Age-differences in functional asymmetry during memory retrieval revisited: no evidence for contralateral over-activation or compensation

Running title: Age-differences in asymmetry during retrieval

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Abstract

Brain asymmetry is inherent to cognitive processing and seems to reflect processing efficiency. Lower frontal asymmetry is often observed in older adults during memory retrieval, yet it is unclear whether lower asymmetry implies an age-related increase in contralateral recruitment, whether less asymmetry reflects compensation, is limited to frontal regions, or predicts neurocognitive stability or decline. We assessed age-differences in asymmetry across the entire cerebral cortex, using fMRI data from 89 young and 76 older adults during associative retrieval, and surface-based methods that allowed direct homotopic comparison of activity between hemispheres. An extensive left-asymmetric network facilitated retrieval in both young and older adults, whereas diverse frontal and parietal regions exhibited lower asymmetry in older adults. However, lower asymmetry was not associated with age-related increases in contralateral recruitment, but primarily reflected either less deactivation in contralateral regions reliably signalling retrieval failure in the young, or lower recruitment of the dominant hemisphere. Lower asymmetry neither predicted current memory performance, nor the extent of memory change across the preceding ~8 years in older adults. Together, these findings are inconsistent with a compensation account for lower asymmetry during retrieval and aging, suggesting that patterns indicative of decline may drive lower asymmetry in older brains.

Keywords:

Aging; compensation; fMRI; HAROLD; hemispheric asymmetry; retrieval

1. Introduction

Episodic memory decline is a hallmark of neurocognitive aging (Park and Reuter-Lorenz 2009; Josefsson et al. 2012). Hence, understanding how alterations in brain functioning relate to aging and memory performance is a major research goal (Grady et al. 2006; Reuter-Lorenz and Park 2010; Spreng et al. 2010; Grady 2012; Nyberg et al. 2012; Fjell et al. 2014). Lower functional asymmetry has been consistently observed in specific cortical regions in older relative to younger adults during memory tasks (Cabeza, 2002), and it has been proposed this may support optimal memory performance in older adults (Cabeza et al. 2002). However, whether older age is associated with more anatomically widespread differences in asymmetry during memory processing, and the impact of age-related asymmetry differences upon memory performance, remain open questions. The purpose of the present study was to identify age-differences in asymmetry across the entire cerebral cortex during successful source memory retrieval, assess asymmetry relationships with current memory performance, and assess whether asymmetry may be a marker for memory preservation or decline over time in neurocognitive aging.

Functional asymmetry is thought to support processing efficiency (Hellige 1993; Ringo et al. 1994; Corballis 2009; Ocklenburg and Güntürkün 2012; Gotts et al. 2013). Previous evidence indicates that prefrontal asymmetry is lower in older adults during episodic memory retrieval tasks (Bäckman et al. 1997; Cabeza et al. 1997, 2002, 2004; Madden et al. 1999; Rossi et al. 2004), and such findings have been generalised within the Hemispheric Asymmetry Reduction in OLDer adults model (HAROLD). Although various theories have been proposed to account for this (Li et al. 2001; Cabeza 2002; Reuter-Lorenz 2002; Reuter-Lorenz and Park 2010; Cabeza and Dennis 2012), most agree that the phenomenon reflects diminished processing efficiency at higher age, such that older brains are less able to rely on asymmetric processing strategies. Arguably the most influential (Cabeza et al. 2005; Reuter-Lorenz and

Lustig 2005; Bishop et al. 2010; Grady 2012), the compensation view proposes that older adults recruit additional resources from the contralateral/subdominant hemisphere to cope with a declining ability of the dominant hemisphere to meet memory demands (Cabeza 2002; Cabeza et al. 2004; Cabeza and Dennis 2012). In line with this, most of the reported age-differences in asymmetry during retrieval-related processing (Bäckman et al. 1997; Cabeza et al. 1997, 2002; Madden et al. 1999; Grady et al. 2002) and successful retrieval (Cabeza et al. 2004; Rossi et al. 2004) appear to show an apparent age-related increase in contralateral prefrontal recruitment, and have consequently been predominantly interpreted as compensatory (Cabeza 2002; Cabeza and Dennis 2012; Grady 2012; Wang and Cabeza 2017).

This interpretation is often reinforced when contralateral recruitment has a beneficial effect on memory performance, either across the group of older adults as a whole, or within low-performing elders thought to rely more on compensation to maintain performance (Morcom and Johnson 2015; Cabeza et al. 2018). However, reported relationships between contralateral recruitment and cognitive function – including memory retrieval – remain highly inconsistent (Eyler et al. 2011; Grady 2012). Furthermore, high stability of individual differences in cognitive function across the lifespan (Deary et al. 2004; Hansen et al. 2014) challenges the assumption that low-performing older adults have undergone the most age-related decline (Rugg 2017). As a result, it is unclear whether lower asymmetry may be a marker for memory preservation or decline with advanced age.

Because the term compensation has typically been invoked to describe instances of enhanced brain activity in older adults (Cabeza et al. 2018; in review), the compensation view of HAROLD arguably places greater emphasis (implicitly or otherwise) on contralateral over-recruitment in driving lower asymmetry effects in older brains. Yet, as noted by others

(Cabeza 2002), lower asymmetry does not necessarily imply greater contralateral recruitment, because insufficient engagement of the ipsilateral/dominant hemisphere could also amount to less asymmetry. Thus, to better understand the role of asymmetry change in aging, one should evaluate asymmetry across large samples in a manner that comprehensively assesses each hemisphere's contribution to the observed age-differences in asymmetry.

In part due to methodological challenges in comparing activity between cerebral hemispheres that are anatomically asymmetric, most of the memory literature has focused on age-differences in prefrontal asymmetry (cf. Berlingeri et al. 2013), and delineated target areas using a region-of-interest approach (Wilke and Lidzba 2007). Although often useful, such an approach limits the study of age-differences in memory-asymmetries to specific brain regions. Further, because hemispheric comparisons are usually informed by qualitative differences in the brain activation patterns of young and older adults, important questions have been overlooked, such as to what extent age-differences in asymmetry are only partial (i.e. reflect only gradual differences in asymmetry; Westerhausen et al. 2014), or whether less asymmetry is also evident in regions that are recruited bilaterally (Cabeza and Dennis 2012). Additionally, because contrasts used to delineate retrieval-related activity have not always isolated activity associated with successful retrieval (Bäckman et al. 1997; Cabeza et al. 1997, 2002; Madden et al. 1999), it is unclear whether putative age-related over-recruitment of the contralateral hemisphere is indicative of higher memory success effects, or reduced negative success effects (i.e. lower retrieval failure effects). To address these questions, it is necessary to rely on an unbiased procedure that allows direct hemispheric comparisons across the entire cortical mantle.

Finally, evidence suggests successful retrieval is associated with a predominantly left-lateralized cortical network (Morcom et al. 2007; McDermott et al. 2009; Spaniol et al. 2009; Kim 2010, 2016; Vidal-Piñeiro et al. 2017). Hence, left-lateralization may represent a prominent feature of retrieval networks, possibly reflecting the relevance of verbal or verbalizable components (McDermott et al. 2009; Spaniol et al. 2009). Given the decline in source memory as we age (Anderson et al. 2008; Cansino et al. 2013), the expected relationship between memory ability and isolated memory success activity (Rugg 2017), and putative reductions in retrieval-asymmetry in older adults, source memory retrieval represents an ideal task to assess age-differences in asymmetry and their relation to neurocognitive aging.

Here, we directly investigated age-differences in functional asymmetry across the entire cerebral cortex during source memory retrieval, using an fMRI task with data from a large sample of participants. Briefly, after first isolating activity associated with source memory success, we delineate asymmetry via surface-based analyses that directly contrast homotopic activity between the cortical hemispheres, applying an unbiased symmetrical template (Greve et al. 2013; Maingault et al. 2015; Tobyne et al. 2016; Greve and Fischl 2017). The main objectives of the study were two-fold.

First, to investigate support for the compensation view of HAROLD, we aimed to 1) examine whether global differences in asymmetry are apparent in older relative to younger adults during retrieval, 2) assess whether the pattern of lower asymmetry is indicative of greater contralateral recruitment in older adults relative to the young, and 3) test whether lower asymmetry predicts current memory performance. The conditions to interpret the data within a neural compensation framework were pre-established; in line with recently published guidelines (see Cabeza et al. 2018; in review), we resolved that support for neural

compensation would require 1) evidence of enhanced brain activity in older adults in 2) the form of greater contralateral recruitment relative to the young, and 3) evidence that lower asymmetry has a beneficial effect on current memory performance.

Second, we aimed to test whether the extent of asymmetry — as a putative proxy for processing efficiency — may be a marker for memory preservation or decline in neurocognitive aging, using multi-timepoint longitudinal data obtained over the ~8 year period prior to scanning in older participants.

2. Materials & methods

2.1 Participants

Participants were drawn from the third waves of ongoing longitudinal projects coordinated by the Center for Lifespan Changes in Brain and Cognition (Department of Psychology, University of Oslo) for which task fMRI data were available: *Cognition and Plasticity through the Lifespan* (Sneve et al. 2015; Vidal-Piñeiro et al. 2017) and *Neurocognitive Development* (Tamnes et al. 2018). The sample consisted of 165 participants, of which 89 were young aged 18-39 (56 female, mean age = 26.8 [standard deviation (SD) = 5.0], age range = 18.5 - 38.9 years) and 76 were older aged 60 and above (40 female, mean age = 67.9 [SD = 5.2], age range = 60.2 – 80.8 years). Additionally, for 54 of the older participants, longitudinal cognitive data spanning back ~8 years were available. 51 of these had data from all three waves, whereas 3 participants were recruited at wave 1 and again at wave 3 (mean years between wave 1 and 3 = 7.7 [SD = 0.9]).

All participants were fluent in Norwegian, reported normal or corrected-to-normal hearing and vision, and no motor difficulties. All reported no history of neurological or psychiatric disorders, and none were taking any medication known to affect CNS functioning. Participants were required to be right-handed, have a score of <16 on the Beck Depression

Inventory (Beck et al. 1961), and score a normal IQ (≥ 85) on the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler 1999), although fMRI data for eight young participants with missing neuropsychological data was also included. Additionally, older participants were required to score ≥ 25 on the Mini Mental Status Exam (MMSE; Folstein et al. 1975), a normative score of t ≥ 30 on the California Verbal Learning Test (CVLT; Delis et al. 1987) encoding and 30 minute delayed recall, and to have recalled ≥ 10% of trials with source memory (see Supplementary Table 1 for sample descriptives and neuropsychological data). For inclusion in longitudinal analyses, CVLT data from the first wave of data collection were required to meet the same criteria. All provided written informed consent, and the study received approval from the Regional Ethical Committee of South Norway. Participants were paid for their participation.

2.2 Experimental Design

The experiment consisted of an incidental source memory encoding task, and a surprise memory test after ~90 minutes. Both encoding and retrieval phases were performed in the MRI scanner. At encoding, participants were asked to decide whether a particular action (either “can you lift it?” or “can you eat it?”) could be performed on an item, and were later tested on their memory for these item-action associations under a test phase occurring ~1.5 hours later. The entire experiment consisted of 2 incidental encoding runs and 4 test runs, and has been thoroughly described elsewhere (Sneve et al. 2015; Vidal-Piñeiro et al. 2017). Only fMRI data from the test phase is used here. Briefly, encoding stimuli consisted of 100 monochromatic line drawings (50 per run) depicting everyday objects and items (Fig. 1; left). At encoding, each question (lift/eat; aurally presented by a female voice in the Norwegian language) was presented 25 times per run in a pseudorandom order, and one second after question onset, an image of an item was presented on screen together with a response indicator that instructed participants which button to press to respond with a ‘yes’ [the item

can be lifted/eaten] or ‘no’ [the item cannot be lifted/eaten]. Button-response mapping was counterbalanced and participants had the 2 seconds (s) stimulus duration to respond.

Approximately 90 minutes later participants received a surprise memory test, where each of the 100 ‘old’ items were tested intermixed with 100 new ‘foils’ in an event-related fMRI paradigm. Each of the 4 test runs consisted of 25 ‘old’ mixed with 25 ‘new’ items, presented in a pseudorandom order. All runs started and ended with a 11s baseline recording period in which a black central fixation-cross was presented against a white background. An additional baseline period was presented once in the middle of each run. A test trial began with the same female voice asking the Norwegian equivalent of: “Have you seen this item before?” This constituted the first question (Q1) in a three-question procedure (see Fig. 1), where progression to the next question was contingent upon a ‘yes’ response to the previous. 1s after question onset, an item appeared on screen together with the response indicator. For Q1, participants were to respond either ‘yes’ [I saw the item during the encoding phase] or ‘no’ [I did not see the item during the encoding phase] within the 2s duration the stimulus remained on screen. A ‘no’ response (or a missed response) to Q1 ended the trial. A fixation-cross remained on screen throughout the following inter-trial interval (ITI), which lasted for 1-7s (exponential distribution over four discrete intervals; ITI order tentatively optimized using optseq2 (http://surfer.nmr.mgh.harvard.edu/optseq/)). If the participant believed they remembered seeing the item (responded ‘yes’), the trial proceeded to the second question (Q2): “Do you remember what you were asked to do with it?”. A ‘no’ response to Q2 ended the trial. A ‘yes’ response indicated that the participant remembered the associated action, and prompted the final two-alternative forced-choice control question (Q3): “Were you asked to lift it or eat it” [I was asked whether the item was liftable/edible during the encoding phase]. Q2 was thus included to dissuade per-item guessing behaviour prior to the control question.

Memory was then determined for each old item according to each participant's response at test.

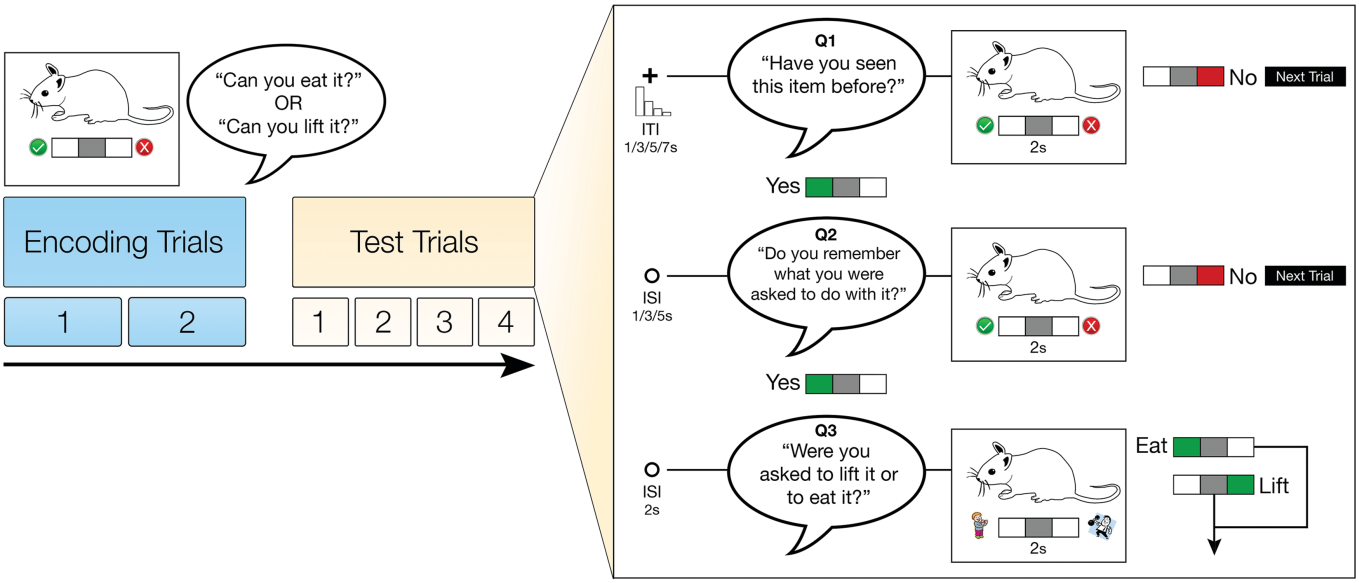

Figure 1. Experimental paradigm. Participants underwent 100 incidental encoding trials (2 fMRI runs) and were tested for memory for item + action (lift/eat) associations (4 fMRI runs) ~1.5 hours later. At test, old items were randomly mixed with 100 new items. The fMRI retrieval paradigm consisted of a three-question (Q1-Q3) procedure (2s duration per Q) where progression to the next was contingent upon a 'Yes' response to the previous. Q3 consisted of a two-alternative forced choice between actions (lift/eat). The trial ended on 'No' responses to Q1 or Q2. Response cues were present on screen, and button response mapping was counterbalanced across participants. ITI/ISI = Inter-trial/-stimulus interval, respectively

2.3 Behavioural analysis

Test trial responses to old items were behaviourally classified as follows: (1) *source memory* ('yes' response to Q1 and Q2, and correct response to Q3); (2) *item-only memory* (correct 'yes' response to Q1 and either a 'no' response to Q2 or incorrect response to Q3); or (3) *miss* (incorrect 'no' response to Question 1). New items were classified either as correct rejections or false alarms based on the response at Q1. Although the three-question procedure was optimised to disentangle true source memories from item-only and missed memories, it nevertheless remained possible to achieve 100% source memory given straight "yes" responses to all three questions on all trials. Thus, the raw percentage of source

memory hits was corrected for by subtracting the number of incorrect responses at Q3 (source memory – incorrect source memory). This correction tentatively controls for individual differences in false source memories, threshold criteria at Q2, or guessing behaviour that affects raw source memory estimates (Vidal-Piñeiro et al. 2017). All behavioural analyses were performed in R (https://www.r-project.org; v. 3.3.2), and Bonferroni correction was applied where appropriate, as indicated.

2.4 MRI acquisition and equipment

All functional and anatomical images were acquired on a Siemens Skyra 3T scanner using a Siemens 24-channel head coil (Siemens Medial Solutions, Germany) at Rikshospitalet, Oslo University Hospital. Functional data were acquired using a BOLD sensitive T2*-weighted EPI sequence, with equivalent acquisition parameters across all fMRI runs; each EPI volume consisted of 43 transversally-oriented slices taken using interleaved acquisition (no gap) acquired with the following parameters: TR = 2390ms; TE = 30ms; flip angle = 90°; voxel size = 3 x 3 x 3mm, FOV = 224 x 224mm; GRAPPA acceleration factor = 2). At the onset of each run, 3 dummy volumes were taken to account for a potentially imperfect flip angle due to T1 saturation effects, and were subsequently discarded. The mean number of volumes per retrieval run was 208.

Anatomical T1-weighted magnetization prepared gradient echo (MPRAGE) scans composed of 176 sagittally-oriented slices were acquired using a turbo-field echo pulse sequence with the following parameters: TR = 2300ms, TE = 2.98ms, flip angle = 8°, voxel size = 1 x 1 x 1mm, FOV = 256 x 256mm. Additionally, a standard double gradient-echo field map sequence was acquired for distortion of the echo planar images. Stimuli were presented on a NNL 32” LCD screen (resolution = 1920 x 1080px; NordicNeuroLab, Norway) viewed through a mirror mounted onto the scanner head-coil (176cm from mirror to screen). Auditory stimuli

were presented via the scanner intercom to participant headphones, and responses were given using the ResponseGrip system (NordicNeuroLab). All stimuli were presented using E-Prime 2.0 stimulus presentation software (Psychology Software Tools, PA), and stimulus presentation was synchronised with MRI image acquisition via a NNL SyncBox (NordicNeuroLab).

2.5 MRI preprocessing

Cortical reconstruction and volumetric segmentation of the T1-weighted anatomical images was performed using Freesurfer 5.3 (http://surfer.nmr.mgh.harvard.edu/; Dale et al. 1999; Fischl et al. 1999; Fischl and Dale 2000). Briefly, this automated pipeline included motion correction, removal of non-brain tissue, Talairach transformation, intensity normalisation, demarcation of grey/white and grey/CSF boundaries at the locations where the greatest intensity shifts reflect the transition between tissue classes, and inflation of the cortical surface (Fischl, Sereno, and Dale 1999b; Fischl, Sereno, Tootell, et al. 1999).

fMRI data was preprocessed using a combination of FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki) and Freesurfer Functional Analysis Stream (FSFAST; https://surfer.nmr.mgh.harvard.edu/fswiki/FsFast). First, using FSL's fMRI Expert Analysis Tool functional images were corrected for distortions caused by B0 inhomogeneities in EPI scans, slice-timing corrected to the middle TR in the volume, high-pass filtered with a cutoff of 0.01Hz, and smoothed in volume space (5mm FWHM). Next, FSL´s Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) was used together with FMRIB´s ICA-based Xnoiseifier (FIX) tool, applying a custom training file (28 participants aged 18-80) to auto-classify components into "good" and "bad" components, and remove the bad components from the 4D data (Salimi-Khorshidi et al. 2014). Such ICA-based procedures for denoising fMRI data have been shown to effectively reduce motion-induced variability, outperforming methods based on removing motion spikes (Pruim et al.

2015). Functional datasets were then intensity normalised and resampled to the reconstructed cortical hemispheres of each individual subject, and smoothed in 2D surface space (8mm FWHM) prior to first-level statistical analyses.

2.6 fMRI analysis

2.6.1 First-level fMRI analysis

Each of the 100 encoding items was assigned to a condition/regressor based on the memory condition classified at test. A first-level GLM was set up modeling the onset times and stimulus durations (2s) for each retrieval regressor through convolution with a double-gamma canonical hemodynamic response function. The task regressors-of-interest were: *source memory* (item correctly remembered with associated action) and *miss* trials (item not remembered). Each regressor-of-interest modelled the onsets and durations corresponding to the initial stimulus presentation within the three-question procedure (i.e. Q1). A set of nuisance regressors were included to account for BOLD variance of non-interest, and included regressors for trials classified as item-only memory (item correctly remembered/recognised without associated action) and trials where stimuli could not be classified into a memory condition (due to failure to respond at any question). Additional regressors were included to model the BOLD response at Q2 and Q3, false alarms and correctly rejected new items. The temporal derivatives of all regressors were included to improve model fit, as well as a set of polynomial nuisance regressors (up to the order of 2), and temporal autocorrelations in the model residuals were corrected using pre-whitening. For each individual, a contrast of parameter estimates was computed for further analysis, consisting of *source memory v. miss* conditions (*source memory success* contrast).

2.6.2 Asymmetry approach

The first-level analyses were performed on the reconstructed cortical left and right hemispheres of each participant, and thus respected the individual cortical geometry of each subject. We then leveraged the symmetrical template that exists in Freesurfer (fsaverage_sym) to apply reregistration between the left and right cortical surfaces of each individual, and the *left* hemisphere of the symmetrical template. This allowed mapping of the first-level data from both hemispheres into a common analysis space. Crucially, given the symmetry of the template, the mapping was not biased to the cortical geometry of either hemisphere (Greve et al. 2013). See Figure 2 for a schematic illustration of the symmetrical registration (note the 'flipping' of right hemisphere data to the left symmetrical surface; bottom right). Next, the contrast maps in symmetrical space were fed into second-level group analyses.

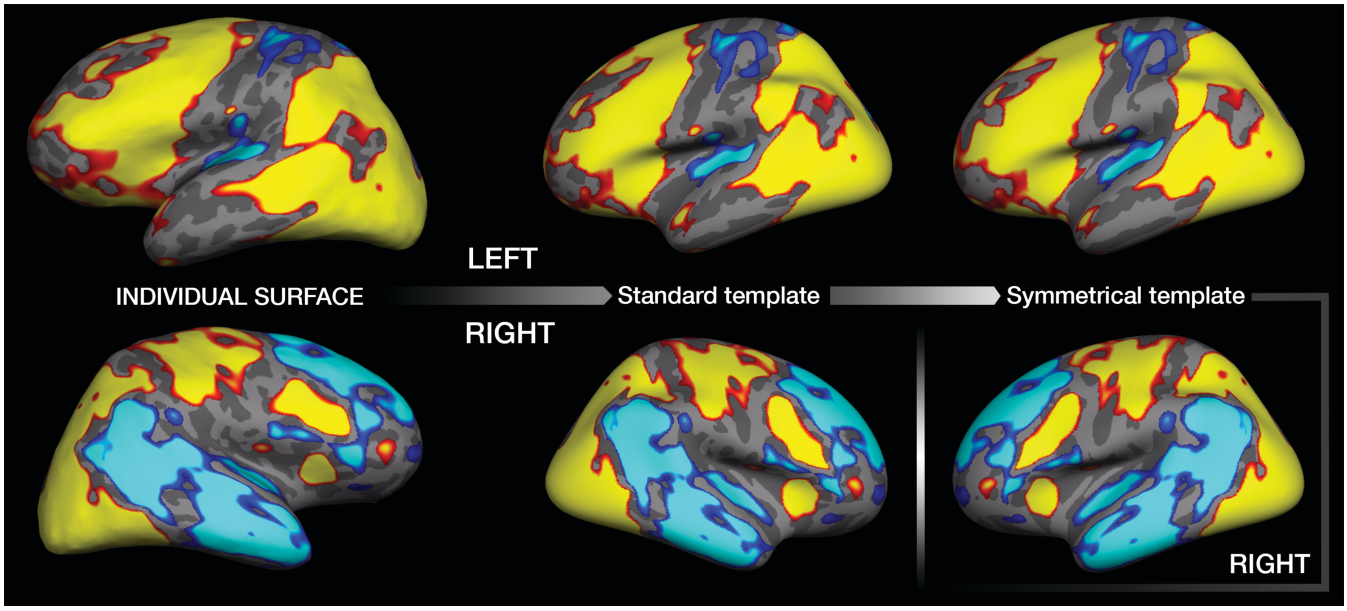

Figure 2. Single subject reregistration example. First level analyses were performed on the individual's reconstructed cortical surface (left panel) and the results were subsequently reregistered to the standard symmetrical template provided by Freesurfer (fsaverage_sym; right panel) prior to group-level analyses. Data corresponding to the left and right hemispheres are shown in the top and bottom panels, respectively. For visual comparison only, data is also shown reregistered to the non-symmetrical standard template (fsaverage; middle panel), although at no point was this used during processing. Note the 'flipped' right

hemisphere data after reregistration to the left symmetrical template (bottom right panel). Data is shown for visualisation purposes only.

2.6.3 Conventional fMRI analysis

Firstly, we performed vertex-wise group analyses following a conventional approach — that is, analyses were performed separately for each hemisphere — but within the symmetrical space. Group-level estimates for mean BOLD activity were computed on the cortical surface for 1) *Left* hemisphere (LH) source memory success activity in *Young*, 2) *Right* hemisphere (RH) source memory success activity in *Young*, 3) *LH* source memory success activity in *Old*, and 4) *RH* source memory success activity in *Old*. Ordinary least squares GLM analysis was performed for each, controlling for age and corrected source memory performance.

2.6.4 fMRI asymmetry analysis

Having brought the data from each hemisphere into the symmetrical analysis space, age-differences in asymmetry between young and older adults could be directly assessed via whole-cortical comparisons of homotopic activity on a vertex-wise basis. Here, individual cortical maps were fed into a mixed-effect 2 (Age-Group: young vs. old) × 2 (Hemisphere: left vs. right) ANOVA design, where group differences in brain activation asymmetry were tested with the Age-Group × Hemisphere interaction.

To better delineate the patterns of activity from the resulting interaction effects, the resulting clusters were split according to whether both hemispheres showed positive memory effects, negative memory effects, or whether the direction of the effect differed between the hemispheres. This approach allowed us to avoid averaging activity across functionally heterogeneous clusters. Here, we performed an interhemispheric conjunction analysis on the resulting clusters from the Age-Group × Hemisphere analysis (following correction and statistical thresholding; see below). For each hemisphere we computed the mean young and

old *source memory v. miss* simple effect size map, binarised the maps on positive or negative values, and performed whole-cortical left × right multiplications of the binary maps to identify regions that on average exhibited positive effects in both hemispheres, negative effects in both hemispheres, or differential effects across hemispheres (i.e. positive in one and negative in the other). This approach yielded 9 functionally distinct ROI's (>25 vertices). Importantly, as the ROI identification was based on the mean activation across age-groups, the signal change within ROI's could be meaningfully compared between groups. Signal change was then extracted after averaging across all vertices in each ROI per participant, to describe the patterns underlying the Age-Group × Hemisphere interaction in post-hoc analyses.

Further analyses performed on the cortical surface investigated the separate main effects of Hemisphere and Age-Group in the mixed-effect design. The effect of hemisphere within both young and older adults was further explored via separate paired post-hoc *t*-tests (*left v. right*). This was performed to assess the degree of overlap in cortical activation patterns showing an asymmetry effect between young and old age-groups. Dice Similarity Coefficient was employed to compute the overlap (Crum et al. 2006).

Finally, since the main effect of Hemisphere does not differentiate between sites of absolute (i.e. significant effects only in one hemisphere) and relative asymmetry (i.e. significant effects in both hemispheres but significantly greater in one; Westerhausen et al. 2014), we performed post-hoc analyses to isolate absolute from relative asymmetry effects. Here, the mean RH activation map was calculated across age-groups, and a conjunction analysis was performed between the RH significance map and the significance map for the main effect of Hemisphere where the effects were positive (i.e. showed significantly greater effects in LH). The resulting map revealed cortical regions showing relative asymmetry, where both left and

right homotopic cortex exhibited significant memory effects but where the effects in LH were still significantly greater.

For all cortical analyses, statistical significance was tested on a vertex-wise basis. The resulting maps were then corrected for multiple comparisons using cluster-based methods; vertices were thresholded at $p < 0.01$ and the remaining clusters were tested through non-parametric permutation inference across 10,000 iterations (PALM; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/PALM; Winkler et al. 2014). Cluster significance was then considered at a family-wise error-corrected level of $p < 0.05$ (two-sided).

2.6.5 Asymmetry relationships with current memory performance

Next, we tested whether the magnitude of asymmetry was associated with source memory performance on the fMRI task. For each participant we computed an asymmetry metric by subtracting the right from the left signal change (LH - RH). Since ROI analyses revealed consistently higher activation in the left hemisphere relative to the right, higher values corresponded to a greater leftward asymmetry. In ROI's that were positively activated in LH and deactivated in RH, this asymmetry index reflected the span between positive LH and negative RH activation. The relationship between asymmetry and source memory performance was then tested for each ROI separately for young and old age-groups, with linear regression models controlling for age and sex. In addition, in line with the current opinion that compensation is not necessarily expected to be prevalent in older high-performers, we tested the view that compensatory brain responses may instead be most prominent in older participants with the greatest need (Cabeza and Dennis 2012; Morcom and Johnson 2015; Cabeza et al. 2018). Here, we post-hoc tested these relationships separately within low and high performing older participants, splitting the old sample by median corrected source memory performance.

2.6.6 Asymmetry relationships with longitudinal memory change

We next performed longitudinal analyses using a subset of older participants (N=54) to assess whether the extent of functional asymmetry in ROI's showing age-differences in asymmetry could be predicted by the degree of memory change exhibited across the preceding ~8 years. Longitudinal memory change was estimated using data from multiple timepoints (Tp's) in a memory task where performance was highly correlated with memory on our fMRI task (CVLT delayed recall). This was done via a 3-step procedure: 1) the intercept and slope of the linear model of age (years since Tp1) on raw delayed CVLT score was calculated for each participant; 2) the slopes of participants were modeled as a linear function of chronological age, partialling out the effects of sex (to account for differences in memory rates-of-change; Josefsson et al. 2012) and baseline performance at Tp1; 3) residuals were calculated for the slopes of each participant relative to this model, resulting in a continuous measure reflecting the deviation in predicted longitudinal memory change relative to age and baseline memory performance. The residuals from the model were considered as a proxy for memory change. Linear regressions between asymmetry (see previous section) and memory change were then computed for each ROI.

Finally, we computed the estimated effect size for memory change upon asymmetry that would be detectable by our current sample size via a posteriori sensitivity analysis using G*power 3.1 ($\alpha = 0.05$, $\beta = 0.80$; Faul et al. 2007).

2.6.7 Control analysis

As a final step, we performed vertex-wise analyses to test whether older adults, relative to young adults, exhibit more bilaterality in trials associated with their source memory hits than trials associated with their source memory misses. If so, this may be indicative of an interhemispheric compensation in older adults that aids task performance. Here, the raw parameter estimates associated with source memory hits (versus the implicit fixation

baseline) and source memory misses (vs. baseline) as modelled by the first-level GLM (and computed on the reconstructed cortical hemispheres of each participant) were fed into group-level analyses, again after reregistering the data from each individual and hemisphere to the symmetrical space (see section 2.6.2). Individual maps in symmetrical space were then fed into a mixed-effect 2 (Age-Group: young vs. old) × 2 (Hemisphere: left vs. right) × 2 (Source: hit vs. miss) ANOVA, where group differences in asymmetry between *source memory hit* and *source memory miss* activity were tested via the Age-Group × Hemisphere × Source interaction. All control analyses followed the statistical correction procedures outlined previously. Next, we performed additional vertex-wise analyses to confirm that asymmetry was specifically associated with source memory hits in each age-group: individual maps were fed into separate 2 (Hemisphere: left vs. right) × 2 (Source memory: hit vs. miss) repeated-measures ANOVA's, performed separately for each age-group. The Hemisphere × Source memory interaction in each revealed cortical regions exhibiting differential asymmetry depending on source memory outcome in each age-group. To explore the underlying effects, a set of exploratory ROI's were created based on four local maxima significance peaks within the resulting interaction clusters for the older age-group (each single peak vertex dilated across 15 iterations), and the effects were plotted for each age-group, hemisphere and source memory condition (i.e. *hits* and *misses*). Such an approach is useful for describing activity patterns across multiple conditions but should be reserved for exploratory purposes (Poldrack 2007). For the present analysis – where the resulting clusters showed both high overlap between age-groups, and high similarity to previous analyses – this approach was considered descriptively useful to illustrate whether functional asymmetry was specific to source memory hits, and thus related to success on the memory task.

3. Results

3.1 Behavioural results

Following correction for the percentage of incorrect source memories (source memory hits minus incorrect source memories; see Table 1 to compare with raw source memory hits), young participants remembered on average 48.6% (± SD 13.5%) trials with source memory, whereas older participants remembered on average 28.4% (± 17.5%) trials with source. Source memory was significantly above chance level (0 post-correction) in both young ($t(88)= 34.0$, $p < 10^{-16}$) and older age-groups ($t(75) = 14.1$, $p < 10^{-16}$), and older participants remembered significantly fewer trials with source than the young ($t(163) = -8.3$, $p = 10^{-14}$, Cohen's d (d) = -1.3). For item-only memories (remembered without associated action), the difference between young (18.8% ± 6.6%) and older (21.2% ± 9.0%) participants was not significant ($t(163) = 1.9$, $p = 0.06$), and the number of forgotten items was also not significant between young (M = 22.3% ± 9.7%) and older adults (M = 25.1% ± 11.3%; $t(163) = 1.7$, $p = 0.10$). Additionally, the percentage of incorrect source memories (incorrect responses to Q3 for 'old' items) was significantly greater in older participants (M = 14.8% ± 7.7%) relative to young (M = 5.8% ± 5.2%; $t(163) = 8.8$, $p = 10^{-15}$, $d = 1.4$). See Table 1 for full behavioural statistics.

Table 1
fMRI task behaviour

Behavioural measures	Young ($\bar{x}$ [sd])	Old ($\bar{x}$ [sd])	Old v Young (T [p])	Effect (d')
Source memory (corrected)	48.6 (13.5)	28.4 (17.5)	-8.3 ($2.9e^{-14}$)*	-1.3
Source memory (raw)	54.4 (12.1)	43.2 (13.4)	-5.7 ($6.5e^{-8}$)*	-0.9
Incorrect source memory	5.8 (5.2)	14.8 (7.7)	8.8 ($2.2e^{-15}$)*	1.4
Item-only	18.8 (6.6)	21.2 (9.0)	1.9 (0.06)	0.3
Miss	22.3 (9.7)	25.1 (11.3)	1.7 (0.1)	0.3
Correct rejection	93.6 (5.4)	87.5 (8.7)	-5.5 ($1.8e^{-7}$)*	-0.9
False alarm	4.5 (3.4)	7.2 (4.8)	4.2 ($3.6e^{-5}$)*	0.7
Recognition (corrected)	14.4 (6.7)	14 (7.9)	-0.3 (0.7)	-0.1
Recognition d'	2.5 (0.5)	2.1 (0.5)	-5.6 ($1.0e^{-7}$)*	-0.9

Table 1. Main behavioural measures from the fMRI memory task and results from *Old v. Young t*-tests for each measure (*Bonferroni corrected at $p < [0.05/9]$ 0.006). Source memory (corrected) = Source memory (raw) – Incorrect source memory; Recognition (corrected) = Item-only – False alarms.

3.2 Conventional fMRI analysis: Exploring hemispheric effects irrespective of asymmetry

Vertex-wise analyses of the BOLD response associated with source memory success were first conducted separately for each hemisphere and age-group, following a conventional approach. Significant activation was observed in a widespread cortical network of the LH in both young and older age-groups (Fig. 3; top row). Specifically, lateral regions of LH activation were observed encompassing large portions of frontal, middle temporal, and inferior and superior parietal cortex, whereas left medial sites included occipital, posteromedial parietal and superior frontal regions. Similar activation maps were obtained in the RH (Fig. 3; bottom row), albeit to a seemingly lesser degree, particularly in frontal and temporal regions. Dice similarity coefficient (DSC) revealed that cortical regions exhibiting significant positive source memory success effects were highly similar between young and older participants in both LH (DSC = 0.89) and RH (DSC = 0.79). In contrast, cortical regions exhibiting significant negative source memory success effects were only evident in young participants. These negative memory effects were encompassed within regions including bilateral supramarginal gyrus, superior temporal and insular cortices.

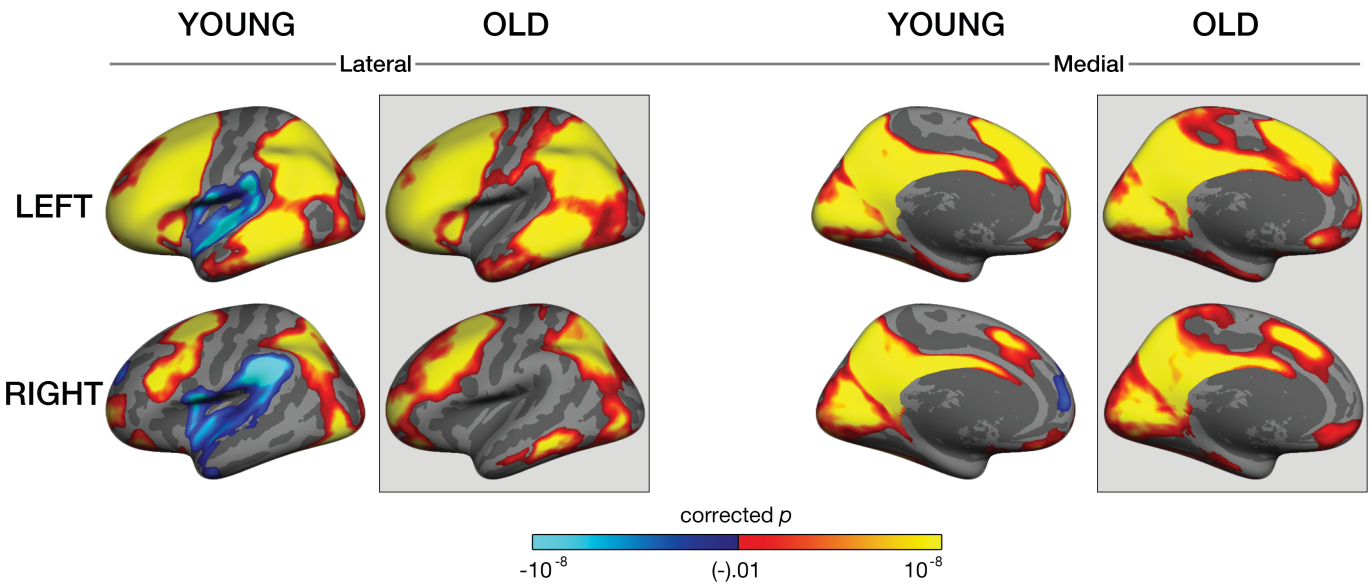

Figure 3. Results from conventional fMRI analyses performed separately by hemisphere for young and older adults. All group analyses were performed within the symmetrical space (the left symmetrical surface). Note that the data from both left (top panel) and right (bottom panel) hemispheres is registered to the left symmetrical surface.

3.3 fMRI Asymmetry analysis

Next, we directly tested for differences in functional asymmetry across the whole cortex between young and older adults. A mixed-effect ANOVA revealed three clusters showing a significant Age-Group × Hemisphere interaction, indicating group differences in brain asymmetry (Fig. 4A). The significant clusters were localised in the lateral frontal, the supramarginal and the superior parietal cortices. An interhemispheric conjunction analysis revealed that these clusters consisted of 9 functionally distinct regions (Fig. 4B), which constituted the ROI's for post-hoc analysis. Of these, 4 showed positive effects in both hemispheres (middle frontal, precentral, superior parietal and superior supramarginal cortex), 4 showed differential effects across hemispheres (i.e. positive in one and negative in the other; pars triangularis and opercularis of the inferior frontal gyrus, and two regions in supramarginal gyrus), and 1 showed negative effects in both hemispheres (anterior supramarginal gyrus). Significant age-differences in asymmetry remained after partialling out

between-subject differences in source memory performance and sex in all except one ROI (precentral gyrus).

In all 9 ROI's, descriptive plots revealed that the interaction between Age-Group and Hemisphere pertained to markedly lower asymmetry in older adults relative to the young. We observed higher activation of the left –vs. right-hemisphere in all ROI's (Fig. 4C,D). Subsequent *left v. right* paired *t*-tests revealed that left-dominant functional asymmetry was present in both young and older participants in all but one ROI (not in anterior supramarginal in old), and the difference between left and right activation magnitude was typically reflected by large effect sizes (see Table 2). Thus, functional asymmetry was nevertheless also present in older participants in these regions, but to a lesser extent.

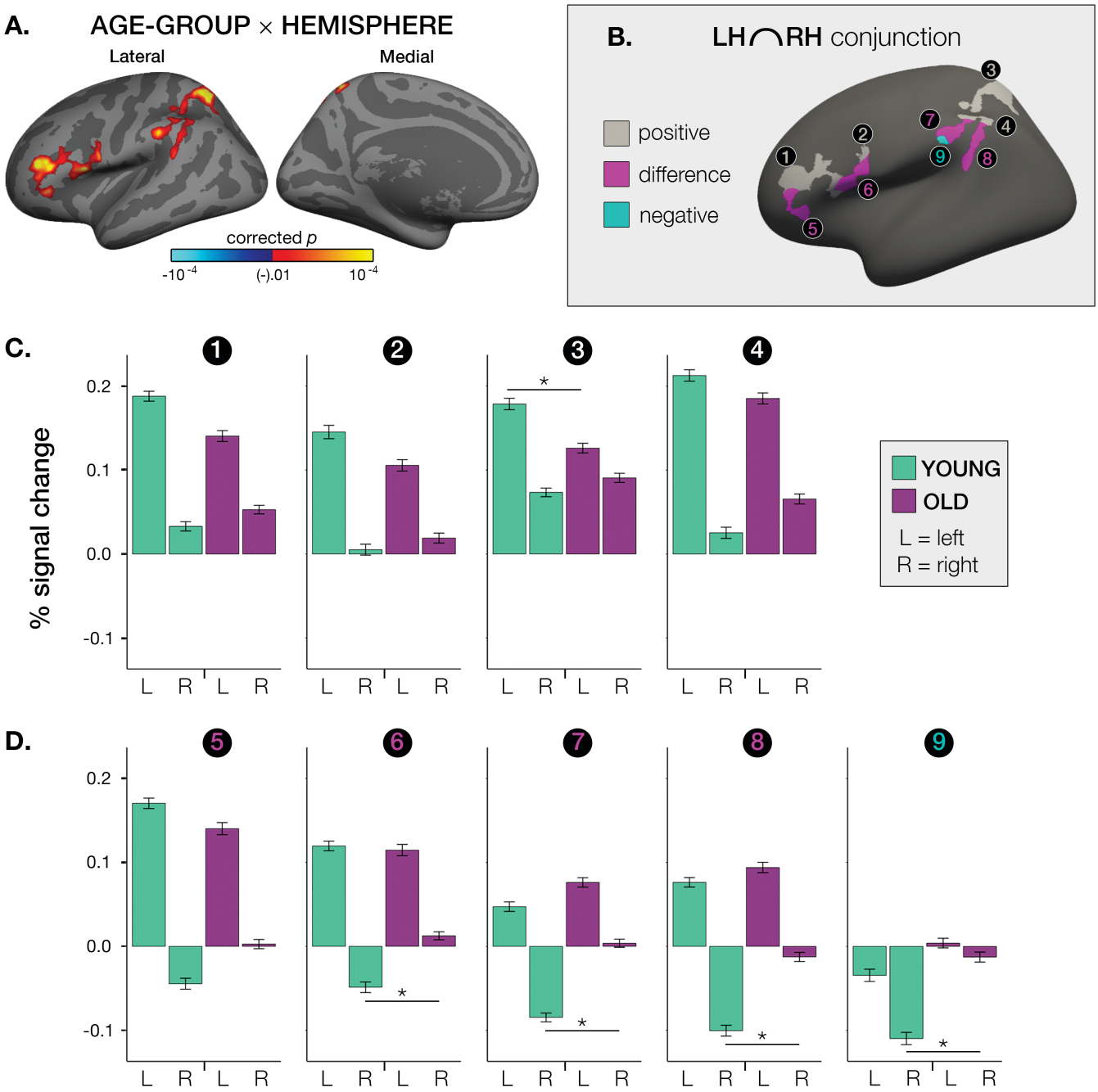

Figure 4. **A.** Cortical regions showing a significant Age-Group × Hemisphere interaction (clusters surviving FWE multiple comparison correction; vertex-wise $p < 0.01$; cluster-based $p < 0.05$). **B.** Resulting clusters were split according to average interhemispheric activation profile (Positive = positive effect in both hemispheres; Negative = negative effect in both hemispheres; Different = positive effect in one hemisphere and negative effect in the other) via interhemispheric conjunction analyses, resulting in 9 functionally distinct ROI's (numbered 1-9 on the lateral surface). **C.** Activity plotted for each age-group and hemisphere in the 4 ROI's showing positive effects in both hemispheres. **D.** Activity plotted for each age-group and hemisphere in the 4 ROI's showing different effects in each hemisphere, and 1 ROI showing negative effects in both hemispheres. All significant differences between young and older adults are shown on plots. All group analyses were performed within the symmetrical

space (the left symmetrical surface) which allowed direct homotopic comparison of activity between the hemispheres on a vertex-to-vertex basis. Error bars indicate SEM. LH = left hemisphere, RH = right hemisphere. See Tables 2, 3 and 4 for all post-hoc significance tests.

Table 2
Asymmetry in ROI's

		LEFT v RIGHT			
		YOUNG		OLD	
Interhemispheric activation profile	ROI's	LH-RH ($\bar{x}$ [SD])	Effect (d')	LH-RH ($\bar{x}$ [SD])	Effect (d')
Positive	rostral middle frontal	0.16 (0.08)*	1.8	0.09 (0.07)*	1.3
	precentral	0.14 (0.14)*	1.0	0.09 (0.11)*	0.8
	superior parietal	0.11 (0.09)*	1.2	0.04 (0.06)*	0.6
	supramarginal	0.19 (0.14)*	1.4	0.12 (0.09)*	1.3
Different	pars triangularis	0.21 (0.12)*	1.7	0.14 (0.10)*	1.4
	pars opercularis	0.17 (0.10)*	1.6	0.10 (0.09)*	1.1
	supramarginal	0.13 (0.11)*	1.2	0.07 (0.08)*	0.9
	supramarginal	0.18 (0.13)*	1.4	0.11 (0.11)*	1.0
Negative	anterior supramarginal	0.08 (0.14)*	0.5	0.02 (0.11)	0.2

Table 2. Asymmetry tests in regions of interest (ROI's) from the Age-Group × Hemisphere interaction. Descriptives for the difference in hemispheric activation (left – right) and *significance results for *left v. right* paired *t*-tests (Bonferroni corrected at $p < [0.05/18]$ 0.003) and corresponding effect sizes (Cohen's d') within young (columns 3:4) and older (columns 5:6) adults. ROI's are ordered by interhemispheric activation profile (Positive = positive effect in both hemispheres; Negative = negative effect in both hemispheres; Different = positive effect in one hemisphere and negative effect in the other). LH = left hemisphere, RH = right hemisphere.

Of the four ROI's that showed differing activation profiles depending upon hemisphere, plots indicated that the asymmetry pertained to positive memory effects in LH (in young and old) together with negative memory effects in the homotopic RH site in young participants, but not in older participants (Fig. 4D). Post-hoc one sample *t*-tests confirmed that within these regions, negative RH effects were significant in all cases in the young, and in all cases not significant in older participants (see Table 4). Further post-hoc *Old v. Young t*-tests across all 9 ROI's revealed that older participants showed significantly greater RH effects only in regions exhibiting significant negative effects in the young (see Table 4; right columns). These age-differences were typically reflected by medium and large effect sizes. Importantly

then, we observed no significant age-related increase in contralateral RH activation in regions exhibiting positive effects in both hemispheres. Only one of these regions exhibited a trend towards higher recruitment in older adults (post-Bonferonni correction; superior supramarginal). Descriptive plots and post-hoc *Old v. Young t*-tests indicated that lower asymmetry in these regions was primarily driven by an apparent age-related decrease in LH memory effects (see Table 3; right columns). This was also substantiated by larger effect sizes for the age-group contrast in the LH (typically medium negative effect sizes) relative to the contralateral RH (typically low positive effect sizes). Together, these results indicate that all apparent age-related increases in contralateral recruitment pertained exclusively to regions that exhibited significant negative memory effects in the young, but showed no significant memory effects in older participants. Thus, lower asymmetry in older adults during source memory success was driven primarily either by less activity in the dominant left hemisphere, or a lack of negative memory effects in the contralateral right hemisphere.

Table 3
Left ROI activation and age-related differences

		Left				OLD v YOUNG		
Interhemispheric activation profile	ROI's	YOUNG (T [p])	Sig	OLD (T [p])	Sig	Left (T [p])	Sig	Effect (d')
Positive	rostral middle frontal	15.9 (1.2e^{-27})	*	10.8 (6.7e^{-17})	*	-2.7 (7.6e^{-3})	O	-0.4
	precentral	9.1 (2.1e^{-14})	*	7.7 (4.3e^{-11})	*	-1.9 (6.5e^{-2})		-0.3
	superior parietal	13.2 (1.6e^{-22})	*	10.9 (3.6e^{-17})	*	-2.9 (4.3e^{-3})	*	-0.5
	supramarginal	15.5 (6.2e^{-27})	*	14.1 (9.9e^{-23})	*	-1.4 (0.2)		-0.2
Different	pars triangularis	13.7 (1.4e^{-23})	*	9.7 (7.9e^{-15})	*	-1.6 (0.1)		-0.2
	pars opercularis	10.4 (5.8e^{-17})	*	8.6 (1.0e^{-12})	*	-0.3 (0.8)		0.0
	supramarginal	4.2 (7.3e^{-5})	*	6.8 (2.6e^{-9})	*	1.8 (7.5e^{-2})		0.3
	supramarginal	6.8 (1.5e^{-9})	*	7.6 (7.1e^{-11})	*	1.1 (0.3)		0.2
Negative	anterior supramarginal	-2.4 (2.0e^{-2})	O	0.3 (0.7)		2.0 (5.0e^{-2})	O	0.3

Table 3. Columns 3-6: Results from one sample *t*-tests in left hemisphere ROI's for each age-group, ^{O}pre- and *post-Bonferroni correction $p <$ [0.05/18] 0.003. Column 7:9: Results from *Old v. Young t*-tests of left hemisphere activity, ^{O}pre- and *post-Bonferroni correction $p <$ [0.05/9] 0.006 and corresponding effect sizes (Cohen's d'). Note that in ROI's exhibiting a positive interhemispheric activation profile, lower left hemisphere activity was most apparent in older adults. ROI's are ordered by interhemispheric activation profile (Positive = positive effect in both hemispheres; Negative = negative effect in both hemispheres; Different = positive effect in one hemisphere and negative effect in the other). Sig = significance.

Table 4

Contralateral right ROI activation and age-related differences

Interhemispheric activation profile	ROI's	Right				OLD v YOUNG		
		YOUNG (T [p])	Sig	OLD (T [p])	Sig	Right (T [p])	Sig	Effect (d')
Positive	rostral middle frontal	3.0 (3.8e^{-3})	O	5.1 (2.1e^{-6})	*	1.3 (0.2)		0.2
	precentral	0.4 (0.7)		1.6 (0.1)		0.8 (0.4)		0.1
	superior parietal	7.2 (2.0e^{-10})	*	8.3 (3.4e^{-12})	*	1.2 (0.2)		0.2
	supramarginal	1.9 (6.2e^{-2})		5.5 (4.6e^{-7})	*	2.2 (2.7e^{-2})	O	0.3
Different	pars triangularis	-3.4 (9.2e^{-4})	*	0.2 (0.8)		2.7 (7.1e^{-3})	O	0.4
	pars opercularis	-3.9 (1.9e^{-4})	*	1.3 (0.2)		3.8 (2.1e^{-4})	*	0.6
	supramarginal	-8.1 (3.3e^{-12})	*	0.4 (0.7)		6.1 (8.7e^{-9})	*	0.9
	supramarginal	-7.8 (1.2e^{-11})	*	-1.2 (0.3)		5.1 (9.3e^{-7})	*	0.8
Negative	anterior supramarginal	-7.5 (4.4e^{-11})	*	-1.1 (0.3)		5.0 (1.2e^{-6})	*	0.8

Table 4. Columns 3-6: Results from one sample *t*-tests in contralateral right hemisphere ROI's for each age-group, ^{O}pre- and *post-Bonferroni correction $p <$ [0.05/18] 0.003. Columns 7:8: results from *Old v. Young t*-tests of activity in the contralateral right hemisphere, ^{O}pre- and *post-Bonferroni correction $p <$ [0.05/9] 0.006. Note that regions showing significantly greater contralateral activation in older adults were reliably associated with negative effects in young but not older adults. ROI's are ordered by interhemispheric activation profile (Positive = positive effect in both hemispheres; Negative = negative effect in both hemispheres; Different = positive effect in one hemisphere and negative effect in the other). Sig = significance.

In agreement with ROI results, vertex-wise cortical analyses revealed that source memory success was associated with activation in a large-scale left-asymmetric network, irrespective of age (main effect of Hemisphere; Fig. 5, left column). Only one region in lateral occipital cortex showed rightward asymmetry. For further illustration of overall age-group similarity, we conducted separate paired *t*-tests in the two age-groups. Comparable leftward asymmetric networks were observed in both young and old samples (Fig. 5, middle and right panels, respectively). Further, a DSC of 0.87 substantiated the overlap in cortical asymmetry maps between age-groups.

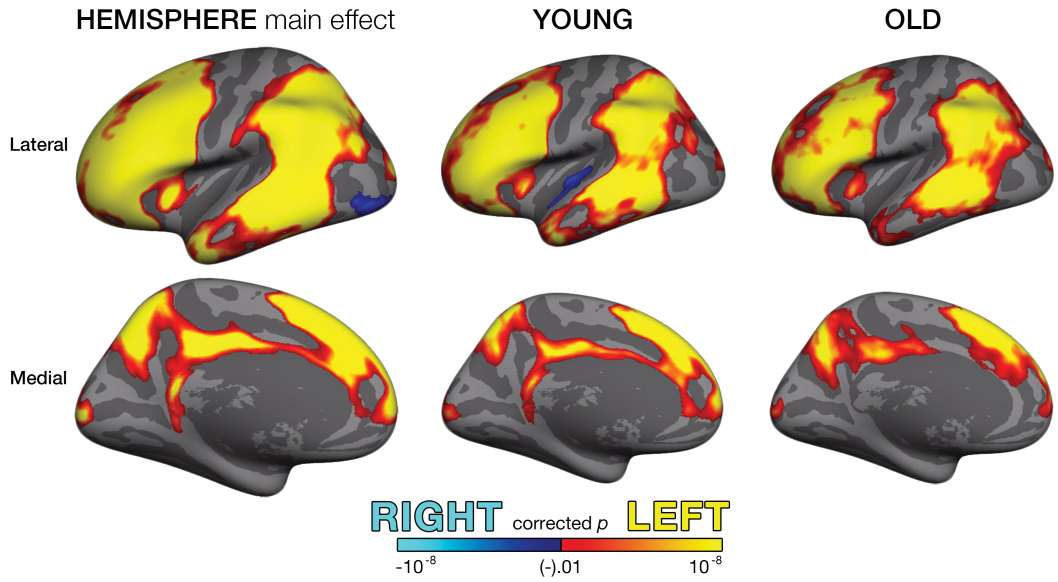

Figure 5. Functional asymmetry maps. Warm colours represent regions where homotopic activity was significantly greater in the left hemisphere, whereas cold colours represent regions where homotopic activity was significantly greater in the right hemisphere. Results are shown for the main effect of Hemisphere (irrespective of age-group; left panel) and *left v. right* paired *t*-tests performed separately in young (middle panel) and older (right panel) age-groups. Note the extensive left-dominant functional asymmetry and high consistency between age-groups. All group analyses were performed within the symmetrical space (the left symmetrical surface) which allowed direct homotopic comparison of activity between the hemispheres on a vertex-to-vertex basis. All clusters survived FWE multiple comparison correction; vertex-wise $p < 0.01$; cluster-based $p < 0.05$.

Further vertex-wise analyses revealed a group difference in source memory success activity – irrespective of hemisphere – in a large cluster in supramarginal gyrus, extending along inferior postcentral and precentral gyrus into the anterior insula (main effect of Age-Group; Fig. 6). Although activity was significantly greater in these regions in older adults, descriptive plots confirmed that the difference pertained to a significant negative memory effect in younger participants not seen in older participants (see also Fig. 3).

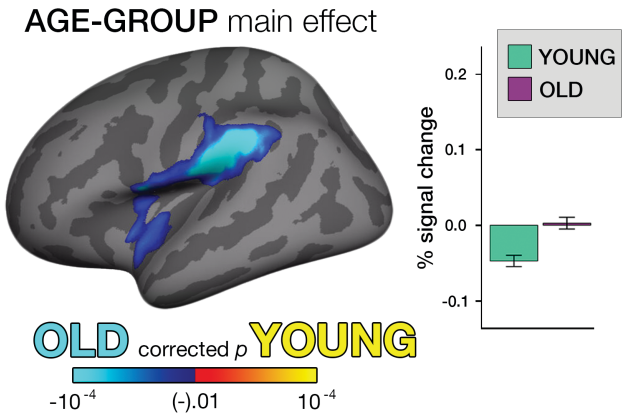

Figure 6. Main effect of Age-Group and plotted effects irrespective of hemisphere in young and older adults. Cold colours represent regions where activity was significantly greater in older adults, irrespective of hemisphere. All group analyses were performed within the symmetrical space (the left symmetrical surface) which allowed direct homotopic comparison of activity between the hemispheres on a vertex-to-vertex basis. All clusters survived FWE multiple comparison correction; vertex-wise $p < 0.01$; cluster-based $p < 0.05$. Error bars indicate SEM.

Finally, we tested whether RH regions exhibiting source memory success effects nevertheless showed a left-dominant relative asymmetry. Here, conjunction analyses revealed that 59% of the vertices exhibiting significant activity in RH nevertheless exhibited significantly greater source memory success activity in the LH. Thus, left-dominant asymmetry was evident in a large proportion of the retrieval network also where RH activation was significant (Fig. 7).

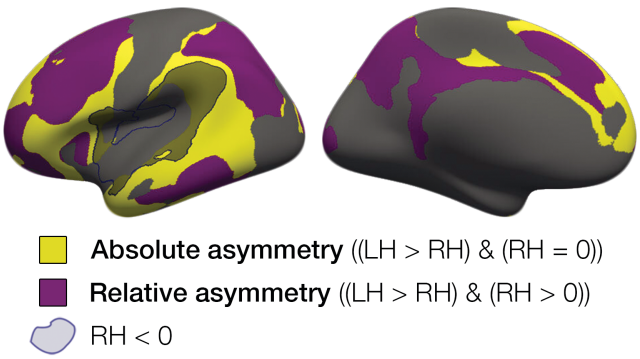

Figure 7. Cortical regions exhibiting absolute asymmetry (yellow; only significant in left) and relative asymmetry (purple; significant bilateral activation but significantly greater in left), and negative right effects (blue outline) on average across age-groups. All clusters survived FWE multiple comparison correction; vertex-wise $p < 0.01$; cluster-based $p < 0.05$. LH = left hemisphere, RH = right hemisphere.

3.4 Testing asymmetry relationships with memory and longitudinal memory change

We then tested whether asymmetry was related to memory performance. None of the tests (linear regressions; controlled for age and sex) revealed any significant relationships between memory performance and asymmetry in any ROI in older participants ($p > .3$ [uncorrected]), old-low performers ($p > .06$ [uncorrected]; $t = 2.0$; superior supramarginal), old-high performers ($p > .4$ [uncorrected]) or young participants ($p > .1$ [uncorrected]). Next, in a subset of our older participants (N=54) we used CVLT scores to estimate the extent of longitudinal memory change exhibited across the preceding ~8 years (see Supplementary Fig. 1). CVLT delayed recall at Tp3 and memory performance in the fMRI task (conducted at Tp3) were highly correlated in the complete sample ($r = .52$, $p = 10^{-12}$; see Supplementary Fig. 1A) and the older longitudinal subsample ($r = .43$, $p = 10^{-3}$). We observed no significant relationships between asymmetry and longitudinal memory change in any ROI ($p > .07$ [uncorrected]). Further, no relationships between asymmetry and longitudinal memory change were found when using CVLT normative scores, i.e. T scores according to age and sex.

We additionally tested the relationship between memory performance and activation in the contralateral RH only. Again, we observed no significant relationships in any ROI for any of the above tests ($p > .07$ [uncorrected]).

Thus, out of a total 108 tests probing brain-behaviour relationships with current memory performance or longitudinal memory change, none revealed any significant relationships using a liberal statistical threshold even prior to multiple comparison correction ($\alpha = .05$). Finally, a posteriori power sensitivity analyses revealed that medium population effect sizes (13% explained variance) could be excluded given our sample size (power = .80; $\alpha = .05$; two-tailed testing).

3.5 Control analysis

Finally, a compensation account to lower asymmetry may be supported if, relative to younger adults, older adults rely on more bilateral patterns of (raw) *source memory hit* activity compared with *source memory miss* activity. This would indicate that bilateral recruitment aids successful memory performance in older adults more than in younger adults. A mixed-effects ANOVA testing age-differences in asymmetry between raw *source memory hit* and raw *source memory miss* activity (Age-Group × Hemisphere × Source interaction) yielded no significant clusters (post-correction; Supplementary Fig. 2B). Of note, however, clusters exhibiting a trend towards vertex-wise significance ($p < 0.05$) were largely encompassed within the set of ROI's identified as showing age-differences in asymmetry in the main analysis (i.e. after isolating source memory success activity; Supplementary Fig. 2B; bottom and Fig. 4). Thus, we found no evidence to indicate that older adults benefit from more bilateral recruitment than the young. Finally, we performed confirmatory analyses to show that the observed left-dominant asymmetry was specifically associated with source memory hits. Repeated-measures ANOVA's for each age-group confirmed that the extent of asymmetry was significantly different between *source memory hit* and *source memory miss* trials in a comparable network of regions identified as exhibiting left-dominant asymmetry in the main analysis (see Supplementary Fig. 2A and Fig. 5). Again, these maps showed high overlap between age-groups (DSC = 0.82). Finally, descriptive plotting of the values underlying these interactions in four exploratory ROI's confirmed that the asymmetry was specific to source memory hits (Supplementary Fig. 2C). Thus, we confirmed that asymmetry was directly related to whether retrieval was successful or not, and that asymmetry facilitated memory performance in older adults – similar to younger adults.

4. Discussion

We investigated whether functional brain asymmetry during successful memory retrieval is lower in older relative to younger adults, using methods to test asymmetry across the entire cortex. Our study yielded three main findings. First, the analyses revealed lower asymmetry in older adults in widespread prefrontal and parietal regions. However, we observed no evidence that lower asymmetry corresponded to an apparent age-related increase in recruitment of the opposite hemisphere in older adults. Rather, contralateral activations that were significantly greater in older adults pertained exclusively to regions that reliably signalled retrieval failure in the young (i.e. exhibited negative memory success effects), but that showed no significant effects in older adults. Results thus indicated that the pattern of lower asymmetry in older adults was primarily driven by either reduced deactivation in contralateral cortex, or by less retrieval activity in the ipsilateral/dominant hemisphere. Second, we found evidence that activation of the cerebral cortex during associative memory retrieval may be characterised by an extensive left-dominant functional asymmetry, encompassing a large proportion of the cortical retrieval network. This result proved to be highly reproducible in both age-groups. Hence, despite the apparent age-related reduction in asymmetry, our results indicate that the older brain relies on processing strategies that are largely asymmetric during retrieval — similar to younger adults — and that asymmetry facilitated successful retrieval in both age-groups. Third, we found no evidence that individual differences in the magnitude of asymmetry were related to current memory performance, nor the extent of longitudinal memory change exhibited across an ~8 year period prior to scanning in older adults.

4.1 Age-differences in asymmetry

In line with previous research, our results indicate that lower prefrontal asymmetry may be a feature of the older brain during memory retrieval (Bäckman et al. 1997; Cabeza et al. 1997,

2002, 2004; Madden et al. 1999; Grady et al. 2002; Rossi et al. 2004; Morcom and Johnson 2015). Yet our findings also extend the previous literature. Firstly, we observed that lower asymmetry in older age may be a more widespread phenomenon across the cortex when recalling a memory, occurring across large swathes of parietal cortex where retrieval-induced activation is often evident (Wagner et al. 2005; Frithsen and Miller 2014). Of importance, however, we observed that lower asymmetry was manifest in a different pattern than what is typically reported (Cabeza 2002; Cabeza and Dennis 2012). Namely, we found no evidence to indicate that older adults exhibit significantly greater activation of the contralateral hemisphere than younger adults — or show a shift towards bilaterality — during retrieval. Rather, in frontal and parietal regions exhibiting positive memory effects in both hemispheres (hereafter termed contralateral co-activation), the data indicated a reduction in responsivity of the dominant left hemisphere in older adults, combined with no significant age-related change in right homotopic cortex. Thus, our study yielded no convincing evidence to indicate that older adults recruit additional resources from the contralateral hemisphere; the pattern arguably emphasised within a compensation framework of HAROLD, given consensus that the term typically describes a situation in which brain activity is greater in older adults (Cabeza et al. 2018). Previously, additional contralateral recruitment in older adults has been proposed to account for insufficient engagement of the hemisphere more specialised to perform the task (Cabeza et al. 1997, 2004; Cabeza 2002; Persson and Nyberg 2006; Cabeza and Dennis 2012). Since we observed primarily lower activation of the dominant left hemisphere in these regions, our results are inconsistent with the compensation view of HAROLD during retrieval.

Secondly, we found that all regions that did show significantly greater contralateral activity in older adults were reliably associated with negative memory effects in young participants (i.e. greater activation during retrieval failure). In these, homotopic regions exhibited a functional

dissociation between hemispheres, such that positive left activation was associated with contralateral right deactivation in the young, but neither activation nor deactivation of contralateral cortex in the old. These included two clusters located in inferior frontal cortex and two in supramarginal gyrus, and broadly corresponded to regions typically encompassed within either the so-called default network (anterior frontal ROI; (Buckner et al. 2008; Yeo et al. 2011) or the ventral network associated with stimulus-driven attentional capture (Corbetta et al. 2008; Yeo et al. 2011). The lack of negative memory effects in older adults suggests that a similar level of regional neural activity was present in trials recalled successfully and trials associated with retrieval failure. Thus, the present results may complement previous reports claiming that aging may be associated with either a reduction in the ability to suspend neural processing not conducive to current cognitive goals (Grady et al. 2006; Maillet and Rajah 2014), or deficits in retrieval monitoring activity during trials not remembered (McDonough et al. 2013). For example, given its established role in attention reorienting (Corbetta and Shulman 2002; Corbetta et al. 2008), it is reasonable to infer that the suppression of activity in right supramarginal cortex may be facilitative to memory goals, yet older adults showed an apparent deficit in this ability. Because previous studies imply a role for callosal connections in establishing memory-related brain asymmetries (Kompus et al. 2011), age-related degeneration of the corpus callosum might affect the balance in the distribution of hemispheric processing in general (Buckner and Louis 2004; Head 2004; Persson et al. 2006; Sullivan and Pfefferbaum 2006), but also during memory retrieval. For example, it is possible that cortical regions we identified showing no contralateral deactivation in elderly participants could reflect reduced functional inhibition of homotopic cortex as a result of callosal degeneration (Buckner and Logan 2002; Persson et al. 2006), possibly in line with a hemispheric inhibition account during attentional processes (Szczepanski et al. 2010; Szczepanski and Kastner 2013). Nevertheless, the pattern we observed in cortical regions exhibiting contralateral co-activation does not support a

disinhibition account, because we observed no significant age-related increase in contralateral activation. Since there is evidence the corpus callosum mediates both contralateral excitation and inhibition in a manner that may be regionally dependent (van der Knaap and van der Ham 2011), future research could assess the longitudinal link between regional callosal atrophy and regional changes in asymmetry. This may shed light on mechanisms mediating hemispheric distribution of neural resources, and potential alterations in this ability during aging.

In sum, the pattern of lower asymmetry in older adults observed here primarily reflected either a lack of negative contralateral memory effects, or lower activation of the dominant left hemisphere. Overall this pattern suggests that age-related deficits in the brain activity associated with memory retrieval can drive lower asymmetry in older adults. In previous cross-sectional work, findings indicating higher contralateral activation in older adults have frequently been interpreted as evidence for functional compensation in aging (Bäckman et al. 1997; Cabeza et al. 1997, 2004; Madden et al. 1999; Cabeza 2002; Rossi et al. 2004; Bishop et al. 2010). In our large cross-sectional sample, we were unable to detect convincing evidence for the presence of apparent age-related over-activations of the contralateral hemisphere during retrieval — except in the context of lower negative memory effects in older adults. Thus, our results may call into question the focus on higher contralateral brain responses in older adults during memory retrieval (Cabeza et al. 2002, 2018; Grady 2012), highlighting instead that lower asymmetry does not imply a higher contralateral brain response, and that patterns driving lower asymmetry in older brains may reflect age-related decline.

4.2 Asymmetry: memory performance and memory change

The degree of asymmetry was not related to current memory performance. Thus, none of the accepted premises for compensation were found for the apparent asymmetry reduction observed here (Cabeza et al. 2018): we observed no age-related contralateral over-activation, and lower asymmetry conferred no beneficial effect on memory performance. It has recently been proposed that lower asymmetry may rather correlate with performance on a trial-by-trial basis within individuals, as opposed to memory performance compared across individuals (Wang and Cabeza 2017). Although the present study was not designed to assess hypotheses pertaining to intra-individual compensation, this would arguably still be dependent on evidence that older adults benefit more from bilateral activation than the young (across trials). However, our results indicated that asymmetry was specific to successful retrieval attempts in both age-groups. Thus, at the group level, both young and older adults benefited from the asymmetric recruitment of cortical circuits, indicating that both young and older brains relied on similar neural processes during retrieval.

The magnitude of asymmetry was also unrelated to the extent of longitudinal memory decline exhibited across the preceding ~8 years in a subset of 54 older participants. Thus, we found no evidence that asymmetry is a marker for age-related cognitive preservation or decline. Given that research is conflicting regarding the cognitive outcomes of lower frontal asymmetry (Eyler et al. 2011), and that an age-related difference in activity is not synonymous with a change in activity occurring with age (Rugg 2017), we note that future large-scale longitudinal studies are needed to test the relationship between changes in asymmetry over time, and memory maintenance or decline in aging individuals.

4.3 Asymmetry common to young and old

We observed direct evidence that the human cerebral cortex may rely disproportionately on memory signals localised in the left hemisphere during associative retrieval, and that this potentially occurs on an unprecedented scale throughout the retrieval network. Moreover, this left-dominant asymmetry showed high consistency between young and old age-groups, and facilitated successful memory retrieval in both. This is in line with some previous reports indicating an age-invariant left-dominant asymmetry during retrieval (Morcom et al. 2007; Angel et al. 2013). Hence, we emphasise that we observed extensive asymmetry also in older brains. Indeed, older adults exhibited strong asymmetry even in regions characterised by an apparent age-related asymmetry reduction. Thus, we found only gradual differences in hemispheric asymmetry between age-groups. Furthermore, lower asymmetry was evident also in regions exhibiting significant bilateral activation common to both age-groups, and we observed not only few qualitative differences in the activation maps of young and old participants to indicate asymmetry differences (see Fig. 3), but also a high degree of activation overlap between age-groups in each hemisphere. Taken together, we argue that these observations have implications for future research concerned with identifying asymmetry changes in aging. Given that there is evidence that lower asymmetry may reflect a general phenomenon in aging across tasks — at least in prefrontal cortex (Bäckman et al. 1997; Cabeza et al. 1997, 2004; Madden et al. 1999; Rosen et al. 2002; Cabeza 2002; Logan et al. 2002; Morcom et al. 2003, 2007; Bergerbest et al. 2009; Duverne et al. 2009; Reuter-Lorenz and Park 2010; Morcom and Friston 2012; Davis et al. 2012; Berlingeri et al. 2013) — we suggest that adopting similar methodologies that do not restrict the search for asymmetry to specific brain regions may promote a deeper understanding of processing strategies in the cerebral hemispheres and their relation to aging.

4.4 Overarching considerations

Generally, asymmetries have been reported in frontal and parietal regions during memory retrieval (Kalpouzos and Nyberg 2010), and thus our results contribute evidence that retrieval-induced asymmetry may occur on a more global scale than previously identified. Strengthening the potential generalizability of these findings, the activation patterns we observed delineating source memory success separately by hemisphere were largely in agreement with previous research (McDermott et al. 2009; Spaniol et al. 2009; Huijbers et al. 2013; Kim 2016). The results presented here may thus argue against the notion that retrieval is more dependent on right frontal cortex (Cabeza et al. 1997; Habib et al. 2003). Although after delineating asymmetry effects into regions that showed absolute (only the left hemisphere significantly active) and relative asymmetry (significant bilateral effects but significantly greater in the left), we found that large portions of frontal cortex were characterised by relative asymmetry, thus also evidencing right frontal recruitment. Since fMRI and patient data suggest that left frontal cortex mediates the retrieval of context information (Rugg et al. 1999; Slotnick et al. 2003; Dobbins and Wagner 2005; Duarte et al. 2005), whereas right frontal cortex may support more reflexive familiarity-driven processes (Nolde et al. 1998; Dobbins et al. 2004), we suggest that our results are consistent with a left-dominant prefrontal response during source memory recollection processes.

Finally, we note that because our paradigm tested item-action associations using visual and auditory probes, we chose to always contrast activity elicited during successful retrieval versus that elicited during unsuccessful retrieval (as opposed to a task versus baseline contrast), to control for asymmetries potentially elicited by the sensory conditions present during testing — using each age-group as its own control. In addition, our use of a symmetrical surface template to perform hemispheric comparisons was informed by recent reports demonstrating both the utility of such an approach, and that such methods are

gaining traction (Greve et al. 2013; Maingault et al. 2015; Takaya et al. 2015; Tobyne et al. 2016; Greve and Fischl 2017). However, it might be argued that this method may result in a degree of loss in anatomical specificity, potentially above what is apparent in standard templates modelled on hemisphere-specific landmarks. Nevertheless, we believe that the extent of the effects documented here and the high level of reproducibility in our asymmetry results between richly populated age-samples is encouraging, and together suggest that any anatomical specificity lost during the reregistration process likely had minimal impact on the overall results observed.

4.5 Conclusion

In conclusion, the present results confirm that lower functional asymmetry may be an important feature of the older brain during memory retrieval. Yet our study challenges common assumptions of a neural compensation account to HAROLD, suggesting instead that apparent age-related asymmetry reduction may arise from less activation or less deactivation in older adults — a pattern more suggestive of age-related neural decline — and is unrelated to either current memory performance, memory preservation or decline in neurocognitive aging. Future research should assess longitudinal alterations in brain asymmetry using unbiased methods to delineate asymmetry, and assess the relevance of this for understanding episodic memory change in the aging brain.

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Disclosure statement

The authors have no conflicts of interest to disclose.

References

Anderson ND, Ebert PL, Jennings JM, Grady CL, Cabeza R, Graham SJ. 2008. Recollection- and Familiarity-Based Memory in Healthy Aging and Amnestic Mild Cognitive Impairment. Neuropsychology. 22:177–187.

Angel L, Bastin C, Genon S, Balteau E, Phillips C, Luxen A, Maquet P, Salmon E, Collette F. 2013. Differential effects of aging on the neural correlates of recollection and familiarity. Cortex. 49:1585–1597.

Bäckman L, Almkvist O, Andersson J, Nordberg a, Winblad B, Reineck R, Långström B. 1997. Brain activation in young and older adults during implicit and explicit retrieval. J Cogn Neurosci. 9:378–391.

Beck AT, Ward C, Mendelson M, Mock J, Erbaugh J. 1961. An Inventory for Measuring Depression. Arch Gen Psychiatry. 4:561.

Bergerbest D, Gabrieli JDE, Whitfield-Gabrieli S, Kim H, Stebbins GT, Bennett D a, Fleischman D a. 2009. Age-associated reduction of asymmetry in prefrontal function and preservation of conceptual repetition priming. Neuroimage. 45:237–246.

Berlingeri M, Danelli L, Bottini G, Sberna M, Paulesu E. 2013. Reassessing the HAROLD model: Is the hemispheric asymmetry reduction in older adults a special case of compensatory-related utilisation of neural circuits? Exp Brain Res. 224:393–410.

Bishop NA, Lu T, Yankner BA. 2010. Neural mechanisms of ageing and cognitive decline. Nature. 464:529–535.

Buckner RL, Andrews-Hanna JR, Schacter DL. 2008. The brain's default network. Ann N Y Acad Sci. 1124:1–38.

Buckner RL, Logan JM. 2002. Frontal contributions to episodic memory encoding in the young and elderly. In: Parker AE,, Wilding EL,, Bussey T, editors. The cognitive neuroscience of memory encoding and retrieval. Philadelphia: Psychology Press. p. 59–81.

Buckner RL, Louis S. 2004. Memory and Executive Function Review in Aging and AD : Multiple Factors that Cause Decline and Reserve Factors that Compensate. 44:195–208.

Cabeza R. 2002. Hemispheric asymmetry reduction in older adults: The HAROLD model. Psychol Aging. 17:85–100.

Cabeza R, Albert M, Belleville S, Craik F, Duarte A, Grady C, Lindenberger U, Nyberg L, Park D, Reuter-lorenz PA, Rugg MD, Steffener J, Rajah MN. 2018. Cognition and the Aging Brain: Maintenance, Reserve, and Compensation. Nat Rev Neurosci. In review.

Cabeza R, Anderson ND, Locantore JK, McIntosh AR. 2002. Aging Gracefully: Compensatory Brain Activity in High-Performing Older Adults. Neuroimage. 17:1394–1402.

Cabeza R, Daselaar SM, Dolcos F, Prince SE, Budde M, Nyberg L. 2004. Task-independent and Task-specific Age Effects on Brain Activity during Working Memory, Visual Attention and Episodic Retrieval. Cereb Cortex. 14:364–375.

Cabeza R, Dennis NA. 2012. Frontal lobes and aging: deterioration and compensation. In: Stuss DT,, Knight RT, editors. Principles of Frontal Lobe Function. 2nd ed. New York: Oxford University Press. p. 628–652.

Cabeza R, Grady CL, Nyberg L, McIntosh AR, Tulving E, Kapur S, Jennings JM, Houle S, Craik FI. 1997. Age-related differences in neural activity during memory encoding and retrieval: A positron emission tomography study. J Neurosci. 17:391–400.

Cabeza R, Nyberg L, Park D. 2005. Cognitive Neuroscience of Aging: Linking Cognitive and Cerebral Aging. New York, NY: Oxford University Press.

Cansino S, Estrada-manilla C, Herna E, Martı JG, Torres-trejo F, Go T, Ayala-herna M, Osorio D, Cedillo-tinoco M, Garce L, Go S, Beltra K, Cadena-arenas Y, Ferna L, Bärtschi A, Resendiz-vera J, Rodrı D. 2013. The Rate of Source Memory Decline Across the Adult Life Span. 49:973–985.

Corballis MC. 2009. The evolution and genetics of cerebral asymmetry. 867–879.

Corbetta M, Patel G, Shulman GL. 2008. The reorienting system of the human brain: from environment to theory of mind. Neuron. 58:306–324.

Corbetta M, Shulman GL. 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat

Rev Neurosci. 3:201–215.

Crum WR, Camara O, Hill DLG. 2006. Generalized overlap measures for evaluation and validation in medical image analysis. IEEE Trans Med Imaging. 25:1451–1461.

Dale AM, Fischl B, Sereno MI. 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage. 9:179–194.

Davis SW, Kragel JE, Madden DJ, Cabeza R. 2012. The architecture of cross-hemispheric communication in the aging brain: Linking behavior to functional and structural connectivity. Cereb Cortex. 22:232–242.

Deary IJ, Whiteman MC, Starr JM, Whalley LJ, Fox HC. 2004. The Impact of Childhood Intelligence on Later Life: Following Up the Scottish Mental Surveys of 1932 and 1947. J Pers Soc Psychol. 86:130–147.

Delis DC, Kramer JH, Kaplan E, Thompkins BAO. 1987. CVLT: California verbal learning test-adult version: manual. Psychological Corporation.

Dobbins IG, Simons JS, Schacter DL. 2004. fMRI Evidence for Separable and Lateralized Prefrontal Memory Monitoring Processes. J Cogn Neurosci. 16:908–920.

Dobbins IG, Wagner AD. 2005. Domain-general and domain-sensitive prefrontal mechanisms for recollecting events and detecting novelty. Cereb Cortex. 15:1768–1778.

Duarte A, Ranganath C, Knight RT. 2005. Effects of Unilateral Prefrontal Lesions on Familiarity, Recollection, and Source Memory. J Neurosci. 25:8333–8337.

Duverne S, Motamedinia S, Rugg MD. 2009. The relationship between aging, performance, and the neural correlates of successful memory encoding. Cereb Cortex. 19:733–744.

Eyler LT, Sherzai A, Kaup AR, Jeste D V. 2011. A review of functional brain imaging correlates of successful cognitive aging. Biol Psychiatry. 70:115–122.

Faul F, Erdfelder E, Lang AG, Buchner A. 2007. G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 39:175–191.

Fischl B, Dale AM. 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A. 97:11050–11055.

Fischl B, Sereno MI, Dale AM. 1999a. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage. 9:195–207.

Fischl, Sereno MI, Dale AM. 1999b. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage. 9:195–207.

Fischl, Sereno MI, Tootell RB, Dale AM. 1999. High-resolution intersubject averaging and a coordinate

system for the cortical surface. Hum Brain Mapp. 8:272–284.

Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB. 2014. What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. Prog Neurobiol. 117:20–40.

Folstein MF, Folstein SE, McHugh PR. 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 12:189–198.

Frithsen A, Miller MB. 2014. The posterior parietal cortex: Comparing remember/know and source memory tests of recollection and familiarity. Neuropsychologia. 61:31–44.

Gotts SJ, Jo HJ, Wallace GL, Saad ZS, Cox RW, Martin A. 2013. Two distinct forms of functional lateralization in the human brain. Proc Natl Acad Sci U S A. 110:E3435-44.

Grady C. 2012. The cognitive neuroscience of ageing. Nat Rev Neurosci. 13:491–505.

Grady C, Springer M, Hongwanishkul D, McIntosh A, Winocur G. 2006. Age-related changes in brain activity across the adult lifespan. J Cogn Neurosci. 18:227–241.

Grady CL, Bernstein LJ, Beig S, Siegenthaler AL. 2002. The effects of encoding task on age-related differences in the functional neuroanatomy of face memory. Psychol Aging. 17:7–23.

Greve D, Van der Haugen L, Cai Q, Stufflebeam S, Sabuncu M, Fischl B, Brysbaert M. 2013. A Surface-based Analysis of Language Lateralization and Cortical Asymmetry. J Cogn Neurosci. 25:1477–1492.

Greve DN, Fischl B. 2017. False positive rates in surface-based anatomical analysis. Neuroimage. 171:6–14.

Habib R, Nyberg L, Tulving E. 2003. Hemispheric asymmetries of memory: The HERA model revisited. Trends Cogn Sci. 7:241–245.

Hansen NL, Lauritzen M, Mortensen EL, Osler M, Avlund K, Fagerlund B, Rostrup E. 2014. Subclinical cognitive decline in middle-age is associated with reduced task-induced deactivation of the brain's default mode network. Hum Brain Mapp. 35:4488–4498.

Head D. 2004. Differential Vulnerability of Anterior White Matter in Nondemented Aging with Minimal Acceleration in Dementia of the Alzheimer Type: Evidence from Diffusion Tensor Imaging. Cereb Cortex. 14:410–423.

Hellige JB. 1993. Hemispheric asymmetry: What's right and what's left. Harvard University Press.

Huijbers W, Schultz AP, Vannini P, McLaren DG, Wigman SE, Ward AM, Hedden T, Sperling RA. 2013. The encoding/retrieval flip: Interactions between memory performance and memory stage and relationship to intrinsic cortical networks. J Cogn Neurosci. 25:1163–1179.

Josefsson M, Luna X, Pudas S, Nilsson L, Nyberg L. 2012. Genetic and Lifestyle Predictors of 15-Year Longitudinal Change in Episodic Memory. J Am Geriatr Soc. 60:2308–2312.

Kalpouzos G, Nyberg L. 2010. Hemispheric Asymmetry of Memory. In: Westerhausen R,, Hugdahl K, editors. The Two Halves of the Brain. Information Processing in the Cerebral Hemispheres. Cambridge, MA: MIT Press. p. 499–530.

Kim. 2010. Dissociating the roles of the default-mode, dorsal, and ventral networks in episodic memory retrieval. Neuroimage. 50:1648–1657.

Kim H. 2016. Default network activation during episodic and semantic memory retrieval: A selective meta-analytic comparison. Neuropsychologia. 80:35–46.

Kompus K, Kalpouzos G, Westerhausen R. 2011. The size of the anterior corpus callosum correlates with the strength of hemispheric encoding-retrieval asymmetry in the ventrolateral prefrontal cortex. Brain Res. 1419:61–67.

Li SC, Lindenberger U, Sikström S. 2001. Aging cognition: From neuromodulation to representation. Trends Cogn Sci. 5:479–486.

Logan JM, Sanders AL, Snyder AZ, Morris JC, Buckner RL. 2002. Under-recruitment and nonselective recruitment: Dissociable neural mechanisms associated with aging. Neuron. 33:827–840.

Madden DJ, Turkington TG, Provenzale JM, Denny LL, Hawk TC, Gottlob LR, Coleman RE. 1999. Adult age differences in the functional neuroanatomy of verbal recognition memory. Hum Brain Mapp. 7:115–135.

Maillet D, Rajah MN. 2014. Age-related differences in brain activity in the subsequent memory paradigm: A meta-analysis. Neurosci Biobehav Rev. 45:246–257.

Maingault S, Tzourio-Mazoyer N, Mazoyer B, Crivello F. 2015. Regional correlations between cortical thickness and surface area asymmetries: A surface-based morphometry study of 250 adults. Neuropsychologia. 93:350–364.

McDermott KB, Szpunar KK, Christ SE. 2009. Laboratory-based and autobiographical retrieval tasks differ substantially in their neural substrates. Neuropsychologia. 47:2290–2298.

McDonough IM, Wong JT, Gallo DA. 2013. Age-related differences in prefrontal cortex activity during retrieval monitoring: Testing the compensation and dysfunction accounts. Cereb Cortex. 23:1049–1060.

Morcom A, Johnson W. 2015. Neural Reorganization and Compensation in Aging. J Cogn Neurosci. 27:1275–1285.

Morcom AM, Friston KJ. 2012. Decoding episodic memory in ageing: A Bayesian analysis of activity

patterns predicting memory. Neuroimage. 59:1772–1782.

Morcom AM, Good CD, Frackowiak RSJ, Rugg MD. 2003. Age effects on the neural correlates of successful memory encoding. Brain. 126:213–229.

Morcom AM, Li J, Rugg MD. 2007. Age effects on the neural correlates of episodic retrieval: Increased cortical recruitment with matched performance. Cereb Cortex. 17:2491–2506.

Nolde SF, Johnson MK, Raye CL. 1998. The role of prefrontal cortex during tests of episodic memory. Trends Cogn Sci. 2:399–406.

Nyberg L, Lövdén M, Riklund K, Lindenberger U, Bäckman L. 2012. Memory aging and brain maintenance. Trends Cogn Sci. 16:292–305.

Ocklenburg S, Güntürkün O. 2012. Hemispheric asymmetries: The comparative view. Front Psychol. 3:1–9.

Park DC, Reuter-Lorenz P. 2009. The adaptive brain: aging and neurocognitive scaffolding. Annu Rev Psychol. 60:173–196.

Persson J, Nyberg L. 2006. Altered brain activity in healthy seniors: what does it mean? Prog Brain Res. 157.

Persson J, Nyberg L, Lind J, Larsson A, Nilsson LG, Ingvar M, Buckner RL. 2006. Structure-function correlates of cognitive decline in aging. Cereb Cortex. 16:907–915.

Poldrack RA. 2007. Region of interest analysis for fMRI. Soc Cogn Affect Neurosci. 2:67–70.

Pruim RHR, Mennes M, Buitelaar JK, Beckmann CF. 2015. Evaluation of ICA-AROMA and alternative strategies for motion artifact removal in resting state fMRI. Neuroimage. 112:278–287.

Reuter-Lorenz PA. 2002. New visions of the aging mind and brain. Trends Cogn Sci. 6:394–400.

Reuter-Lorenz PA, Lustig C. 2005. Brain aging: Reorganizing discoveries about the aging mind. Curr Opin Neurobiol. 15:245–251.

Reuter-Lorenz PA, Park DC. 2010. Human Neuroscience and the Aging Mind : A New Look at Old Problems. J Gerontol Psychol Sci. 65(B):405–415.

Ringo JL, Don RW, Demeter S, Simard PY. 1994. Time Is of the Essence: A Conjecture that Hemispheric Specialization Arises from Interhemispheric Conduction Delay. Cereb Cortex. 331–343.

Rosen A, Hara RO, Rosen AC, Prull CAMW, Hara RO, Race EA, Desmond JE, Glover GH, Jerome AY. 2002. Variable effects of aging on frontal lobe contributions to memory. Neuroreport. 13:2425–2428.

Rossi S, Miniussi C, Pasqualetti P, Babiloni C, Rossini PM, Cappa SF. 2004. Age-Related Functional

Changes of Prefrontal Cortex in Long-Term Memory: A Repetitive Transcranial Magnetic Stimulation Study. J Neurosci. 24:7939–7944.

Rugg MD. 2017. 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. New York: Oxford University Press.

Rugg MD, Fletcher PC, Chua PML, Dolan RJ. 1999. The role of the prefrontal cortex in recognition memory and memory for source: An fMRI study. Neuroimage. 10:520–529.

Salimi-Khorshidi G, Douaud G, Beckmann CF, Glasser MF, Griffanti L, Smith SM. 2014. Automatic denoising of functional MRI data: Combining independent component analysis and hierarchical fusion of classifiers. Neuroimage. 90:449–468.

Slotnick SD, Moo LR, Segal JB, Hart J. 2003. Distinct prefrontal cortex activity associated with item memory and source memory for visual shapes. Cogn Brain Res. 17:75–82.

Sneve MH, Grydeland H, Nyberg L, Bowles B, Amlien IK, Langnes E, Walhovd KB, Fjell AM. 2015. Mechanisms Underlying Encoding of Short-Lived Versus Durable Episodic Memories. J Neurosci. 35:5202–5212.

Spaniol J, Davidson PSR, Kim ASN, Han H, Moscovitch M, Grady CL. 2009. Event-related fMRI studies of episodic encoding and retrieval: Meta-analyses using activation likelihood estimation. Neuropsychologia. 47:1765–1779.

Spreng RN, Wojtowicz M, Grady CL. 2010. Reliable differences in brain activity between young and old adults: A quantitative meta-analysis across multiple cognitive domains. Neurosci Biobehav Rev. 34:1178–1194.

Sullivan E V, Pfefferbaum A. 2006. Diffusion tensor imaging and aging. 30:749–761.

Szczepanski SM, Kastner S. 2013. Shifting attentional priorities: Control of spatial attention through hemispheric competition. Ann Intern Med. 158:5411–5421.

Szczepanski SM, Konen CS, Kastner S. 2010. Mechanisms of Spatial Attention Control in Frontal and Parietal Cortex. J Neurosci. 30:148–160.

Takaya S, Kuperberg GR, Liu H, Greve DN, Makris N, Stufflebeam SM. 2015. Asymmetric projections of the arcuate fasciculus to the temporal cortex underlie lateralized language function in the human brain. Front Neuroanat. 9:119.

Tamnes C, Overbye K, Ferschmann L, Fjell AM, Walhovd KB, Blakemore S-J, Dumontheil I. 2018. Social perspective taking is associated with self-reported prosocial behavior and regional cortical thickness across adolescence. Dev Psychol. 54:1745–1757.

Tobyne SM, Boratyn D, Johnson JA, Greve DN, Mainero C, Klawiter EC. 2016. A surface-based technique for mapping homotopic interhemispheric connectivity: Development, characterization, and clinical application. Hum Brain Mapp. 37:2849–2868.

van der Knaap LJ, van der Ham IJM. 2011. How does the corpus callosum mediate interhemispheric transfer ? A review. Behav Brain Res. 223:211–221.

Vidal-Piñeiro D, Sneve MH, Storsve AB, Roe JM, Walhovd KB, Fjell AM. 2017. Neural correlates of durable memories across the adult lifespan: brain activity at encoding and retrieval. Neurobiol Aging. 60:20–33.

Wagner AD, Shannon BJ, Kahn I, Buckner RL. 2005. Parietal lobe contributions to episodic memory retrieval. Trends Cogn Sci. 9:445–453.

Wang W-C, Cabeza R. 2017. 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. New York: Oxford University Press.

Wechsler D. 1999. Wechsler abbreviated intelligence scale. San Antonio: The Psychological Corporation.

Westerhausen R, Kompus K, Hugdahl K. 2014. Mapping hemispheric symmetries, relative asymmetries, and absolute asymmetries underlying the auditory laterality effect. Neuroimage. 84:962–970.

Wilke M, Lidzba K. 2007. LI-tool: A new toolbox to assess lateralization in functional MR-data. J Neurosci Methods. 163:128–136.

Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE. 2014. Permutation inference for the general linear model. Neuroimage. 92:381–397.

Yeo BTT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, Roffman JL, Smoller JW, Zöllei L, Polimeni JR, Fischl B, Liu H, Buckner RL. 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol. 106:1125–1165.