefrontal cortex (mPFC), hippocampus, middle temporal gyrus (MTG), and posterior cingulate cortex (PCC). The magnitude of recollection-related activity in these regions has been reported to vary across different age groups; however, the extent and direction of this variation depends on factors such as whether memory performance was equated across age groups and the operational definition employed to characterize the neural correlates of successful recollection (de Chastelaine et al., 2016a; Duarte et al., 2008; Morcom et al., 2007; T.H. Wang et al., 2016; for review see W.C Wang and Cabeza, 2016). For instance, there is evidence that relative to older adults, young adults show greater recollection-related activity in core recollection regions when objective (e.g., source memory) but not subjective (e.g., Remember/Know) tests of recollection are employed (Duarte et al., 2008; T.H. Wang et al., 2016). There is also evidence that age effects on recollection-related activity may be better explained by individual differences in performance than by age, per se. For example, de Chastelaine and colleagues (2016a) reported larger recollection effects in young than in middle-aged and older adults in several core recollection regions. However, when individual differences in associative recognition (i.e., recollection) performance were statistically controlled for, these age differences were no longer significant. In summary, the balance of the evidence suggests that recollection-related enhancement of activity throughout the core recollection network is relatively stable across much of the healthy adult lifespan.

Other studies have investigated age-related differences in patterns of functional connectivity and how these differences relate to age-related memory deficits. The majority of functional connectivity studies to date have investigated time-dependent correlations of the BOLD signal among distributed regions while participants are in a “resting-state.” Both age-related increases and decreases in resting-state functional connectivity have been reported (Andrews-Hanna et al., 2007; Campbell et al., 2013; Damoiseaux et al., 2008; Ferreira and Busatto, 2013; Salami et al., 2014; Westlye et al., 2011). For instance, Salami et al. (2014) demonstrated an age-related increase in inter-hemispheric connectivity between homotopic regions of the hippocampus, and a weakening of connectivity between the hippocampus and other members of the ‘default mode network’. After controlling for age, interhemispheric hippocampal connectivity was negatively correlated across participants with episodic memory performance. The same group also reported that longitudinal decline in memory performance was associated with longitudinal increases in connectivity within the posterior medial temporal lobe (Salami et al., 2014). Increased resting state functional connectivity among core recollection regions has also been reported for carriers of the e4 APOE allele, a risk factor for Alzheimer’s Disease (Westlye et al., 2011). However, age-related decreases in resting state functional connectivity among core recollection regions have also been reported (Toussaint et al., 2014), and there is evidence to suggest that age-related differences in connectivity are at least partially dependent on cognitive state. For example, Geerlings et al.

(2015) reported that such differences varied according to whether connectivity was assessed at rest, during movie watching, or while performing a sensorimotor task. Future studies will be necessary to better explain the complex nature through which age influences patterns of resting state functional connectivity (see Geerligs et al., 2017, for an extensive treatment of relevant methodological issues). In addition, the integration of resting-state functional connectivity data with task-based data will likely prove necessary to fully account for how age-related changes in brain function and organization relate to changes in cognition (see Campbell and Schacter, 2016, and Geerligs and Tsvetanov, 2016, for discussion).

As just noted, an alternative to the approach of assessing resting state functional connectivity is to examine how connectivity varies as a function of task performance. A number of studies have examined age effects on connectivity during performance of a memory task (Leshikar et al., 2010; Tsukiura et al., 2011). However, none to our knowledge have examined how aging relates to changes in connectivity as a function of memory *success*, in a manner analogous to how changes in mean fMRI BOLD signal are commonly assessed. One approach for examining event-related changes in connectivity is referred to as psychophysiological interactions (PPI) analysis (Friston et al., 1997; for a recent review of the methods, see Smith et al., 2016). PPI analysis identifies task-related changes in connectivity between a ‘seed region’ and the rest of the brain after partialling out variance due to task-related differences in signal amplitude and task-unrelated or “background” connectivity. We recently used PPI to examine how functional connectivity differed on trials associated with successful versus unsuccessful recollection in young healthy adults (King et al., 2015). We found evidence for recollection-related enhancement of connectivity between core recollection regions and both other members of the core network and regions extrinsic to the network, including members of the ‘multiple demand network’ (pre-supplementary motor area, and lateral frontal and dorsal parietal cortex; Duncan, 2010). We also reported that the magnitude of recollection-related increases in connectivity between core recollection regions and much of the rest of the brain were correlated, across participants, with recollection performance.

These observations led us to the conjecture that the group-level, recollection-related enhancement of connectivity and the changes in connectivity that correlated across participants with recollection accuracy might be functionally distinct. The group-level increases in connectivity could reflect enhanced interactions between core recollection and other regions, such as those comprising the multiple demand network, during successful relative to unsuccessful recollection (Duncan, 2010; Westphal et al., 2017). In contrast, we hypothesized that the changes in connectivity that co-varied with recollection performance reflect a ‘driving’ input from one or more of the ascending neuromodulatory systems that can transiently influence neural synchrony throughout much of the brain (Lee and Dan, 2012; Schölvinck et al., 2010). Recent studies have demonstrated that phasic release of neuromodulators, on the scale of seconds, can modulate specific cognitive operations (Clayton et al., 2004; Edeline, 2012; Parikh et al., 2007; Usher et al., 1999). The ascending neuromodulatory systems send diffuse projections to much of the forebrain, and hence represent a plausible candidate for the source of the widely distributed synchronization of activity we found to be associated with recollection performance. Indeed, measures of neuromodulatory function have been associated with individual differences in functional

connectivity (Klostermann et al., 2012; Rieckmann et al., 2011). In addition, pharmacological manipulation of catecholamine availability has been reported to modulate resting state connectivity (van den Brink et al., 2016). Researchers have also demonstrated that the degree to which the brain is in an ‘integrated’ state, that is, when distinct brain regions are highly interconnected, is related to better performance on a working memory task (Shine et al., 2016). Furthermore, level of integration co-varied with pupil dilation, held to be a measure of noradrenergically-mediated arousal (e.g., Ang et al., 2015; Aston-Jones et al., 1994; Aston-Jones and Cohen, 2005; Joshi et al., 2016; Murphy et al., 2011; Usher et al., 1999). This finding suggests that fluctuations in whole-brain connectivity may be driven by dynamic changes in the ascending neuromodulatory input to the cortex. Here we hypothesize that the relative strength of the neuromodulatory input co-varies with the magnitude of the recollection ‘memory signal,’ and hence, co-varies with estimates of recollection performance. That being said, we note that while our previous findings of a relationship between accuracy and connectivity change can be explained in terms of neuromodulatory processes, other factors could also account for these results, such as individual differences in motivation, amount of attention paid to the retrieval cues, or arousal level. Like our previous study, the present study was not designed to directly test the neuromodulatory hypothesis, but instead was simply motivated by it.

In light of the foregoing hypothesis, we were particularly interested in examining how recollection-related changes in connectivity and their relationship with performance differed across different age groups. Positron emission tomography (PET) studies have demonstrated an age-related decline in several neuromodulatory systems (Erixon-Lindroth et al., 2005; Suhara et al., 1991; Wong et al., 1984). The bulk of research on the relationship between aging and neuromodulatory function has however focused on the dopamine (DA) system (for reviews see Bäckman et al., 2010, 2006). It appears that several neuronal mechanisms contribute to the general down regulation of the DA system with advancing age. For instance, age is associated with a reduction in dopamine receptor (i.e., D1 and D2) availability (Cortés et al., 1989; Severson et al., 1982; Suhara et al., 1991; Y. Wang et al., 1998), and in the density of the dopamine transporter (DAT), a protein that regulates DA reuptake (Allard and Marcusson, 1989; Erixon-Lindroth et al., 2005; van Dyck et al., 1995). There is evidence that this age-related decline in dopaminergic function is related to both altered cortical connectivity in aging (Klostermann et al., 2012; Rieckmann et al., 2011) and to age-related cognitive decline (Erixon-Lindroth et al., 2005 see also Bäckman et al., 2010 for review). For instance, one study reported that age-related reduction in dopamine synthesis was related to both reduced frontal-caudate connectivity and decreased performance on a working memory task (Klostermann et al., 2012). In addition, Nyberg and colleagues (2016) reported that connectivity between ventral caudate and medial temporal lobe in older adults mediated the relationship between caudate dopamine receptor availability and episodic memory performance (Nyberg et al., 2016).

Given the interdependency between aging, neuromodulatory function, functional connectivity, and cognitive performance, here we investigated how recollection-related changes in connectivity and their relationship with performance varied across age groups. We conducted an additional set of analyses on data from a large-scale fMRI study that employed samples of young, middle-aged, and older adults who were scanned during an

associative recognition task (results of univariate analyses of these data are reported in de Chastelaine et al., 2016a; connectivity analyses from the young group only are reported in King et al., 2015). We used PPI analysis to identify brain regions that exhibited recollection-related increases in functional connectivity. We tested for age-group differences in both the magnitude of recollection-related increases in connectivity and in the relationship between recollection-related connectivity and recollection performance. We also extended our previous PPI analyses to examine ‘whole-brain’ recollection-related changes in connectivity between a large number of seed regions evenly distributed throughout the brain (Gerchen et al., 2014; Gerchen and Kirsch, 2017). Given the paucity of prior findings, we had no prediction as to the direction of any age-related differences in recollection-related changes in connectivity. In light of the evidence for age-related weakening of neuromodulatory input to the forebrain (see above), however, we predicted that the relationship between recollection-related connectivity enhancement and recollection performance would likewise be weaker with increasing age.

Methods

The present study has been described in prior publications (de Chastelaine et al., 2016a, 2017; King et al., 2015). The principal findings reported below, pertaining to the comparisons across age groups of retrieval-related functional connectivity parameters, have not been previously reported. Further details of the methods and the participant samples can be found in the above-cited publications.

Participants

Participants were 36 young adults (17 female) aged 18–29 yrs ($M = 22.2$ yrs, $SD = 3.0$ yrs), 36 middle-aged adults (19 female) aged 43–55 yrs ($M = 49.4$ yrs, $SD = 3.4$ yrs), and 64 older adults (35 female) aged 63–76 yrs ($M = 68.4$ yrs, $SD = 3.6$ yrs). Data from an additional 12 participants were excluded from analysis due to inadequate behavioral performance at either study or test (2 young, 1 middle-aged, and 2 older), an insufficient number of trials in one or more of the conditions of interest (<10 trials; 3 young, 1 older), technical problems during scanning (1 middle-aged), or abnormalities in their anatomical scan (2 older). When data were excluded due to insufficient trials within a condition, this was always because of too few associative misses (i.e., intact items erroneously called rearranged). Participants were healthy, right-handed, had normal or corrected-to-normal vision, had learned English prior to the age of five, had no history of cardiovascular, neurological, or psychiatric disease, were not taking central nervous system-active medication, and were either non-hypertensive or were receiving medication to control their hypertension (see de Chastelaine et al., 2016a for a full description of inclusion and exclusion criteria along with neuropsychological test scores of the included participants). Participants were recruited from the University of Texas at Dallas and surrounding communities. All participants gave informed consent according to the procedures approved by the UT Dallas and UT Southwestern Institutional Review Boards and were compensated with \$30 per hour for their participation. The data collected from the young age group were the same data that were analyzed in our previous connectivity study and presented as Experiment 2 (King et al., 2015). Although the results of the neuroimaging analyses for this

age group are highly consistent across the prior and present studies, there are some subtle differences, which are due to the different method by which seed regions were defined (see fMRI Data Acquisition and Analysis - Recollection-related changes in functional connectivity with core recollection regions).

Materials and Apparatus

Experimental materials comprised 320 semantically unrelated, visually presented word pairs selected from the word association norms list compiled by Nelson et al., 2004. Words were concrete nouns denoting common objects that ranged from 3 to 9 letters in length. The words were randomly divided into 4 lists of 80 pairs. For each set of yoked participants (1 young, 1 middle-aged, and 1 or 2 older participants), 2 of these lists were assigned to the 'intact' condition, while the remaining two lists were assigned to either the 'rearranged' or the 'new' condition. During the study phase, all of the word pairs except for those assigned to the new condition ($n = 240$), were presented in a pseudo-random order. At test, participants made judgments about all 320 word pairs: 160 of the test pairs had been presented at study (intact pairs), 80 of the pairs were items that had been presented at study but were re-paired for the test phase (rearranged pairs), and 80 were unstudied pairs (new pairs). The sequence of events in the study and test lists were pseudo-randomly ordered such that the same type of event did not occur more than 3 times in succession. All words were presented in white capital letters in Helvetica 30-point font against a black background. At both study and test, word pairs were presented just above and below a central fixation cross, so that they appeared at an approximate vertical visual angle of 1.8 degrees and an approximate horizontal visual angle of 5.1 degrees at the virtual 56.6cm viewing distance. Items were presented onto a projector situated at the head of the scanner, made visible to participants via a mirror mounted onto the head coil. The items were presented and responses recorded using Cogent software (<http://www.vislab.ucl.ac.uk/cogent.php>).

Procedure

Prior to scanning, participants were given a practice session with abbreviated study and test lists. Participants were then situated in the scanner for the study phase of the experiment, which was divided into two consecutive blocks (see Figure 1 for schematic representation of task design). Each study trial began with a red fixation cross that was presented at the center of the screen for 0.5s. Words were then presented simultaneously above and below a white central fixation cross for 2s, followed by a 1s presentation of a white fixation cross. The task was to judge which of the two objects denoted by the words was more likely to 'fit' into the other and to respond with a key press. Study trials were randomly intermixed with 80 null trials, which involved the presentation of a white fixation cross against a black background for 3.5s (matching the duration of task trials). A 30s rest period occurred halfway through each of the study and test blocks. After the study session, participants exited the scanner for a 15 minute rest period.

Following the rest period, participants re-entered the scanner for the second phase of the experiment, which involved an associative recognition test. This phase was divided into three consecutive blocks. Each test trial began with a red warning fixation cross presented for 0.5s. Word pairs were then presented above and below a white fixation cross for 2s,

followed by a 2s presentation of a white fixation cross. Participants were required to make one of three key press responses based on their memory for the current test pair. They were asked to respond 'intact' if they recognized both of the words and specifically remembered the two items being presented together at study. A 'rearranged' response indicated that both words were recognized from the study phase, but that they were not remembered as having been presented together. A 'new' response indicated that one or both words were not recognized from study. Responses were recorded from 300ms after the cue onset, up until the appearance of the retrieval cue for the next trial. Test trials were randomly intermixed with 106 null trials where a white fixation cross was presented on the screen for 4.5s. A T1-weighted anatomical scan was acquired at the end of the second scan session.

fMRI Data Acquisition and Analysis

Data acquisition and preprocessing—Functional and anatomical images were acquired with a 3T Philips Achieva MRI scanner (Philips Medical Systems, Andover, MA, USA) equipped with a 32 channel receiver head coil. Functional images were acquired using a T2*-weighted, blood oxygen level-dependent echoplanar (EPI) sequence (SENSE factor 2, flip angle 70°, 80 × 78 matrix, FOV = 24 cm, TR = 2000 ms, TE = 30 ms). EPI volumes consisted of 33 slices (1mm inter-slice gap) with a voxel size of 3×3×3 mm. Slices were acquired in ascending order, oriented parallel to the AC-PC line. T1-weighted anatomical images were acquired with a magnetization-prepared rapid gradient echo (MPRAGE) pulse sequence (FOV = 240×240, 1×1×1mm isotropic voxels, 160 slices, sagittal acquisition).

MRI data were preprocessed in SPM8 (Wellcome Department of Cognitive Neurology, London, UK). Functional scans were realigned to the mean EPI image, subjected to slice timing correction, and normalized using a sample-specific template. The template was created by normalizing the mean volume of each participant's functional time series with reference to a standard EPI template based on the Montreal Neurological Institute (MNI) reference brain (Cocosco et al., 1997). The normalized images were averaged within each age group individually, and then the resulting mean images were averaged to create a template that was weighted equally with respect to the three different age groups. Normalized images were resampled into 3mm isotropic voxels and smoothed using an 8mm full-width half maximum Gaussian kernel. Anatomical images were normalized using a similar procedure, except that the initial normalization step was based on the standard MNI T1-weighted template. Framewise displacement (FD) was calculated as the sum of the absolute values of the differentials of the six realignment parameters (Power et al., 2012), which provides a single index of motion corresponding to each scan. FD values were averaged across all scans to provide an estimate of total motion for each participant. Mean FD was used as an across participant covariate in seed-based and whole-brain connectivity analyses (see Results – Control Analyses).

Recollection-related changes in BOLD signal amplitude—Statistical Parametric Mapping (as implemented in SPM8; Wellcome Department of Cognitive Neurology, London, UK) based on a General Linear Model (GLM) was used to analyze the functional data acquired during the test phase (results from encoding phase data are reported elsewhere - de Chastelaine et al., 2016b, 2015). As in de Chastelaine et al. (2016a), for each

participant, several events of interest were modeled which included, critically, intact test trials that were correctly identified as ‘intact’ (II) and intact trials mistakenly endorsed as ‘rearranged’ (IR). These trial types were considered to reflect successful associative recollection, and item recognition in the absence of recollection, respectively (cf. de Chastelaine et al., 2016a; King et al., 2015; Mickes et al., 2010). Additional events that were modeled included intact trials mistakenly called new (IN), rearranged trials correctly identified as rearranged (RR), new trials correctly identified as new (NN), and an additional event representing all other trial types, as well as trials that involved either no response or multiple responses. The neural response on each trial was modeled as a delta function corresponding to the onset of each trial. Delta functions were convolved with a canonical hemodynamic response function (HRF) to model the predicted BOLD response. Other covariates of no interest entered into the first-level models included six parameters reflecting the motion-related variance in the data (three for rigid-body translation and three for rotation), as well as regressors representing each of the separate scan sessions. An autoregressive AR(1) model was employed during parameter estimation to correct for time-series correlations in the data.

Following estimation of the first-level models, contrast images were constructed for each participant that represented the estimated difference in BOLD activity associated with successful relative to unsuccessful recollection trials (II>IR). The resulting contrast images were then entered into a single, second-level analysis of variance (ANOVA) model, treating participants as the random variable and age group (young, middle, old) as the between-subjects factor. To identify brain regions that showed reliable recollection success effects across age groups, we inclusively masked the main effect, thresholded at a family-wise error (FWE) corrected height threshold of $p < .05$, with the simple effect from each age group (inclusive mask threshold of $p < .01$). Additionally, to eliminate small and potentially unreliable clusters, we imposed a cluster extent threshold of $k=20$.

Recollection-related changes in functional connectivity with core recollection regions—Psychophysiological Interactions analysis (PPI; Friston et al., 1997), implemented in SPM8, was used to identify recollection-related changes in connectivity. PPI identifies task-related changes in functional connectivity between a chosen seed region and the rest of the brain after partialling out the main effect of event-related changes in activity and task-unrelated connectivity. PPI analyses were conducted for five different seed regions, each belonging to the ‘core recollection network’ (Rugg and Vilberg, 2013). Seeds were selected based on the results of the analysis of recollection-related changes in BOLD activity described above and previous research implicating each of these regions in successful recollection (Kim, 2010; Rugg and Vilberg, 2013; Spaniol et al., 2009). The regions were left angular gyrus (AnG), medial prefrontal cortex (mPFC), left hippocampus (hipp), left middle temporal gyrus (MTG), and posterior cingulate cortex (PCC). For each seed, regression models were created at the individual participant level that included three regressors of interest: a physiological regressor, a psychological (task) regressor, and a psychophysiological interaction regressor. To create physiological regressors, we extracted a representative time-course from each seed region in a participant-specific manner. To do so, we created functionally defined masks for each seed that were based on the results of the

group-level univariate recollection success contrast. Masks were defined as 10mm radius spheres centered on the peak of the main effect of recollection success (across age groups). The hippocampal mask was additionally constrained by an anatomical mask, defined according to the SPM anatomy toolbox (Eickhoff et al., 2005), to ensure that voxels within a 10mm radius sphere of the peak that were outside of the hippocampus were excluded from the analysis, which was not a concern for any of the other seeds (group-level peak coordinates of the center of the masks were as follows - AnG: -51, -73, 28; mPFC: -6 53 1; hipp: -27, -19, -20; MTG: -63, -49, -5; PCC: -3 -46 31). We determined the peak of activity within each of the masks for each individual participant, drew a 3mm radius sphere around the peak voxel, and extracted a representative time-course (first eigenvariate) of the included voxels, which served as the physiological regressor. Psychological regressors were constructed by creating a vector that coded successful recollection trials as 1, unsuccessful recollection trials as -1, and all other trials as 0. This task vector was then convolved with the canonical HRF in SPM8 to create the psychological regressor included in the first-level models. To create the PPI regressor of interest, the physiological regressor was deconvolved with the HRF, multiplied by the unconvolved task regressor, and then reconvolved. Additional nuisance covariates included the same motion and session parameters that were included in the first-level models in the analysis of recollection-related changes in BOLD signal.

Following estimation of the first-level models, parameter estimates of the PPI regressor were brought to the second-level where separate group-level analyses were conducted for each seed. First level parameter estimates were entered into a full factorial design, treating age group as a categorical factor, to examine recollection-related changes in connectivity with each seed. To identify regions that showed differences in recollection-related connectivity across age groups we examined the main effect of age group ($p < .05$, FWE-corrected, 20 voxel extent threshold). To determine where recollection-related increases in connectivity occurred consistently across all three age groups, we exclusively masked the main effect of connectivity change (thresholded at $p < .05$, FWE-corrected, voxel extent = 20) with the main effect of age group (mask threshold of $p < .05$).

Relationship between pR and recollection-related increase in connectivity with core recollection regions—Given our previous findings in young adults (King et al., 2015) that recollection performance was correlated with recollection-related increases in connectivity between core recollection regions and regions distributed throughout much of the brain, we tested whether a similar relationship existed in middle-aged and older adults. Recollection accuracy, or the probability of recollection (pR), was indexed as the difference between the proportion of intact test pairs correctly endorsed as intact (associative hits) and the proportion of rearranged test pairs incorrectly judged as intact (associative false alarms). We followed our previous approach of parcellating the brain into 90 regions based on the AAL atlas (Tzourio-Mazoyer et al., 2002; excluding cerebellum). For each participant, we extracted pair-wise estimates of connectivity change between the five core recollection seed regions and the 90 AAL target regions. We then created separate correlation matrices for each age group, where the 90 target regions were represented by different rows in the matrix, and the five core recollection seed regions were represented by different columns of the

matrix. Thus, values within each cell of the matrix represented not the magnitude of recollection-related change in connectivity, but instead, the across participants correlation between recollection-related change in connectivity and performance (cf. King et al., 2015).

Two separate permutation analyses tested a) whether the average correlation, averaged across target regions separately for each age group and seed region, differed significantly from chance; and b) for each seed region, whether the average correlation differed significantly across age groups. The first permutation analyses were conducted separately for each age group and seed region. We randomly scrambled pR values 1,000 times, created new correlation matrices, and then determined the proportion of iterations that yielded average correlation values that exceeded those of the real data. For the second set of permutation analyses, pR values were left paired with their appropriate beta values, and data points were randomly relabeled as either 'young', 'middle-aged,' or 'old.' We then recalculated the average correlation between pR and connectivity for each pseudo-age group, and compared group pair-wise differences between means (e.g., young-middle, young-old, middle-old) and determined the proportion of iterations that resulted in larger group differences than the real data. Because we had unequal sample sizes, we randomly selected 100 subsets of 36 older participants, and for each subset ran 10 iterations of the randomization procedure resulting in a total of 1,000 random iterations that comprised the null distribution.

Whole-brain recollection-related changes in functional connectivity—Given our previous findings that regions outside of the core recollection network exhibited recollection-related increases in connectivity, we extended our seed-based approach to examine recollection-related changes in connectivity between regions distributed throughout the whole brain (Gerchen et al., 2014). To do this, we first parcellated the brain into 271 regions. The parcellation was based mainly on the work of Power and colleagues (2011), who identified 264 functionally segregated brain regions based on a combination of patterns of resting state functional connectivity and task-based activation data. In addition to the 264 regions defined by Power et al. (2011), we included two additional seeds in left and right hippocampus (L: -24 -10 -23; R: 24 -7 -23). These seeds, which were derived from an independent data set (Wang et al., 2016), were included because of the important role of the hippocampus in memory processing and the poor coverage of the region in the Power et al. 2011 partition scheme. We also included the five core recollection seed regions used in the above-described analysis (AnG, mPFC, hipp, MTG, and PCC) resulting in a total of 271 nodes. Regions of interest (ROIs) were defined as 3mm spheres centered on the coordinates defined by Power et al. or our univariate analysis. We conducted 271 separate PPI analyses, iteratively treating each ROI as a seed. For every ROI, parameter estimates of recollection-related change in connectivity with all other ROIs were extracted. This allowed us to create whole-brain seed-target connectivity matrices for each participant. Because PPI does not provide information about directionality of connectivity, we followed Godwin et al., 2015 and rendered the matrices symmetrical by averaging the parameter estimates for each seed-target pair across the diagonal (i.e., $(X_{ij_asymmetrical} + X_{ji_asymmetrical})/2 = X_{ij_symmetrical} = X_{ji_symmetrical}$).

We then tested how whole-brain recollection-related changes in connectivity varied according to age group and recollection performance (as indexed by pR). To do so, we ran two different regression models on every seed-target pair. Each of the regression models included four covariates of no interest: gender, years of education, within-scanner head motion, and mean cortical thickness (see results for description of how these variables differed across age groups). In addition to these covariates, the first set of models predicted the magnitude of recollection-related changes in connectivity from age group (Model(1): $y_{\text{connectivity}} = \beta_0 + \beta_1 \chi_{\text{age}} + \beta[\text{covariates of no interest}] + e$). As we did not sample continuously across the adult lifespan, age group was treated as a categorical variable for all regression analyses. We tested the significance of the beta coefficient associated with the age group variable (β_1) and conducted post-hoc analyses on seed-target pairs that exhibited a significant main effect at $p < .05$, uncorrected. The second set of models predicted the magnitude of recollection-related connectivity change across individuals from age group, pR, and the age by pR interaction (Model(2): $y_{\text{connectivity}} = \beta_0 + \beta_1 \chi_{\text{age}} + \beta_2 \chi_{\text{pR}} + \beta_3 \chi_{\text{age} \times \text{pR}} + \beta[\text{covariates of no interest}] + e$). Here, we were interested in seed-target pairs that showed a significant age group by pR interaction. Accordingly, we examined the significance of the beta coefficient associated with this term (β_3) and ran post-hoc analyses on the seed-target pairs that exhibited a significant age group by performance interaction. With this model, we also re-examined the main effects of age group (β_1) and performance (β_2) and ran post-hoc analyses on seed-target pairs that exhibited significant effects for these predictor variables.

Because the significance of effects was tested against an alpha level of $p < .05$, without adjusting for multiple comparisons, many of the seed-target pairs that exhibited a significant main effect or interaction in the whole brain analyses described above likely reflected false positives. Our aim was not, however, to make inferences about effects in specific seed-target pairs. Instead, we were interested in whether the *overall patterns* of the results driving effects in regions that showed significant effects were different than what would be expected by chance. To examine this question, we ran post hoc analyses on each cell of the seed-target connectivity matrix that exhibited a significant effect. We then categorized the effects in each of these cells as “positive” if the effect reflected increased connectivity with increasing age (or an increase in the relationship between connectivity and pR with increased age for Model 2), “negative” if the opposite pattern emerged, with greater connectivity (or a stronger relationship between connectivity and pR for Model 2) in the younger age groups, and “other” if the effect was due to a difference between the middle-aged group relative to the other two age groups. If the observed effects solely reflected false positives (i.e., were due to chance), then we should expect a roughly equal proportion of positive and negative significant effects. Accordingly, we tested the probability of obtaining the observed proportions of positive and negative effects by chance with binomial tests, allowing us to determine whether, collectively, these effects were more frequently positive or negative than would be expected by chance alone.

Results

Covariates of no Interest

Semi-automated analysis (<http://surfer.nmr.mgh.harvard.edu/>) of T1-weighted structural images revealed that mean cortical thickness differed significantly across the age groups ($F(2,133) = 68.19, p < .001$). Thickness was greater in the young group ($M = 2.53$ mm, $SD = .084$) than the middle aged ($M = 2.39$ mm, $SD = .085$; $t(70) = 2.30, p < .001$) and older group ($M = 2.30$ mm, $SD = .107$; $t(98) = 11.67, p < .001$), and was also greater in the middle aged than the older group ($t(98) = 4.63, p < .001$). In light of evidence that across-group differences in head motion can result in spurious connectivity differences (Power et al., 2012), we also examined whether within-scanner motion differed across age groups. We computed an average framewise displacement (FD) score for each participant by averaging FD values across all scans (Power et al., 2012; see Methods). There was a significant effect of age group on FD ($F(1,134) = 35.07, p < .001$). Post hoc analyses revealed that head motion increased monotonically with age group; older participants ($M = 0.345$ mm, $SD = 0.145$) had higher FD than middle-aged ($M = 0.278$ mm, $SD = 0.108$; $t(98) = 2.747, p = 0.007$) and young adults ($M = 0.201$ mm, $SD = 0.061$; $t(98) = 5.864, p < .001$), and middle-aged adults had higher FD than young adults ($t(70) = 2.755, p = 0.007$). In addition, self-reported years of education also differed across age groups ($F(2,133) = 5.30, p = .006$). Older participants ($M = 17.14$, $SD = 2.30$) reported greater years of education than the young adults ($M = 15.54$, $SD = 2.40$; $t(98) = 3.19, p = .002$), but years of education did not differ significantly for the middle-aged group ($M = 16.25$, $SD = 2.60$) relative to either of the other two age groups ($ps > .1$). Based on these findings, cortical thickness, FD, years of education, and gender were included as covariates of no interest in each of the regression analyses described below. Although the proportion of males and females did not differ across age groups, we included gender as a covariate of no interest to ensure that results were not driven disproportionately by only one gender.

Behavioral Results

Only a brief description of associative recognition performance is presented here. A full description and discussion of the age-group differences in memory performance can be found in de Chastelaine et al. (2016a, 2017). A one-way analysis of variance (ANOVA) tested for differences in recollection accuracy (indexed by pR, see Methods) across age groups. The results revealed a significant effect of age group on recollection accuracy ($F(2,135) = 12.80, p < .001$). Follow-up pair-wise contrasts (t tests, equal variances not assumed) indicated that young adults ($M = .48$, $SD = .19$) were more accurate than middle-aged ($M = .39$, $SD = .14$; $t(64) = 2.25, p < .05$) and older ($M = .31$, $SD = .15$; $t(59) = 4.50, p < .001$) adults, and that middle-aged adults out-performed older adults ($t(76) = 2.60, p < .01$). There was no age-related difference in the average response time to test trials ($p > .05$).

BOLD signal changes associated with successful recollection

As described in the Methods section, to identify regions demonstrating greater activity during successful relative to unsuccessful recollection across age groups we inclusively masked the main effect of recollection success (main effect threshold, $p < .05$, FWE-corrected, voxel extent threshold = 20) with the simple effect (that is, the group-wise

recollection effect) from each age group (mask threshold, $p < .01$). This procedure identified a set of brain regions that correspond closely to regions that have previously been reported to exhibit such effects (Kim, 2010; Rugg and Vilberg, 2013; Spaniol et al., 2009), including left angular gyrus, left inferior/middle temporal gyrus, mPFC, PCC, bilateral hippocampus, and striatum (Figure 3). A more detailed description of these recollection-related changes in BOLD signal and their relationship with age can be found in de Chastelaine et al., 2016a.

Recollection-related changes in connectivity with core recollection regions

To determine whether the magnitude of recollection-related changes in connectivity with core recollection regions varied across age groups, we entered first level parameter estimates of the PPI effect into separate second-level analyses for each seed and tested for main effects of age group throughout the whole brain. For each of these analyses, we failed to identify any brain regions that demonstrated a significant main effect of age group on the magnitude of recollection-related change in connectivity with core recollection regions. This remained the case when our pre-experimentally chosen threshold was reduced to $p < .001$, uncorrected.

As described in Methods, to identify regions that showed a main effect of recollection-related change in connectivity with core recollection regions across all age groups, we exclusively masked the main PPI effect (across age groups) with the simple effect from each age group. The results of these masking procedures are depicted for each seed region in Figure 4. Regions exhibiting age-invariant recollection-related changes in connectivity with each of the five seed regions were identified both in other core recollection regions, such as the AnG, MTG, and PCC, and regions extrinsic to the core recollection network, including dorsolateral prefrontal cortex (DLPFC), the intraparietal sulcus (IPS), dorsal mPFC/supplementary motor area (SMA), extrastriate visual cortex, and the thalamus. These findings closely resemble those reported in our prior study (King et al., 2015), where the present data for the young sample were combined with data from two other independent studies of young individuals.

Relationship between pR and recollection-related increase in connectivity with core recollection regions

Given our previous findings in young adults that recollection performance is correlated with recollection-related changes in connectivity between core recollection regions and regions distributed throughout much of the brain, we tested whether similar relationships existed in middle-aged and older adults (see Methods). The correlation matrices are depicted in Figure 5. Permutation analyses tested a) for each age group and seed region whether the average correlation between connectivity change and performance averaged across all target regions differed significantly from chance, and b) for each seed region, whether the average correlation differed significantly across age groups. Average correlations were tested against an alpha level of $p < .05$, corrected for multiple comparisons ($c=5$ comparisons, adjusted $\alpha=.01$). We repeated these same analyses using the Power et al. (2011) parcellation scheme to separate the brain into 271 different target regions. The results are presented for both parcellation schemes below, referring to the AAL parcellation as the ‘anatomical’ parcellation and the Power et al. parcellation as the ‘functional’ parcellation.

As is evident from Figure 5, for young adults the average correlation between connectivity change and pR was significantly greater than zero in all seed regions and for both brain parcellation schemes. However, for the middle-aged group, average correlations significantly exceeded zero only in the hippocampus and MTG seeds for the anatomical parcellation and in the mPFC for the functional parcellation. In older participants, the average correlation was greater than zero in the hippocampus and mPFC seeds for both parcellations, and the MTG seed for the functional parcellation. The permutation analyses that tested for age group differences in average correlations revealed that, for the anatomical parcellation, average correlations for the young age group were significantly greater than for both the middle-aged and older groups in all regions except for the hippocampus, where there were no age group differences. In addition, correlations were significantly greater for the middle-aged than the older age group in the MTG seed. A comparable pattern of results was found for the functional parcellation: the young age group showed stronger correlations than the middle-aged group in all five seeds, and stronger correlations than the older age group in all regions with the exception of the mPFC. There were no differences in mean correlations between the middle-aged and older age groups. Overall, these results suggest that in comparison to young adults, the relationship between connectivity change and performance was weaker and less reliable in older and middle-aged adults, particularly in AnG and PCC seeds.

Recollection-related changes in whole-brain connectivity

In addition to the seed-based PPI analyses described above, we examined whether there was evidence of age group differences in recollection-related changes in connectivity between ROIs distributed throughout the entire brain. Whole-brain, seed-target connectivity matrices were created for each participant (see Methods). Recollection-related change in connectivity matrices averaged across participants separately for each age group are depicted in Figure 6, where it can be seen that there is a seeming age-related decline in connectivity change. To examine how recollection-related change in connectivity varied as a function of age group and performance, for every seed-target pair we ran two separate regression models and then created whole-brain seed-target regression matrices based on the results of these analyses. The model used for the first set of regression analyses predicted recollection-related change in connectivity from age-group (i.e., tested for a main effect of age group on connectivity; Model(1): $y_{\text{connectivity}} = \beta_0 + \beta_1 \chi_{\text{age}} + \beta[\text{covariates}] + \epsilon$). We then tested the significance of the parameter estimate associated with the age group variable (β_1). To test whether there were age group differences in the relationship between pR and connectivity, the second set of models predicted connectivity from age group, recollection performance (pR) and the age by pR interaction term (Model(2): $y_{\text{connectivity}} = \beta_0 + \beta_1 \chi_{\text{age}} + \beta_2 \chi_{\text{pR}} + \beta_3 \chi_{\text{age} \times \text{pR}} + \beta[\text{covariates}] + \epsilon$); we then examined the significance of the parameter estimates associated with each of the terms of interest (age group (β_1), performance (β_2), and the age by performance interaction (β_3)). The effects of performance and age group reported below for this regression model were essentially unchanged when the interaction term was omitted from the model, allaying concerns that the effects were underestimated or otherwise biased because of collinearity between the regressors modeling age group and performance and the interaction regressor).

Relationship between age group and recollection-related change in

connectivity—For the first set of models, which predicted recollection-related change in connectivity from age group, there was a significant relationship among these variables for a substantial number of seed-target pairs (2,062 pairs, or 2.81%, of all pairs). See Figures 7a and 7b for the whole-brain matrices representing the F statistics and p-values associated with the main effect of age for each seed-target pair. For every seed-target pair that exhibited a main effect of age group, we ran post hoc analyses using multiple independent samples t tests to determine the direction of the effect. As was described in the Methods section, effects were categorized as ‘positive’ if recollection-related change in connectivity was greater in older groups (e.g., if effect was due to greater connectivity for older than young, older than middle, or middle than young), ‘negative’ if the recollection-related change in connectivity was greater for younger groups (e.g., effect was due to greater connectivity for young than old, young than middle, or middle than old), and as ‘other’ if the effect resulted from a combination of positive and negative effects (e.g., if the middle-aged group differed significantly from both the young and older age groups).

The proportions of significant effects categorized as positive, negative and other are shown in Figure 7c. As is evident from the figure, the vast majority of significant main effects were categorized as negative, indicating a decrease in the magnitude of recollection-related change in connectivity with increasing age (2,002 or 97.09% of seed-target pairs exhibiting a main effect of age group were labeled as negative). In contrast, only 52 seed-target pairs, or 2.52% of the pairs that showed a main effect were driven by positive effects, with greater connectivity in the older relative to the younger age groups. The remaining seed-target pairs that exhibited a significant main effect of age group were labeled as other (9 seed-target pairs, 0.39%). Given that there is an equal likelihood of detecting positive and negative effects by chance, we used a binomial test to test the hypothesis that the proportion of positive effects among all directional effects (positive and negative effects, excluding those categorized as other; 2,002/2,054 or 97.47% of the directional effects) differed significantly from chance (50%). The results indicated that the observed proportion of positive effects was significantly greater than that expected by chance ($p < 10^{-10}$). To illustrate these same data in a different manner, we took the within-subjects average parameter estimate of connectivity-change averaged across all seed-target pairs that exhibited a main effect of age group, giving us a single value of connectivity change per participant. An ANCOVA tested for a main effect of age group on average connectivity change, controlling for the same four covariates of no interest as employed in the original regression model (Figure 7d). Importantly, note that although these pairs of regions were selected because they exhibited a main effect of age group, the selection process was non-directional (i.e., parameter estimates were extracted from pairs that exhibited both positive and negative effects), allowing us to test for evidence against the null hypothesis of no main effect of age group on the average recollection-related change in connectivity averaged across all pairs. Contrary to the null hypothesis, there was a significant main effect of age group ($F(2,129) = 5.10, p=.007$). Post hoc analyses revealed that both the young and middle-aged group showed overall greater average connectivity change within these regions than the older age group ($t(94)=3.10, p=.002$ and $t(94)=2.30, p=.023$, respectively), but that the middle-aged group did not differ significantly from the young age group ($p=.11$).

Age by pR interaction on recollection-related change in connectivity—To test whether the relationship between recollection performance and recollection-related change in connectivity between pairs of regions differed as a function of age group, we ran separate regression models on each seed-target pair, this time predicting the magnitude of recollection-related change in connectivity from age group, recollection performance (indexed by pR), and the age by pR interaction. We examined the beta coefficient for the age by pR interaction term to determine the extent to which the relationship between recollection-related change in connectivity and pR varied across the different age groups. Whole-brain matrices representing the F statistic and p -value associated with the interaction term for each seed target pair are shown in Figures 8a and 8b. We found evidence for a significant age group by pR interaction in 2,251, or roughly 3.07% of the whole-brain seed-target pairs. Post-hoc analyses were conducted to characterize the pattern of results driving the interactions in these pairs of regions. Interactions were classified as ‘positive’ if the relationship between pR and connectivity increased with age (e.g., there was a more positive relationship between pR and connectivity for the older than young, older than middle, or middle than older age groups), ‘negative’ if this relationship decreased with age (e.g., there was a more positive correlation between pR and connectivity for the young than older, young than middle, or middle than older age group), and ‘other’ if the interaction reflected a combination of positive and negative effects (e.g., a difference in the relationship between pR and connectivity differed for the middle-aged relative to both the young and older age groups).

The proportions of significant interactions categorized as positive, negative, and other are depicted in Figure 8c. The great majority of interaction effects were categorized as negative, indicating a more positive correlation between connectivity change and pR for the younger relative to the older age groups (2,103 seed-target pairs, or 93.43% of the pairs where there was a significant interaction). Only 30 seed-target pairs, or 1.33% of the significant interactions were driven by the opposite effect, with a more positive correlation between pR and connectivity associated with the older age groups. The remaining interaction effects (118, or 5.24% of significant interactions) were categorized as other, as they were driven by a difference in the correlation between pR and connectivity for the middle-aged compared to both young and older age groups. We tested whether the ratio of positive to negative effects differed from what would be expected from chance using a binomial test (excluding seed-target pairs where the interaction was categorized as ‘other’). The results indicated that the observed proportion of negative effects (2,103/2,133 or 98.59% of directional effects) was significantly greater than chance (50%; $p < 10^{-10}$). To further elucidate these findings, within each participant, we averaged parameter estimates across all seed-target pairs that showed a significant age X pR interaction. We then used the same model (Model(2): $Y_{\text{connectivity}} = \beta_0 + \beta_1\chi_{\text{age}} + \beta_2\chi_{\text{pR}} + \beta_3\chi_{\text{ageXpR}} + \beta[\text{covariates}] + \epsilon$) to examine the age by performance interaction on the average connectivity for each participant, after partialling out variance shared with the covariates of no interest. Scatterplots depicting the relationship between pR and the residualized average connectivity change are shown in Figure 8d. The age X pR interaction was significant ($F(2,126) = 7.71, p < .001$). Post hoc analyses revealed that the relationship between pR and connectivity was stronger for the young relative to the older age group ($t(98)=3.93, p < .001$). Together, these findings indicate that amongst the

seed-target pairs where there was a significant age by pR interaction on recollection-related change in connectivity, the vast majority of the effects were driven by a more positive relationship between age and pR in the younger relative to the older age groups.

Effect of age group on recollection-related change in connectivity, controlling for performance and the age by performance interaction—For the second set of regression models, we also examined the significance of the beta coefficient associated with the age group factor. This allowed us to examine the effect of age group on connectivity after controlling for individual differences in recollection performance and the age by performance interaction (Figure 9). Using this model, we were able to identify a significant effect of age group on connectivity in only 648 (0.88%) seed-target pairs. To determine the direction of the effects for these pairs, we examined the direction and significance of the pairwise age group coefficients, labeling each seed-target pair that exhibited a main effect of age group as either “positive,” “negative,” or “other” in a similar manner as for Model 1. In comparison to Model 1, where the majority of effects were labeled as negative, when pR and the age by pR interaction were included as a covariates in the models, the majority of age effects on connectivity were now positive (Figure 9c). Specifically, 520, or 80.25%, of significant seed-target pairs were labeled as positive, whereas 104 (16.05%) were labeled as negative, and only 24 (3.70%) were labeled as other. A binomial test confirmed that the probability of observing this proportion of positive effects was significantly less than chance ($p < 10^{-10}$). Again, to illustrate these same data in a different way, for each participant, we averaged the residualized parameter estimates of connectivity change across all seed-target pairs that showed a significant main effect of age in Model 2, and the average values across participants for each age group are depicted in Figure 9d. We used the same regression model (Model(2): $y_{\text{connectivity}} = \beta_0 + \beta_1\chi_{\text{age}} + \beta_2\chi_{\text{pR}} + \beta_3\chi_{\text{age}\times\text{pR}} + \beta[\text{covariates}] + \epsilon$) to predict average connectivity. There was a significant main effect of age group on the average connectivity residuals ($F(2,126)=3.70$, $p=.027$). Post hoc analyses revealed that the young group showed significantly lower recollection-related connectivity change than either the older ($t=3.04$, $p=.003$) or the middle-aged group ($t=2.67$, $p=.009$). Connectivity change did not differ between the middle-aged relative to the older adults ($p>.1$).

Effect of performance on recollection-related change in connectivity, controlling for age group and the age by performance interaction—In addition to exploring effects of age on recollection-related changes in connectivity, we were also interested in examining the relationship between connectivity change and performance, after controlling for age. To do this, we examined the significance of the performance (pR) coefficient from Model 2: ($y_{\text{connectivity}} = \beta_0 + \beta_1\chi_{\text{age}} + \beta_2\chi_{\text{pR}} + \beta_3\chi_{\text{age}\times\text{pR}} + \beta[\text{covariates}] + \epsilon$). Reminiscent of our prior findings (King et al., 2015), after controlling for age group and the age by performance interaction, there was a significant relationship between connectivity change and performance in 71,157, or 96.89% of the seed-target pairs (Figures 10a–b). Every one of these effects (100%) was positive (Figure 10c), indicating that, controlling for age group, better performance was associated with enhanced recollection-related changes in connectivity for regions distributed throughout the whole brain. To illustrate this result in a different way, for each participant, we averaged parameter estimates of recollection-related change in connectivity across all of the seed-target pairs that exhibited a significant

relationship with pR, and then ran the same regression model predicting average connectivity change among these regions. Unsurprisingly, performance was significantly associated with average connectivity change ($F(2,126) = 45.515, p < .0001$). The residualized average connectivity change measures are plotted against performance in Figure 10d.

Discussion

The goal of the current study was to examine whether task-related changes in functional connectivity and their relationship with performance vary across different age groups. Using a seed-based approach and conventional statistical thresholding, we failed to identify any effects of age group on recollection-related change in connectivity between core recollection regions and the rest of the brain. When we extended our analysis to explore age effects on recollection-related change in connectivity among regions distributed throughout the whole brain, we did find evidence for age group differences among a subset of regions. The vast majority of these effects were due to greater recollection-related increases in connectivity for the younger relative to the older age groups. However, after controlling for performance, most of these effects were either no longer significant or were reversed, with greater recollection-related increases in connectivity for the older compared to the younger age groups. Regardless of whether we adopted a seed-based or whole-brain approach, there was evidence for an age-related decline in the strength of the relationship between recollection performance and recollection-related change in connectivity. These findings are described in greater detail below, along with a discussion of their implications.

Before turning to the fMRI findings, however, we briefly discuss the behavioral results. As already noted (see Behavioral Results above), these results have been reported and discussed previously (de Chastelaine et al., 2015, 2016a, b, 2017). At the request of a reviewer, we note here that our finding of a graded decline in recollection with increasing age (here, operationalized through associative recognition performance) is consistent with findings from numerous prior cross-sectional studies that have employed both associative recognition and a variety of other memory tests that also depend heavily on recollection (see Koen and Yonelinas, 2016, for review and meta-analysis). These studies include a recent large, population-based study (Henson et al., 2016) in which recollection (operationalized by performance on a test of source memory) was reported to decline linearly across the adult lifespan (age range ca. 20 yrs to 85 yrs). As we discuss further in a later paragraph, it is difficult however to determine the specific contribution of aging (within-participant change over time) to age-related differences in memory performance from cross-sectional data such as that reported here and by Henson et al. (2016).

As noted previously, the seed-based analyses revealed that core recollection regions exhibited robust recollection-related increases in connectivity in all three age groups. Similar to our prior findings in young adults (King et al., 2015; see also Geib et al., 2017, 2015; Schedlbauer et al., 2014), increased connectivity was found with areas that included left dorsolateral prefrontal and parietal cortex, anterior and posterior cingulate, insula, extrastriate visual cortex, putamen, and thalamus. These findings suggest that numerous regions where the mean BOLD signal does not vary as a function of recollection success

might nonetheless be contributing to recollection by interacting with the core network. Further, these findings suggest that similarly to recollection-related enhancement of activity (e.g., de Chastelaine et al., 2016a), recollection-related increases in connectivity between core recollection regions and the rest of the brain appear to be relatively stable across much of the healthy adult lifespan. However, our failure to detect a significant, albeit subtle, age group effect in these analyses could be due to insufficient power, and hence, inferences based on this null finding require caution.

In light of our previous findings demonstrating that brain regions that do not show recollection-related modulation of activity nonetheless exhibit recollection-related changes in connectivity (King et al., 2015), we extended our seed-based analysis to examine recollection-related changes in connectivity between regions distributed throughout the whole brain. We found evidence for a significant main effect of age group on a subset of seed-target pairs. In the vast majority of cases (>95%) this was due to greater recollection-related change in connectivity in the younger than the older age groups (Figure 7). Although a significant main effect of age was detected in fewer than 5% of the seed-target pairs, the likelihood of observing such a disproportionate number of positive (increased connectivity with increased age) relative to negative (decreased connectivity with increased age) effects due to chance was extremely low. These findings suggest that when individual differences in memory performance are not taken into account, younger adults showed greater recollection-related changes in connectivity than older adults among a subset of brain regions.

This finding of a main effect of age group on recollection-related change in connectivity should however be interpreted with caution, as age group was confounded with memory performance. In such cases, it can be difficult to disambiguate whether age-related differences in a neural measure reflect ‘true’ effects of age on brain function, or instead, an age-independent relationship between the neural measure and memory performance (for discussion of this issue see Angel et al., 2013; de Chastelaine et al., 2016b; Rugg and Morcom, 2004, Rugg, 2016). Indeed, in a recent prior study it was reported that age group effects on memory-related brain activity were not reliable when individual differences in memory performance were statistically controlled for (de Chastelaine et al., 2016a). In the current study, to examine whether performance could account for age-group differences in connectivity, we re-ran the regression analyses on the whole-brain connectivity matrices while controlling for individual differences in recollection performance. Now, the number of seed-target pairs exhibiting a main effect of age was considerably reduced (0.88% vs. 2.81%). Furthermore, among the pairs demonstrating an effect, the vast majority showed greater recollection-related increases in connectivity for the *older* relative to the younger age group. In other words, when recollection performance was statistically equated across participants, older adults showed greater recollection-related increases in connectivity than younger adults within this subset of brain regions. These findings are reminiscent of previous reports that, when memory performance is experimentally matched across age groups, older adults can show greater or more widespread memory-related activity than younger adults (for review see Grady, 2012). The findings can perhaps be explained in terms of a compensation model of age-related differences in brain function. According to such models (Cabeza, 2002; de Chastelaine et al., 2016b; Grady, 2012; Reuter-Lorenz and

Cappell, 2008), age-related ‘over-activation’ reflects the recruitment of additional neural resources to counteract or ameliorate the adverse influence of aging on neural efficiency, opposing the deleterious effects of age on cognitive performance. Here, we provide evidence that such compensatory mechanisms may extend beyond age-related increases in mean signal to include enhancement of task-related connectivity among distributed brain regions. In other words, equivalent memory performance between older and younger individuals comes at the cost of the expenditure of greater neural ‘resources’ (here, connectivity change) on the part of the older group.

It is important to note that we adopted different approaches for statistically thresholding the data and controlling for Type I error in our seed-based and whole-brain analyses. With the whole-brain analysis, we applied a relatively liberal statistical threshold ($p < .05$) to identify pairs of regions that showed an effect of age group, and then used a binomial test to determine whether, across all pairs, the age effects demonstrated a directional bias greater than would be expected by chance. Hence, this analysis allowed for inferences about age group effects on the general patterning of whole-brain recollection-related changes in connectivity, but not in respect of specific pairs of regions. This data-driven, whole-brain approach provided insights beyond what the seed-based approach revealed.

In addition to examining main effects of age group on recollection-related changes in connectivity, we were also interested in whether there would be age-group differences in the strength of the relationship between recollection performance and recollection-related change in connectivity. We previously reported that, in young adults, recollection accuracy was correlated across participants with recollection-related changes in connectivity between core recollection regions and regions distributed throughout much of the brain (King et al., 2015). Here, we examined whether this relationship differed across age groups. We first applied the same seed-based approach as was adopted in our original study (King et al., 2015). As for the young sample, the averaged correlations for the middle-aged and older adults were all positive, and in some cases significantly greater than zero. With few exceptions, however, the correlations were significantly weaker in these age-groups compared with the correlations in the young age group.

In a complementary analysis, we examined the relationship between performance and recollection-related connectivity changes using our whole-brain approach. Consistent with the seed-based approach, in the vast majority of seed-target pairs that exhibited an age-group by performance interaction (see Figure 8) the interaction effect was driven by a stronger positive correlation between performance and connectivity change in the young relative to the older age groups.

As outlined in the Introduction, we hypothesize that at least two distinct neural mechanisms contribute to recollection-related changes in connectivity. One of these mechanisms is the enhanced inter-regional and inter-network exchange of information that is associated with successful recollection (see also Geib et al., 2015; Schedlbauer et al., 2014; Westphal et al., 2017). In the present findings, this mechanism is reflected by the enhanced connectivity observed between members of the core recollection and multiple demand (‘control’) networks in each age group. In addition, we hypothesize that recollection-related changes in

connectivity that co-vary across individuals with recollection performance reflect the influence of one or more of the neuromodulatory systems that transiently influence synchronicity throughout much of the neo-cortex (Schölvinck et al., 2010; Shine et al., 2016). These systems project diffusely to much of the brain, and variations in neuromodulatory input have previously been linked to variation in the magnitude of functional connectivity (Schölvinck et al., 2010; Shine et al., 2016). For instance, as noted in the Introduction, Shine et al., 2016 reported that variability in the strength of inter-regional connectivity co-varied within-subjects with both task performance (n-back working memory) and pupil dilation. On the assumption that variations in pupillary diameter reflect neuromodulatory drive (notably, from ascending noradrenergic systems; Ang et al., 2015; Aston-Jones et al., 1994; Aston-Jones and Cohen, 2005; Joshi et al., 2016; Murphy et al., 2011; Usher et al., 1999), these findings are consistent with the proposal that inter-regional connectivity is influenced by ascending neuromodulatory input. Hence, neuromodulatory input is a potential source of the widely distributed changes in connectivity found here to correlate with recollection performance. While the focus of the current study was on episodic memory, we strongly suspect that the same proposed neuromodulatory mechanism exerts an influence on other cognitive processes (e.g., working memory) in a similar manner.

We have previously suggested that there is a relationship between the average strength of the memory signal elicited by recollected memory test items and the strength of a corresponding transient increase in neuromodulatory drive, and that this relationship mediates across-subjects correlations between recollection accuracy and recollection-related connectivity change (King et al., 2015). Importantly, we noted previously, and do so again here, that the *causal* relationships between these variables is currently opaque. That being said, in light of the evidence that neuromodulatory drive (and hence its dynamic range) decreases with age (Bäckman et al., 2010, 2006; Erixon-Lindroth et al., 2005; Severson et al., 1982; Suhara et al., 1991; Y. Wang et al., 1998), we predicted that the influence of neuromodulatory systems on recollection-related changes in connectivity, and hence the relationship between connectivity change and recollection performance, would also decrease with age. The present findings are consistent with this prediction. Further support for this hypothesis will require studies in which neuromodulatory input is experimentally manipulated, and the effects of these manipulations on connectivity change and recollection performance examined.

Before closing, we note several caveats to our interpretation of the present findings. First, the whole brain connectivity analyses were based on ROIs identified on the basis of resting-state and task-based analyses of young participants only. It is currently not known whether equivalent analyses in older participants would identify the same set of regions. Thus, it remains to be established whether the assumption underlying the present (and some prior) findings that a common set of ROIs can be employed across the lifespan for the purposes of connectivity analyses is justified (cf. Goldstone et al., 2016).

Second, interpretation of our findings in terms of age-related differences in neural activity depends on the assumption that non-neural determinants of recollection-related changes in connectivity were equivalent across the age-groups. While we took care to minimize any influence of head motion in our analyses (including the employment of motion parameters

as covariates of no interest in both our first and second-level analyses), we cannot entirely rule out the possibility of some residual impact of this variable. In addition, Geerligs et al. (2017) recently demonstrated that physiological artifacts linked to differences in cardiovascular health (e.g., pulse and respiration artifact) can contribute to age-related differences in patterns of resting state connectivity. Since it is currently unknown whether measures of event-related connectivity change are similarly vulnerable to these artifacts, they must also be acknowledged as a possible source of bias.

Third, cerebro-vascular reactivity (CVR) – an important non-neural determinant of the magnitude of the BOLD signal – has been shown to decline with age (e.g., Lu et al., 2011; Liu et al., 2013). Thus, it is possible that the age differences reported here might at least partially reflect differences in CVR rather than true modulation of inter-regional connectivity. The extent of this bias is presently unknown, but can be assessed in future research with the help of methods that allow correction for individual differences in CVR.

Finally, it is important to note that a significant proportion of the variance across the lifespan in both memory performance and the neural correlates of memory processing is likely attributable to factors such as birth cohort (Rönnlund and Nilsson, 2009; Baxendale, 2010; Nyberg et al., 2012) and sampling bias (Nyberg et al., 2010; Rugg, 2016), rather than to age-related changes in brain structure and function. Importantly, current longitudinal evidence suggests that cross-sectional data likely over-estimate the impact of aging on episodic memory, particularly in relation to the age at which memory decline begins (Rönnlund et al., 2005). Disentangling the contributions of the different factors driving age-related differences in brain function and cognitive performance will necessitate a longitudinal approach rather than the cross-sectional approach adopted here.

In summary, extending prior findings, we identified a set of brain regions that exhibited consistent and age-invariant recollection-related increases in connectivity with core recollection regions in groups of young, middle-aged and older adults. While a relatively conservative seed-based approach failed to identify any effects of age group on recollection-related connectivity change, an arguably more sensitive whole-brain approach identified a widely distributed subset of regions where connectivity change differed across age groups. In the vast majority of cases this difference was due to greater recollection-related increase in connectivity in the younger relative to the older age groups. However, when controlling for recollection accuracy, these age-related effects were either eliminated or reversed, consistent with the ‘compensation hypothesis’ of cognitive aging (Cabeza, 2002; Grady, 2012; Reuter-Lorenz and Cappell, 2008). Crucially, our two analysis approaches yielded converging evidence for an age-related weakening of the relationship between recollection-related connectivity change and recollection accuracy. We propose that this finding reflects age-related decline in the influence of ascending neuromodulatory systems on cortical activity.

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References

- Allard P, Marcusson JO. Age-correlated loss of dopamine uptake sites labeled with [3H]GBR-12935 in human putamen. *Neurobiol Aging*. 1989; 10:661–664. [PubMed: 2628776]
- Andrews-Hanna JR, Snyder AZ, Vincent JL, Lustig C, Head D, Raichle ME, Buckner RL. Disruption of large-scale brain systems in advanced aging. *Neuron*. 2007; 56:924–935. DOI: 10.1016/j.neuron.2007.10.038 [PubMed: 18054866]
- Angel L, Bastin C, Genon S, Balteau E, Phillips C, Luxen A, Maquet P, Salmon E, Collette F. Differential effects of aging on the neural correlates of recollection and familiarity. *Cortex J Devoted Study Nerv Syst Behav*. 2013; 49:1585–1597. DOI: 10.1016/j.cortex.2012.10.002
- Ang Y-S, Manohar S, Apps MAJ. Commentary: noradrenaline and dopamine neurons in the reward/effort trade-off: a direct electrophysiological comparison in behaving monkeys. *Front Behav Neurosci*. 2015; :9.doi: 10.3389/fnbeh.2015.00310 [PubMed: 25691862]
- Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annu Rev Neurosci*. 2005; 28:403–450. DOI: 10.1146/annurev.neuro.28.061604.135709 [PubMed: 16022602]
- Aston-Jones G, Rajkowski J, Kubiak P, Alexinsky T. Locus coeruleus neurons in monkey are selectively activated by attended cues in a vigilance task. *J Neurosci Off J Soc Neurosci*. 1994; 14:4467–4480.
- Bäckman L, Lindenberger U, Li SC, Nyberg L. Linking cognitive aging to alterations in dopamine neurotransmitter functioning: recent data and future avenues. *Neurosci Biobehav Rev*. 2010; 34:670–677. DOI: 10.1016/j.neubiorev.2009.12.008 [PubMed: 20026186]
- Bäckman L, Nyberg L, Lindenberger U, Li SC, Farde L. The correlative triad among aging, dopamine, and cognition: current status and future prospects. *Neurosci Biobehav Rev*. 2006; 30:791–807. DOI: 10.1016/j.neubiorev.2006.06.005 [PubMed: 16901542]
- Baxendale S. The Flynn effect and memory function. *J Clin Exp Neuropsychol*. 2010; 32:699–703. [PubMed: 20119877]
- Cabeza R. Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol Aging*. 2002; 17:85–100. [PubMed: 11931290]
- Campbell KL, Grigg O, Saverino C, Churchill N, Grady CL. Age differences in the intrinsic functional connectivity of default network subsystems. *Front Aging Neurosci*. 2013; 5:73.doi: 10.3389/fnagi.2013.00073 [PubMed: 24294203]
- Campbell KL, Schacter DL. Ageing and the resting state: is cognition obsolete? 2016
- Clayton EC, Rajkowski J, Cohen JD, Aston-Jones G. Phasic activation of monkey locus ceruleus neurons by simple decisions in a forced-choice task. *J Neurosci Off J Soc Neurosci*. 2004; 24:9914–9920. DOI: 10.1523/JNEUROSCI.2446-04.2004
- Cocosco CA, Kollokian V, Kwan RKS, Pike GB, Evans AC. BrainWeb: online interface to a 3D MRI simulated brain database. *NeuroImage*. 1997; 5:425.
- Cortés R, Gueye B, Pazos A, Probst A, Palacios JM. Dopamine receptors in human brain: autoradiographic distribution of D1 sites. *Neuroscience*. 1989; 28:263–273. [PubMed: 2522166]
- Damoiseaux JS, Beckmann CF, Arigita EJS, Barkhof F, Scheltens P, Stam CJ, Smith SM, Rombouts SaRB. Reduced resting-state brain activity in the “default network” in normal aging. *Cereb Cortex N Y N* 1991. 2008; 18:1856–1864. DOI: 10.1093/cercor/bhm207
- de Chastelaine M, Mattson JT, Wang TH, Donley BE, Rugg MD. The neural correlates of recollection and retrieval monitoring: relationships with age and recollection performance. *NeuroImage*. 2016a; 138:164–175. DOI: 10.1016/j.neuroimage.2016.04.071 [PubMed: 27155127]
- de Chastelaine M, Mattson JT, Wang TH, Donley BE, Rugg MD. The relationships between age, associative memory performance, and the neural correlates of successful associative memory encoding. *Neurobiol Aging*. 2016b; 42:163–176. DOI: 10.1016/j.neurobiolaging.2016.03.015 [PubMed: 27143433]
- de Chastelaine M, Mattson JT, Wang TH, Donley BE, Rugg MD. Independent contributions of fMRI familiarity and novelty effects to recognition memory and their stability across the adult lifespan. *NeuroImage*. 2017; 156:340–351. DOI: 10.1016/j.neuroimage.2017.05.039 [PubMed: 28528847]

- de Chastelaine M, Mattson JT, Wang TH, Donley BE, Rugg MD. Sensitivity of negative subsequent memory and task-negative effects to age and associative memory performance. *Brain Res.* 2015; 1612:16–29. DOI: 10.1016/j.brainres.2014.09.045 [PubMed: 25264353]
- Duarte A, Henson RN, Graham KS. The effects of aging on the neural correlates of subjective and objective recollection. *Cereb Cortex N Y N* 1991. 2008; 18:2169–2180. DOI: 10.1093/cercor/bhm243
- Duncan J. The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour. *Trends Cogn Sci.* 2010; 14:172–179. DOI: 10.1016/j.tics.2010.01.004 [PubMed: 20171926]
- Edeline JM. Beyond traditional approaches to understanding the functional role of neuromodulators in sensory cortices. *Front Behav Neurosci.* 2012; 6:45.doi: 10.3389/fnbeh.2012.00045 [PubMed: 22866031]
- Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, Zilles K. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *NeuroImage.* 2005; 25:1325–1335. DOI: 10.1016/j.neuroimage.2004.12.034 [PubMed: 15850749]
- Erixon-Lindroth N, Farde L, Wahlin TBR, Sovago J, Halldin C, Bäckman L. The role of the striatal dopamine transporter in cognitive aging. *Psychiatry Res.* 2005; 138:1–12. DOI: 10.1016/j.psychres.2004.09.005 [PubMed: 15708296]
- Ferreira LK, Busatto GF. Resting-state functional connectivity in normal brain aging. *Neurosci Biobehav Rev.* 2013; 37:384–400. DOI: 10.1016/j.neubiorev.2013.01.017 [PubMed: 23333262]
- Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. Psychophysiological and modulatory interactions in neuroimaging. *NeuroImage.* 1997; 6:218–229. DOI: 10.1006/nimg.1997.0291 [PubMed: 9344826]
- Gallo DA, Bell DM, Beier JS, Schacter DL. Two types of recollection-based monitoring in younger and older adults: recall-to-reject and the distinctiveness heuristic. *Mem Hove Engl.* 2006; 14:730–741. DOI: 10.1080/09658210600648506
- Geerligs L, Rubinov M, Henson RN. Cam-Can. State and trait components of functional connectivity: Individual differences vary with mental state. *J Neurosci.* 2015; 35:13949–61. DOI: 10.1523/jneurosci.1324-15.2015 [PubMed: 26468196]
- Geerligs L, Tsvetanov KA. The use of resting state data in an integrative approach to studying neurocognitive ageing - Commentary on Campbell and Schacter (2016). 2016
- Geerligs L, Tsvetanov KA, Henson RN. Challenges in measuring individual differences in functional connectivity using fMRI: The case of healthy aging. *Hum Brain Mapp.* 2017; n/a-n/a. doi: 10.1002/hbm.23653
- Geib BR, Stanley ML, Dennis NA, Woldorff MG, Cabeza R. From hippocampus to whole-brain: the role of integrative processing in episodic memory retrieval. *Hum Brain Mapp.* 2017; n/a–n/a. doi: 10.1002/hbm.23518
- Geib BR, Stanley ML, Wing EA, Laurienti PJ, Cabeza R. Hippocampal contributions to the large-scale episodic memory network predict vivid visual memories. *Cereb Cortex N Y N.* 2015; 1991. doi: 10.1093/cercor/bhv272
- Gerchen MF, Kirsch P. Combining task-related activation and connectivity analysis of fMRI data reveals complex modulation of brain networks. *Hum Brain Mapp.* 2017; In press. doi: 10.1002/hbm.23762
- Gerchen MF, Bernal-Casas D, Kirsch P. Analyzing task-dependent brain network changes by whole-brain psychophysiological interactions: A comparison to conventional analysis. *Hum Brain Mapp.* 2014; n/a–n/a. doi: 10.1002/hbm.22532
- Godwin D, Barry RL, Marois R. Breakdown of the brain's functional network modularity with awareness. *Proc Natl Acad Sci.* 2015; 112:3799–3804. DOI: 10.1073/pnas.1414466112 [PubMed: 25759440]
- Goldstone A, Mayhew SD, Przydzik I, Wilson RS, Hale JR, Bagshaw AP. Gender specific re-organization of resting-state networks in older age. *Front Aging Neurosci.* 2016; :8.doi: 10.3389/fnagi.2016.00285 [PubMed: 26858639]
- Grady C. The cognitive neuroscience of ageing. *Nat Rev Neurosci.* 2012; 13:491–505. DOI: 10.1038/nrn3256 [PubMed: 22714020]

- Henson RN, Campbell KL, Davis SW, Taylor JR, Emery T, Erzinclioglu S, Kievit RA. Cam-CAN. Multiple determinants of lifespan memory differences. *Sci Rep*. 2016; 6:32527.doi: 10.1038/srep32527 [PubMed: 27600595]
- Jacoby LL, Shimizu Y, Velanova K, Rhodes MG. Age differences in depth of retrieval: memory for foils. *J Mem Lang*, Special Issue on Metamemory. 2005; 52:493–504. DOI: 10.1016/j.jml.2005.01.007
- Joshi S, Li Y, Kalwani RM, Gold JJ. Relationships between pupil diameter and neuronal activity in the locus coeruleus, colliculi, and cingulate cortex. *Neuron*. 2016; 89:221–234. DOI: 10.1016/j.neuron.2015.11.028 [PubMed: 26711118]
- Kim H. Dissociating the roles of the default-mode, dorsal, and ventral networks in episodic memory retrieval. *NeuroImage*. 2010; 50:1648–1657. DOI: 10.1016/j.neuroimage.2010.01.051 [PubMed: 20097295]
- King DR, de Chastelaine M, Elward RL, Wang TH, Rugg MD. Recollection-Related Increases in Functional Connectivity Predict Individual Differences in Memory Accuracy. *J Neurosci*. 2015; 35:1763–1772. DOI: 10.1523/JNEUROSCI.3219-14.2015 [PubMed: 25632149]
- Klostermann EC, Braskie MN, Landau SM, O'Neil JP, Jagust WJ. Dopamine and frontostriatal networks in cognitive aging. *Neurobiol Aging*. 2012; 33:623e15–24. DOI: 10.1016/j.neurobiolaging.2011.03.002
- Koen JD, Yonelinas AP. Recollection, not familiarity, decreases in healthy ageing: Converging evidence from four estimation methods. *Memory*. 2016; 24:75–88. DOI: 10.1080/j.memory.2014.985590 [PubMed: 25485974]
- Lee SH, Dan Y. Neuromodulation of brain states. *Neuron*. 2012; 76:209–222. DOI: 10.1016/j.neuron.2012.09.012 [PubMed: 23040816]
- Leshikar ED, Gutchess AH, Hebrank AC, Sutton BP, Park DC. The impact of increased relational encoding demands on frontal and hippocampal function in older adults. *Cortex J Devoted Study Nerv Syst Behav*. 2010; 46:507–521. DOI: 10.1016/j.cortex.2009.07.011
- Liu P, Hebrank AC, Rodrigue KM, Kennedy KM, Park DC, Lu H. A comparison of physiologic modulators of fMRI signals. *Hum Brain Mapp*. 2013; 34:2078–2088. DOI: 10.1002/hbm.22053 [PubMed: 22461234]
- Lu H, Xu F, Rodrigue KM, Kennedy KM, Cheng Y, Flicker B, Hebrank AC, Uh J, Park DC. Alterations in cerebral metabolic rate and blood supply across the adult lifespan. *Cereb Cortex*. 2011; 21:1426–1434. DOI: 10.1093/cercor/bhq224 [PubMed: 21051551]
- Mandler G. Recognizing: the judgment of previous occurrence. *Psychol Rev*. 1980; 87:252–271. DOI: 10.1037/0033-295X.87.3.252
- McDonough IM, Wong JT, Gallo DA. Age-related differences in prefrontal cortex activity during retrieval monitoring: testing the compensation and dysfunction accounts. *Cereb Cortex N Y N*. 1991. 2013; 23:1049–1060. DOI: 10.1093/cercor/bhs064
- Mickes L, Johnson EM, Wixted JT. Continuous recollection versus unitized familiarity in associative recognition. *J Exp Psychol Learn Mem Cogn*. 2010; 36:843–863. DOI: 10.1037/a0019755 [PubMed: 20565205]
- Mitchell KJ, Ankudowich E, Durbin KA, Greene EJ, Johnson MK. Age-related differences in agenda-driven monitoring of format and task information. *Neuropsychologia*. 2013; 51:2427–2441. DOI: 10.1016/j.neuropsychologia.2013.01.012 [PubMed: 23357375]
- Morcom AM, Li J, Rugg MD. Age effects on the neural correlates of episodic retrieval: increased cortical recruitment with matched performance. *Cereb Cortex*. 2007; 17:2491–2506. DOI: 10.1093/cercor/bhl155 [PubMed: 17204820]
- Morcom AM, Rugg MD. Effects of age on retrieval cue processing as revealed by ERPs. *Neuropsychologia*. 2004; 42:1525–1542. DOI: 10.1016/j.neuropsychologia.2004.03.009 [PubMed: 15246290]
- Murphy PR, Robertson IH, Balsters JH, O'Connell RG. Pupillometry and P3 index the locus coeruleus-noradrenergic arousal function in humans. *Psychophysiology*. 2011; 48:1532–1543. DOI: 10.1111/j.1469-8986.2011.01226.x [PubMed: 21762458]
- Naveh-Benjamin M. Adult age differences in memory performance: tests of an associative deficit hypothesis. *J Exp Psychol Learn Mem Cogn*. 2000; 26:1170–1187. [PubMed: 11009251]

- Naveh-Benjamin M, Craik FI. Memory for context and its use in item memory: comparisons of younger and older persons. *Psychol Aging*. 1995; 10:284–293. [PubMed: 7662187]
- Nelson DL, McEvoy CL, Schreiber TA. The University of South Florida free association, rhyme, and word fragment norms. *Behav Res Methods Instrum Comput*. 2004; 36:402–407. DOI: 10.3758/BF03195588 [PubMed: 15641430]
- Nilsson LG. Memory function in normal aging. *Acta Neurol Scand*. 2003; 107:7–13. DOI: 10.1034/j.1600-0404.107.s179.5.x [PubMed: 12542507]
- Nyberg L, Salami A, Andersson M, Eriksson J, Kalpouzos G, Kauppi K, Lind J, Pudas S, Persson J, Nilsson LG. Longitudinal evidence for diminished frontal cortex function in aging. *Proc Natl Acad Sci USA*. 2010; 107:22682–22686. [PubMed: 21156826]
- Nyberg L, Lövdén M, Riklund K, Lindenberger U, Bäckman L. Memory aging and brain maintenance. *Trends Cogn Sci*. 2012; 16:292–305. DOI: 10.1016/j.tics.2012.04.005 [PubMed: 22542563]
- Nyberg L, Karalija N, Salami A, Andersson M, Wählin A, Kaboovand N, Köhncke Y, Axelsson J, Rieckmann A, Papenberg G, Garrett DD, Riklund K, Lövdén M, Lindenberger U, Bäckman L. Dopamine D2 receptor availability is linked to hippocampal–caudate functional connectivity and episodic memory. *Proc Natl Acad Sci U S A*. 2016; 113:7918–7923. DOI: 10.1073/pnas.1606309113 [PubMed: 27339132]
- Old SR, Naveh-Benjamin M. Differential effects of age on item and associative measures of memory: a meta-analysis. *Psychol Aging*. 2008; 23:104–118. DOI: 10.1037/0882-7974.23.1.104 [PubMed: 18361660]
- Parikh V, Kozak R, Martinez V, Sarter M. Prefrontal acetylcholine release controls cue detection on multiple timescales. *Neuron*. 2007; 56:141–154. DOI: 10.1016/j.neuron.2007.08.025 [PubMed: 17920021]
- Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage*. 2012; 59:2142–2154. DOI: 10.1016/j.neuroimage.2011.10.018 [PubMed: 22019881]
- Power JD, Cohen AL, Nelson SM, Wig GS, Barnes KA, Church JA, Vogel AC, Laumann TO, Miezin FM, Schlaggar BL, Peterson SE. Functional network organization of the human brain. *Neuron*. 2011; 72:665–678. DOI: 10.1016/j.neuron.2011.09.006 [PubMed: 22099467]
- Reuter-Lorenz PA, Cappell KA. Neurocognitive aging and the compensation hypothesis. *Curr Dir Psychol Sci*. 2008; 17:177–182. DOI: 10.1111/j.1467-8721.2008.00570.x
- Rieckmann A, Karlsson S, Fischer H, Bäckman L. Caudate dopamine D1 receptor density is associated with individual differences in frontoparietal connectivity during working memory. *J Neurosci Off J Soc Neurosci*. 2011; 31:14284–14290. DOI: 10.1523/JNEUROSCI.3114-11.2011
- Rönnlund M, Nyberg L, Bäckman L, Nilsson LG. Stability, growth, and decline in adult life span development of declarative memory: Cross-sectional and longitudinal data from a population-based study. *Psychol Aging*. 2005; 20:3–18. [PubMed: 15769210]
- Rönnlund M, Nilsson LG. Flynn effects on sub-factors of episodic and semantic memory: Parallel gains over time and the same set of determining factors. *Neuropsychologia*. 2009; 47:2174–2180. [PubMed: 19056409]
- Rugg, MD. Interpreting age-related differences in memory-related neural activity. In: Cabeza, R.Nyberg, L., Park, DC., editors. *Cognitive Neuroscience of Aging: Linking Cognitive and Cerebral Aging*. 2. Oxford University Press; 2016.
- Rugg, MD., Morcom, AM. The relationship between brain activity, cognitive performance and aging: The case of memory. In: Cabeza, R.Nyberg, L., Park, D., editors. *Cognitive Neuroscience of Aging: Linking Cognitive and Cerebral Aging*. Oxford University Press; 2004.
- Rugg MD, Vilberg KL. Brain networks underlying episodic memory retrieval. *Curr Opin Neurobiol*. 2013; 23:255–260. DOI: 10.1016/j.conb.2012.11.005 [PubMed: 23206590]
- Salami A, Pudas S, Nyberg L. Elevated hippocampal resting-state connectivity underlies deficient neurocognitive function in aging. *Proc Natl Acad Sci U S A*. 2014; 111:17654–17659. DOI: 10.1073/pnas.1410233111 [PubMed: 25422457]
- Schedlbauer AM, Copara MS, Watrous AJ, Ekstrom AD. Multiple interacting brain areas underlie successful spatiotemporal memory retrieval in humans. *Sci Rep*. 2014; :4.doi: 10.1038/srep06431

- Schölvinck ML, Maier A, Ye FQ, Duyn JH, Leopold DA. Neural basis of global resting-state fMRI activity. *Proc Natl Acad Sci*. 2010; :10238–10243. DOI: 10.1073/pnas.0913110107 [PubMed: 20439733]
- Severson JA, Marcusson J, Winblad B, Finch CE. Age-correlated loss of dopaminergic binding sites in human basal ganglia. *J Neurochem*. 1982; 39:1623–1631. [PubMed: 7142992]
- Shine JM, Bissett PG, Bell PT, Koyejo O, Balsters JH, Gorgolewski KJ, Moodie CA, Poldrack RA. The dynamics of functional brain networks: integrated network states during cognitive task performance. *Neuron*. 2016; 92:544–554. DOI: 10.1016/j.neuron.2016.09.018 [PubMed: 27693256]
- Smith DV, Gseir M, Speer ME, Delgado MR. Toward a cumulative science of functional integration: a meta-analysis of psychophysiological interactions. *Hum Brain Mapp*. 2016; 37:2904–2917. DOI: 10.1002/hbm.23216 [PubMed: 27145472]
- Spaniol J, Davidson PSR, Kim ASN, Han H, Moscovitch M, Grady CL. Event-related fMRI studies of episodic encoding and retrieval: meta-analyses using activation likelihood estimation. *Neuropsychologia*. 2009; 47:1765–1779. DOI: 10.1016/j.neuropsychologia.2009.02.028 [PubMed: 19428409]
- Suhara T, Fukuda H, Inoue O, Itoh T, Suzuki K, Yamasaki T, Tateno Y. Age-related changes in human D1 dopamine receptors measured by positron emission tomography. *Psychopharmacology (Berl)*. 1991; 103:41–45. DOI: 10.1007/BF02244071 [PubMed: 1826059]
- Toussaint PJ, Maiz S, Coynel D, Doyon J, Messé A, de Souza LC, Sarazin M, Perlberg V, Habert MO, Benali H. Characteristics of the default mode functional connectivity in normal ageing and Alzheimer's disease using resting state fMRI with a combined approach of entropy-based and graph theoretical measurements. *NeuroImage*. 2014; 101:778–786. DOI: 10.1016/j.neuroimage.2014.08.003 [PubMed: 25111470]
- Tsukiura T, Sekiguchi A, Yomogida Y, Nakagawa S, Shigemune Y, Kambara T, Akitsuki Y, Taki Y, Kawashima R. Effects of aging on hippocampal and anterior temporal activations during successful retrieval of memory for face-name associations. *J Cogn Neurosci*. 2011; 23:200–213. DOI: 10.1162/jocn.2010.21476 [PubMed: 20350057]
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage*. 2002; 15:273–289. DOI: 10.1006/nimg.2001.0978 [PubMed: 11771995]
- Usher M, Cohen JD, Servan-Schreiber D, Rajkowski J, Aston-Jones G. The role of locus coeruleus in the regulation of cognitive performance. *Science*. 1999; 283:549–554. [PubMed: 9915705]
- Van den Brink RL, Pfeffer T, Warren CM, Murphy PR, Tona KD, van der Wee NJA, Giltay E, van Noorden MS, Rombouts SARB, Donner TH, Nieuwenhuis S. Catecholaminergic neuromodulation shapes intrinsic MRI functional connectivity in the human brain. *J Neurosci Off J Soc Neurosci*. 2016; 36:7865–7876. DOI: 10.1523/JNEUROSCI.0744-16.2016
- Van Dyck CH, Seibyl JP, Malison RT, Laruelle M, Wallace E, Zoghbi SS, Zea-Ponce Y, Baldwin RM, Charney DS, Hoffer PB. Age-related decline in striatal dopamine transporter binding with iodine-123-beta-CITSPECT. *J Nucl Med Off Publ Soc Nucl Med*. 1995; 36:1175–1181.
- Wang TH, Johnson JD, de Chastelaine M, Donley BE, Rugg MD. The effects of age on the neural correlates of recollection success, recollection-related cortical reinstatement, and post-retrieval monitoring. *Cereb Cortex N Y N* 1991. 2016; 26:1698–1714. DOI: 10.1093/cercor/bhu333
- Wang, WC., Cabeza, R. Episodic memory encoding and retrieval in the aging brain. In: Cabeza, R., Nyberg, L., Park, DC., editors. *Cognitive Neuroscience of Aging: Linking Cognitive and Cerebral Aging*. 2. Oxford University Press; 2016.
- Wang Y, Chan GL, Holden JE, Dobko T, Mak E, Schulzer M, Huser JM, Snow BJ, Ruth TJ, Calne DB, Stoessl AJ. Age-dependent decline of dopamine D1 receptors in human brain: a PET study. *Synapse N Y N*. 1998; 30:56–61. DOI: 10.1002/(SICI)1098-2396(199809)30:1<56::AID-SYN7>3.0.CO;2-J
- Westlye ET, Lundervold A, Rootwelt H, Lundervold AJ, Westlye LT. Increased hippocampal default mode synchronization during rest in middle-aged and elderly APOE ε4 carriers: relationships with memory performance. *J Neurosci Off J Soc Neurosci*. 2011; 31:7775–7783. DOI: 10.1523/JNEUROSCI.1230-11.2011

- Westphal AJ, Wang S, Rissman J. Episodic memory retrieval benefits from a less modular brain network organization. *J Neurosci*. 2017; 37:3523–3531. [PubMed: 28242796]
- Wong DF, Wagner HN Jr, Dannals RF, Links JM, Frost JJ, Ravert HT, Wilson AA, Rosenbaum AE, Gjedde A, Douglass KH, Petronis JD, Folstein MF, Toung JKT, Burns HD, Kuhar MJ. Effects of age on dopamine and serotonin receptors measured by positron tomography in the living human brain. *Science*. 1984; 226:1393–1396. [PubMed: 6334363]
- Yonelinas AP. The nature of recollection and familiarity: a review of 30 Years of research. *J Mem Lang*. 2002; 46:441–517. DOI: 10.1006/jmla.2002.2864

Highlights

- Examined recollection-related increases in connectivity across three age groups
- Identified age-invariant increases in connectivity with core recollection regions
- With a whole-brain approach, identified age effects on connectivity change
- Relationship between connectivity change and accuracy decreased with increasing age

Figure 1.
Schematic representation of behavioral task.

Figure 2. Recall performance (pR) across young, middle-aged, and older adults. * $p < .05$; ** $p < .01$; *** $p < .001$.

Figure 3.

Successful recollection activity. Regions that exhibit greater activity during successful relative to unsuccessful recollection (Intact pairs judged “Intact” > Intact pairs judged “rearranged”) across age groups. The main effect was height thresholded at $p < .05$, FWE-corrected, voxel extent threshold, $k=20$ and inclusively masked by the simple effect from each age group (inclusive mask threshold of $p < .01$, uncorrected). Peak effects for each of the core recollection regions are projected onto the Caret brains (top) for the angular gyrus (blue), medial prefrontal cortex (green), hippocampus (red), middle temporal gyrus (cyan), and posterior cingulate cortex (magenta). Effects are also rendered onto a coronal slice T1 image at MNI coordinate $y=-19$ (bottom).

Figure 4.

Overlap of regions exhibiting recollection-related changes in activity and connectivity with core recollection regions. Regions exhibiting a main effect of recollection-related increases in activity are shown in blue (main effect height thresholded at $p < .05$, FWE-corrected, voxel extent threshold, $k=20$, inclusively masked by the simple effect of age group, height thresholded at $p < .01$). Regions exhibiting recollection-related increases in connectivity with each of the core recollection regions are shown in green (main effect height thresholded at $p < .05$, FWE-corrected, voxel extent threshold, $k=20$, inclusively masked by the simple effect of age group, height thresholded at $p < .05$). Regions exhibiting both recollection-related increases in activity and connectivity with core recollection regions are displayed in cyan. Angular gyrus (AnG), medial prefrontal cortex (mPFC), hippocampus (Hipp), middle temporal gyrus (MTG), posterior cingulate cortex (PCC).

Figure 5.

Seed-target correlation matrices. Separate correlation matrices for each age group are shown in a) and c) where each column represents a different core recollection seed region, each row represents a different target region, and the color within each cell of the matrix represents the across-participant correlation between recollection accuracy (pR) and recollection-related change in connectivity for each seed-target pair. In a) the rows are the 90 target regions from the AAL atlas, and in c) rows are the 271 target regions based on Power et al., 2011. In b) and d), the average correlation between recollection accuracy and recollection-related change in connectivity is plotted averaged across target regions for each seed region and each age group separately. b) corresponds to the correlation matrices shown in a); d) corresponds to the correlation matrices shown in c). * indicates that the average correlation differs from chance at $p < .01$. Horizontal bars indicate a significant difference between groups at $p < .01$.

Figure 6. Whole-brain recollection-related change in connectivity matrices. Top: from Power et al., 2011, peak coordinates for the whole-brain connectivity analysis. Spheres are color-coded according to their network membership. Bottom: whole-brain connectivity matrices representing the average parameter estimate of recollection-related change in connectivity averaged across participants for the young, middle-aged, and older participants. Cingulo-opercular (C-O), Fronto-parietal (F-P), Core Recollection Network (CRN). *indicates additional ROIs included in the whole-brain connectivity analysis that were not defined by Power et al. (2011) and are not shown on the above rendering.

Figure 7.

Main effect of age group on recollection-related change in connectivity. a) Whole-brain seed-target matrix where the color within each cell represents the F value associated with the main effect of age group on recollection-related change in connectivity for each seed-target pair. b) The associated p-value matrix where seed-target pairs that exhibited a significant main effect of age group on recollection-related change in connectivity at $p < .05$ are shown in black, and all other cells are shown in white. c) Proportion of pairs of regions where the main effect was driven by a positive (increased recollection-related change in connectivity with increased age - blue), negative (decreased recollection-related change in connectivity with increased age - red) or other (recollection-related change in connectivity differed for middle compared to old and young age groups - green) effect. d) To further illustrate the findings in c), for each participant, estimates of recollection-related change in connectivity were averaged across all seed-target pairs that showed a significant main effect of age group on connectivity change. These averages were then residualized, across participants, on covariates of no interest (see Results). The residualized connectivity change estimates are shown here averaged across participants separately for each age group. Error bars represent the across-subject standard error of the mean. ** $p < .01$; † $p < .05$.

Figure 8.

Age by performance interaction on recollection-related change in connectivity. Each panel represents the significance of the beta coefficient associated with the age by performance interaction (β_3) from Model 2 ($y_{\text{connectivity}} = \beta_0 + \beta_1\chi_{\text{age}} + \beta_2\chi_{\text{pR}} + \beta_3\chi_{\text{age}\times\text{pR}} + \beta$ [covariates] + ϵ). a) Whole-brain seed-target matrix where the color within each cell represents the F value associated with the age by performance (pR) interaction on recollection-related change in connectivity for each seed-target pair. b) The associated p-value matrix where seed-target pairs that exhibited a significant age by performance interaction on recollection-related change in connectivity at $p < .05$ are shown in black, and all other cells are shown in white. c) Proportion of pairs of regions where the interaction was driven by a positive (increased relationship between pR and connectivity change with increased age - blue), negative (decreased relationship between pR and connectivity change with increased age - red) or other (the relationship between pR and connectivity change differed for the middle-aged compared to the young and older groups - green) effect. d) To further illustrate these findings, for each participant, estimates of recollection-related change in connectivity were averaged across all seed-target pairs that showed a significant age by performance interaction. The same regression model was then used to predict these average connectivity measures. The residualized connectivity change estimates (y axis) are plotted against pR (x axis) separately for each age group.

Figure 9.

Main effect of age group on recollection-related change in connectivity, controlling for individual differences in recollection accuracy and the accuracy by age group interaction. Each panel represents the significance of the beta coefficient associated with the main effect of age group (β_1) from Model 2 ($y_{\text{connectivity}} = \beta_0 + \beta_1\chi_{\text{age}} + \beta_2\chi_{\text{pR}} + \beta_3\chi_{\text{age}\times\text{pR}} + \beta[\text{covariates}] + \epsilon$). Same as Figure 7 except that in each case, plots represent the main effect of age on recollection-related change in connectivity after controlling for performance (pR) and the performance by age group interaction. ** $p < .01$.

Figure 10.

Relationship between performance (pR) and recollection-related change in connectivity, controlling for age group and the age by accuracy interaction. Each panel represents the significance of the beta coefficient associated with the main effect of performance (β_2) from Model 2 ($y_{\text{connectivity}} = \beta_0 + \beta_1\chi_{\text{age}} + \beta_2\chi_{\text{pR}} + \beta_3\chi_{\text{ageXpR}} + \beta[\text{covariates}] + e$). a) and b) represent the F and p statistics associated with the pR beta coefficient from Model 2, respectively. c) Proportion of positive effects (increased connectivity change associated with better performance; blue) and negative effects (increased connectivity change associated with worse performance; red). d) For each participant, the estimates of connectivity change were averaged across all seed-target pairs that exhibited a significant effect of performance and entered into the same regression model (Model 2) to predict average connectivity change. The residualized connectivity estimates (y axis) are plotted against performance (x axis) for all participants.