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Striking a chord with healthy aging: memory system cooperation is related to preserved configural response learning in older adults

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ABSTRACT

Evidence from tasks that primarily tap either hippocampal- or striatal-based memory systems suggests that although these systems often compete for control of behavior, aging is associated with greater cooperation between them. This may stem from altered prefrontal cortex function. Here, we use a configural response task designed to engage both memory systems to test how age affects their interaction with cortical regions including the prefrontal cortex. We found that although older and younger adults learned just as well, older adults showed greater initial activation in cortical networks associated with visuospatial-action mapping and resolving conflict for competing memory representations. Older adults also showed greater functional coupling of the striatum with the left inferior frontal gyrus, in parallel with similar hippocampal coupling to ventral visual regions as young adults. Overall, our results support the proposal that aging is associated with more cooperative memory systems, but we did not find that greater cooperation is associated with less interaction between the prefrontal cortex and core memory system structures during learning.

1. Introduction

As we get older, our ability to learn declines more for some skills than others, but little is known about the underlying changes in brain systems that produce this uneven pattern of decrements. Typically, learning a new skill requires the interaction of multiple complementary memory systems that compete and cooperate to control performance, including a hippocampal-cortical system that excels at rapid flexible binding and a striatal-cortical system that excels at slower acquisition of shared information across experiences (McClelland et al., 1995; Poldrack and Rodriguez, 2004). A number of studies have shown that while these systems are often in competition in healthy young adults, aging results in patterns of brain activity during learning that are more consistent with cooperation (Dennis and Cabeza, 2011; Rieckmann and Backman, 2009; Rieckmann et al., 2010). The interpretation of these patterns has been that the mechanisms thought to mediate competition between memory systems decline with aging, such as cognitive control processes in the lateral prefrontal cortex (Paxton et al., 2008; Poldrack and Rodriguez, 2004). However, it has been proposed that to maintain the ability to learn, older adults use multiple memory systems simultaneously or cooperatively to guide behavior (Pereira et al., 2015; Rieckmann and Backman, 2009).

Rest, independent of sleep, may also play a critical role in how new skills and knowledge are learned and represented at a systems level. Studies outside the aging literature have shown that periods of wakeful rest immediately following learning involve consolidation and are characterized by spontaneous offline reactivation of hippocampal-cortical and neocortical networks that are involved in the preceding learning experience and that the extent of experience-dependent change in functional connectivity (FC) predicts later memory performance (e.g., Tambini et al., 2010). For the first time, we examine whether experience-dependent changes during postlearning rest in hippocampal- and striatal-cortical connectivity differ for young and older adults using resting-state FC.

The long-standing effort to delineate the functional domains of the hippocampal- and striatal-based memory systems has led to most studies using tasks designed to isolate them. Therefore, few studies have used tasks that encourage contributions from both

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systems. However, such tasks can serve as a model for understanding how aging changes the balance between memory systems and their interaction with neocortical systems across different stages of learning. Therefore, the current study uses a configural response learning task designed to engage both hippocampal- and striatal-based memory systems, and we use functional magnetic resonance imaging (fMRI) to test how aging affects the interaction of memory systems across different phases of skill acquisition and memory formation.

Configural response learning involves incidental encoding of coordinated movements through their frequent co-occurrence (Hazeltine et al., 2007). It entails learning specific combinations of movements, or response configurations that have overlapping elements. An example is learning new piano chords that involve different combinations of fingers, where movements are fluid for practiced chords but difficult for other combinations that involve some of the same fingers. The ability to form distinct, higher-order configural representations is necessary for developing a large repertoire of motor skills with relatively limited effectors. The task also provides a model for word learning processes, where new associations between elements of words (phonemes) must be acquired, and elements are shared across words, but their combinations lead to distinct configural representations during speech (Wifall et al., 2014). In the version of the task used in this study, each of 8 individual elements frequently co-occur with each other to elicit associative binding mechanisms that encode and discriminate among pairs with overlapping content. Here, associative binding is thought to initially rely on a hippocampal-based system which can form new associations rapidly and flexibly such that the same finger can belong to multiple response combinations (Atallah et al., 2004; Poldrack and Rodriguez, 2004). However, as new associations are no longer required, a striatal-based system is thought to also acquire information shared across the training experience and control behavior that is more fluid and automatic (Atallah et al., 2004; Poldrack and Packard, 2003; Toni et al., 2001). This account of memory system interaction aligns with the complementary learning systems framework (McClelland et al., 1995; O'Reilly et al., 2014), which proposes that the slower striatal-based system acquires representations through communication with distributed partially overlapping networks relevant to task demands such as sensory and effector representations and higher-order networks attributed to spatial attention and cognitive control.

Although configural response learning places demands on skill acquisition processes that typically decline with aging such as associative binding (Chen and Naveh-Benjamin, 2012; Old and Naveh-Benjamin, 2008; Saverino et al., 2016), we have found that healthy older adults learn the configural response task similarly to young adults (Clark et al., 2015). Other aging studies suggest that this is possibly due to age-related adaptations in how memory systems interact (for review, see Rieckmann and Backman, 2009). In young adults, the hippocampal- and striatal-cortical systems compete by trading-off control of performance during different stages of learning (Poldrack and Packard, 2003; Poldrack and Rodriguez, 2004), whereas in older adults, the interaction between these systems resembles cooperation as expressed by activation of both systems for motor skill learning and episodic memory tasks and prolonged hippocampal activation during motor learning (Dennis and Cabeza, 2011; Rieckmann et al., 2010).

The coordination of memory systems is thought to be mediated by areas of the prefrontal cortex, such as those involved in cognitive control of conflict in response selection (e.g., dorsolateral prefrontal) or representations for rules and coactivated memories (e.g., ventrolateral prefrontal) (Bunge, 2004; Cieslik et al., 2013). These control processes may bias input from 1 system over another depending on the stage of learning (Poldrack and Packard, 2003), and age-related decline in prefrontal cortex function is thought to potentially "release" competition between systems (Pereira et al., 2015; Rieckmann and Backman, 2009). This account suggests that there should be greater coupling between memory systems and the lateral prefrontal cortex for young compared to older adults. In the present study, we test this prediction by examining age differences in how regions of the prefrontal cortex activated by configural response training couple with hippocampal and striatal memory structures during different stages of training.

In sum, the present study extends current knowledge in 3 primary ways. First, we evaluate age differences in brain activation patterns during training on a configural response task that encourages interaction between associative binding and motor learning processes. This allows us to test whether the brain regions involved in configural response learning indeed overlap with networks involved in language and word learning and whether the regions involved differ for young and older adults. Second, we evaluate age differences in the interaction between memory systems and brain regions whose activation changes during task training. Third, we examine changes in memory system interaction during the resting state from before to after configural response training. This allows us to test the generalizability of age differences in competitive versus cooperative interaction patterns during the immediate consolidation phase when memory processes are still actively occurring in the absence of task performance.

2. Materials and methods

2.1. Overview

The entire experiment consisted of 3 laboratory visits, including a screening day and 2 experimental days. Screening consisted of a mock MRI, collection of basic demographic information and health history, and cognitive screening with the Mini-Mental Status Exam (MMSE). This screening visit was followed by 2 days of experimental data collection. During day 1, participants initially practiced stimulus-response mappings for 8 individual faces that were each mapped to 8 possible finger responses. This was followed by a 90-minute MRI scanning session at the University of Iowa Magnetic Resonance Research Facility that included both structural and functional neuroimaging (see Fig. 1). During functional scans, participants completed five 8-minute training sessions on the configural response task. Day 2 was approximately 1 week later (average of 6.3 days, standard deviation [SD] = 1.2), during which participants completed 5 additional training sessions on the configural response task in our laboratory (outside the scanner). The Institutional Review Board at the University of Iowa approved all procedures, and all participants were compensated for their participation.

2.2. Participants

Participants were recruited from the greater Iowa City community using an approved university email advertisement, local fliers, and approved advertisements at the University of Iowa Hospitals and Clinics. Eligible participants had to (1) demonstrate strong right handedness, with a 75% or above on the Edinburgh Handedness Questionnaire (Oldfield, 1971); (2) be between the ages of 18 and 30 years for young adults or between 60 and 80 years for elderly adults; (3) score >24 on the MMSE-2SV (Folstein et al., 1975; Tombaugh, 2005); (4) have no self-reported neurological and/or psychiatric condition including stroke or clinical depression; (5) have normal color vision; (6) have a corrected visual acuity of at least 20/40; (7) have no self-reported regular use of medication that could affect the central nervous system (e.g., psychotropics, recent

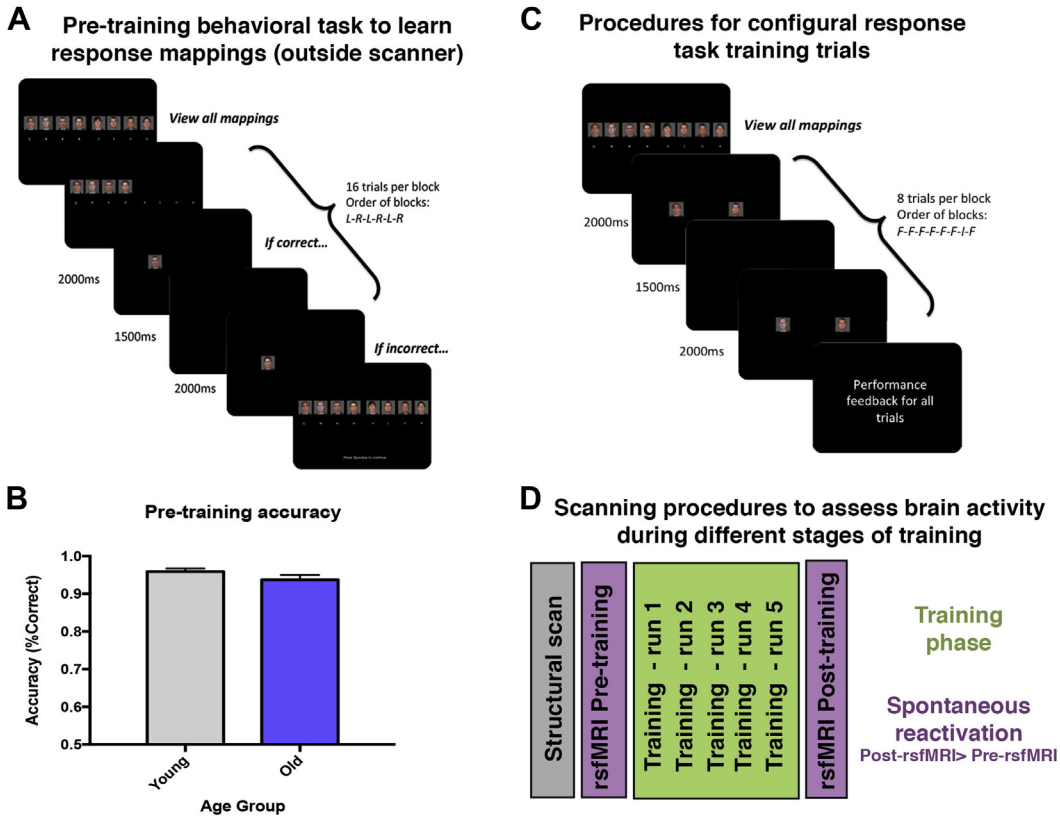

Fig. 1. Design and procedures of configural response task. (A) Example trial from the initial stimulus-response mappings phase that preceded training on the learning task, letters under each face stimulus correspond to the letters on the keyboard mapped to each face stimulus (left hand: q, w, e, r; right hand: u, i, o, p). (B) Pretraining task accuracy did not differ between young and older adults. (C) Example trial sequence for 1 session of configural response trials. Letters under each face stimulus on the first screen correspond to the letters on the keyboard mapped to each face stimulus (left hand: q, w, e, r; right hand: u, i, o, p). (D) Configural learning was assessed during MRI scanning on experimental day 1, including different types of scans to assess acquisition during task training and spontaneous reactivation during resting state. Abbreviation: MRI, magnetic resonance imaging.

or current chemotherapy, hypertension medication); and (8) sign an informed consent.

Young and older adult participants were recruited with a matched groups approach, based on gender and education. Five young and 5 older adults were excluded due to excessive baseline scanner movement that covaried with task onset/offset during task performance. The final sample included 12 young adults (6 F; age 24.8 years [SD = 2.8], education = 17.2 years [SD = 1.5]) and 12 older adults (6 F; age 64.3 years [SD = 3.3], education = 17.9 years [SD = 1.6]). Older adults performed near ceiling on the MMSE-2SV, with a mean score of 29.67 (SD = 0.65), and groups did not differ in musical experience (see Supplementary Materials).

2.3. Configural response task procedures and preprocessing

The configural response task and related preprocessing of behavioral data in the current study is identical to the task used in our previous study (Clark et al., 2015). One exception is that in the present study, on day 1 of experimental data collection, participants completed training sessions of the task during functional MRI scanning. Within an hour before scanning, participants performed a 7-minute pretraining task to learn individual stimulus-response mappings for each finger (Fig. 1). Next, in the training task, we compare the extent to which participants become faster in responding to pairs of faces that they frequently practice (FR), compared to pairs of faces that they infrequently practice (IF). Critically, each face stimulus appears an equal number of times throughout training so that familiarity with individual faces is matched across FR and IF blocks. In this way, the IF blocks serve as a probe to assess the configural learning of specific face pairs rather than individual elements. Therefore, the primary outcome reflecting configural response learning is a learning score reflecting the extent to which responses are faster for FR relative to IF pairs, scaled by the average standard deviation of FR and IF reaction times. See Clark et al. (2015) for further task details, as well as Supplementary Materials of the current report.

With respect to task timing during scanning, each block contained 8 trials. Each trial began with the presentation of a fixation cross for 500 ms, followed by an individual face on either the left or right side for 2000 ms, followed by a 1000 ms intertrial interval. Each task block lasted 26.5 seconds and was followed by a 29.5 seconds rest block during which participants viewed a white fixation cross. Feedback in the form of average performance (response time and accuracy) was given following a “session” of 8 task blocks, which included 7 blocks of the FR pairs and 1 block of IF pairs. FR and IF pairs were sampled randomly without replacement within each block. Participants completed 5 sessions (280 trials FR/40 trials IF) during scanning.

2.4. MRI data acquisition

All images were collected on a 3T head-only Siemens Tim Trio MRI scanner with a receive-only 12-channel phased-array head-coil. Foam pads were used on both sides of the head to reduce head motion–related artifacts. For all participants, high-resolution ($1 \times 1 \times 1$ mm) T1-weighted brain images were acquired using a magnetization-prepared rapid gradient echo imaging protocol with 240 contiguous coronal slices, echo time (TE)/inversion time (TI) = 3.09/900 ms, repetition

time = 2530 ms, matrix size = 256 × 256 mm, field of view = 256 × 256 × 240 mm, and flip angle = 10°. A parallel imaging technique known as generalized autocalibrating partially parallel acquisition with an acceleration factor of 2 was used for the magnetization-prepared rapid gradient echo imaging scan.

Functional neuroimaging data of the blood-oxygen–level dependent (BOLD) effect were acquired with single-shot echo planar imaging. All functional images were acquired with a voxel size of 3.4375 × 3.4375 × 4 mm, with an ascending axial slice acquisition and no gap between slices, and TE = 30 ms, repetition time = 2000 ms, flip angle = 80°, field of view = 220 × 220 × 124 mm, and image matrix of 64 × 64 × 31 mm. There were 237 volumes acquired for each of the 5 configural response training task scans (approximately 8 minutes each) and 180 volumes acquired for each of the pretraining and post-training resting-state scans (6 minutes each). The configural response task was created and presented with E-prime software. Visual stimuli were presented to the participant using a DLP projector (Panasonic 3500) with a rear projection screen. Participants used Psychology Software Tools (PST) fiber optic manipulanda for the left and right hands. When vision needed to be corrected in the scanner, MediGoggles interchangeable prescriptive glasses were used.

2.5. fMRI task data processing and statistical analyses

All fMRI data were converted from DICOM to NIFTI with Freesurfer's *mri_convert* tool. Further task analyses were carried out with FSL 5.0.10/FEAT version 6.00, part of FSL (FMRIB's Software Library). Preprocessing for each of the fMRI scans first included rigid body motion correction using MCFLIRT (Jenkinson et al., 2002), removal of nonbrain structures using BET (Smith, 2002), spatial smoothing using a Gaussian kernel of full width at half maximum 6.0 mm, and denoising with nonaggressive Independent Component Analysis-based Automatic Removal Of Motion Artifacts (ICA-AROMA) (Pruim et al., 2015). ICA-AROMA is a validated data-driven method to identify motion-related signal in the data. The program uses FSL's Multivariate Exploratory Linear Decomposition into Independent Components (MELODIC) tool to extract independent components from the data and classifies them as motion related based on whether they exceed 1 of 3 criteria: (1) a decision boundary combining the edge fraction and maximum realignment parameters correlation; (2) a cerebrospinal fluid fraction higher than 10%; or (3) a high-frequency content larger than 35%. Following denoising with ICA-AROMA, functional data were entered to FEAT using a 120-second high-pass temporal filter applied to both the model and data. Local autocorrelation correction of the time-series data was carried out with FSL's FILM (Woolrich, 2001), and the task model was convolved with a double-gamma hemodynamic response function to form predictors for each task condition.

Of primary interest for the configural response task scans was the contrast of BOLD signal for FR pairs relative to baseline across phases of task training. For consistency with the behavioral model for learning, we tested a linear contrast of increasing or decreasing activation across fMRI runs. All contrasts for whole-brain analyses were first computed at the individual level and then carried forward to a mixed-effects group analysis with age group as a factor. Higher-level mixed-effects analyses were carried out using FLAME (Beckmann et al., 2003) with outlier deweighting across all participants (Woolrich, 2008) on spatially normalized statistical images. To perform spatial normalization, each participant's functional image was registered to their high-resolution structural T1 image using the boundary-based registration algorithm (Greve and Fischl, 2009), and each participant's high-resolution structural image was registered to a study-specific standard space with FNIRT nonlinear registration using a default 10 mm warp resolution (Andersson et al., 2007). These 2 transformations were then concatenated and applied to the participant's functional image to register their functional echo planar image to a standard space. The study-specific template was generated from the full sample with the advanced normalization tools multivariate template construction procedure (http://stnava.github.io/ANTs/) (Avants et al., 2011).

Statistical maps were thresholded nonparametrically using clusters determined by $Z > 3.1$ and a corrected cluster significance threshold of $p < 0.05$ (Worsley, 2001). Together, these procedures have been shown to appropriately control for multiple comparisons in whole-brain statistical mapping (Eklund et al., 2016). Because we did not have a strong a priori prediction about whether activation would increase or decrease or how this pattern would interact with age group, our primary contrast to generate regions of interest (ROIs) was an omnibus F-test of where activation either increased or decreased for either young or older adults. Activation in resulting ROIs was further examined in a linear mixed-effects model with the same approach as the behavioral analyses described in Supplementary Materials.

For FC analyses, an ROI analysis was carried out based on theoretical interest from the literature on aging and skill acquisition. A priori ROIs were 125 standard space voxels before warping to individual subject space. The striatal ROIs included the bilateral dorsal caudate (BDC) (Montreal Neurological Institute [MNI] coordinates: ±13, 15, 9), the bilateral dorsal rostral putamen (BDRP) (MNI ±25, 8, 6), and the bilateral dorsal caudal putamen (BDCP) (MNI ±28, 1, 3) (Di Martino et al., 2008; Postuma and Dagher, 2006). The bilateral hippocampus (HIPP) region was chosen as a posterior hippocampal region previously associated with dedifferentiation of learning systems at MNI coordinates L (−23, −30, −11) and R (23, −30, −11) (Dennis and Cabeza, 2011).

2.6. fMRI data processing for FC analyses

FC analyses were carried out on the pretraining and post-training 6-minute resting-state scans (180 volumes each) and on the first 6 minutes of each configural response training scan (180 volumes each). Configural response scans were truncated so that only FR blocks were included and to match the length of the resting-state scans. This allowed us to conduct the same FC analyses during rest and task. Analyses were carried out with an in-house script library using tools from FSL 5.0.4, AFNI, FreeSurfer, and MATLAB. Briefly, preprocessing included motion correction using AFNI's *3dvolreg* function, brain extraction with FSL's *bet* tool, spatial smoothing (6 mm full width at half maximum), ICA-AROMA as described previously, temporal filtering ($0.008 < f < 0.08$ Hz), and nuisance regression (6 motion parameters, white matter, CSF). Volumes above a frame-wise displacement threshold of 0.5 mm that coincided with BOLD signal changes in the residual time series were removed from subsequent FC analyses (Hallquist et al., 2013). Overall, this only affected 4% of all volumes for young adults and 2% of volumes for older adults. To examine the interaction of core memory system structures with regions showing strong evoked response during task training, we examined targeted changes in FC between memory structure ROIs (HIPP, BDC, BDRP, and BDCP) and regions changing in activity during training for young and older adults. These FC estimates are Pearson's correlation coefficients transformed to Fisher's Z correlations.

3. Results

3.1. Configural response task performance

Young and old adults performed with similar accuracy on the pretraining task (see Supplementary Materials). This indicates that

young and older adults started with similar strength of response mappings before training on their combinations. Configural response task performance during scanning replicated our results from an independent sample of young and older adults in our previous study (Clark et al., 2015). To briefly summarize the results, young adults performed more accurately on the configural response task across both FR and IF conditions ($t(22.10) = -3.547$, $p < 0.05$), but neither young or older adults had significantly different accuracy for FR and IF conditions (see Fig. S1A). Therefore, we measured configural response learning as the relative speeding in FR practiced pairs compared to IF practiced pairs. After accounting for older adults' general slowing in response speed, a linear mixed model showed there was no difference in rate of change for configural response learning scores between young and older adults (see Fig. S1C). We direct readers to the Supplementary Materials for a full statistical report of the behavioral findings.

3.2. Are there age-related differences in spatiotemporal activation patterns during configural response training?

To answer whether the regions involved in configural response learning differ for young and older adults, we first compared activation patterns of young and older adults during configural response training. We examined where the evoked BOLD response changed over the course of training with a similar temporal pattern as learning by using an analysis of variance (ANOVA) to identify regions that showed either a linearly increasing or decreasing pattern of FR > baseline activation for either young or older adults. The ANOVA resulted in a broad network of regions shown in Fig. 2 and described anatomically in Table 1. The right and left inferior lateral occipital cortices (RILOC and LILOC) showed the highest evoked BOLD response to the task for both age groups, which is consistent with their anatomical placement on the fusiform gyrus associated with face processing. Next, we observed a cluster in the dorsal pons of the brain stem that included the pendunculopontine nucleus, aspects of the dorsal raphe nucleus, and extended into a functional-anatomically distinct cluster in the left parahippocampus. Although it is difficult with our spatial resolution to demarcate different subregions of the brain stem, for further ROI analyses we separated the brain stem (BSTEM) from the cortical aspects of this cluster in the left parahippocampus (LPHIPP) to preserve their known functional distinctions in learning and memory processes. We also observed clusters in the right and left superior lateral occipital cortices (RSLOC and LSLOC), which are known to be associated with the dorsal attention network involved in goal-directed spatial attention (Corbetta et al., 2008). Finally, we observed a cluster in the left ventrolateral prefrontal cortex that included the left inferior frontal gyrus (LIFG) and the anterior insula (LINS).

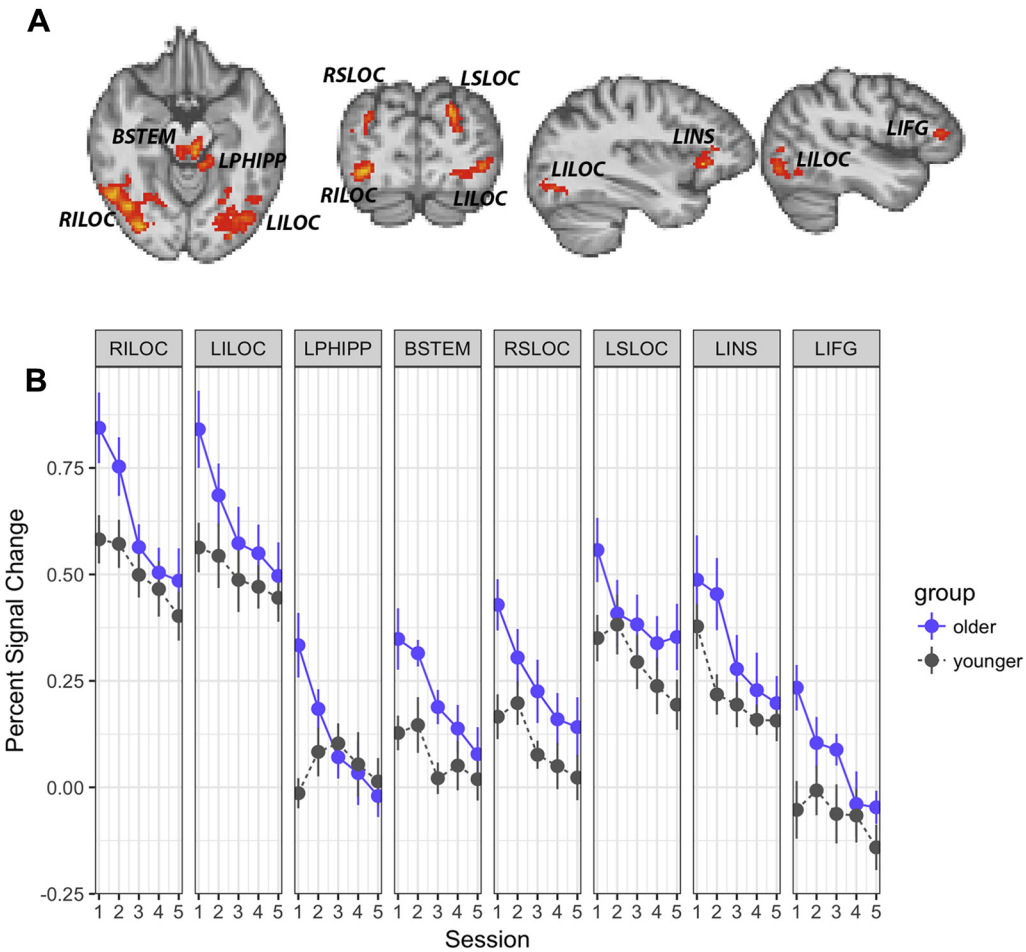

Fig. 2. Average activation pattern for the contrast of FR > baseline F-test of linearly increasing or decreasing activity for young or older adults. (A) All statistical maps were thresholded at $Z > 3.1$, $p < 0.05$, for all images L = R, acronyms correspond to those in Table 1. (B) Each line graph shows observed percent signal change for each fMRI session ± standard error at each session. All regions except RSLOC and LSLOC showed a significant session × group interaction in a follow-up region of interest (ROI) analysis with linear mixed-effects modeling. Abbreviations: fMRI, functional magnetic resonance imaging; FR, frequently practice; LSLOC, left superior lateral occipital cortex; RSLOC, right superior lateral occipital cortex.

Table 1
Statistical peaks for omnibus F-test for linear decrease or increase of activation in the FR condition for young or older adult group

Cluster anatomical description	Cluster size ($2\ mm^3$ voxels)	Peak in custom template (x, y, z)	Peak Z-value	Derived regions of interest (ROIs)
Right lateral occipital cortex, inferior, and extending into occipital fusiform cortex	951	33.8, −12.7, −18.6	5.01	RILOC
Left lateral occipital cortex, inferior, and extending into occipital fusiform cortex	426	−40.2, −30.7, −4.57	4.33	LILOC
Brain stem, including primarily subdivisions of	291	−6.17, 15.3, −10.6	5.17	BSTEM
Dorsal pons in brain stem				LPHIPP
Left paraphippocampal gyrus				
Right lateral occipital cortex, superior, and extending into parietal cortex	287	29.8, −38.7, 27.4	4.35	RSLOC
Left lateral occipital cortex, superior, and extending into parietal cortex	220	−20.2, −28.7, 35.4	5.16	LSLOC
Left ventrolateral prefrontal cortex including subdivisions of	212	−36.2, 69.3, 9.43	4.91	LIFG
Left inferior frontal gyrus				LINS
Anterior insula				

Group-level mixed-effects analyses were conducted in study-specific template space with 2 mm isotropic voxels. All clusters significant at voxelwise threshold of $Z > 3.1$ and cluster corrected at $p < 0.05$. Acronyms provided for ROIs that characterized distinct functional-anatomical regions within the cluster identified with voxel-level analyses. Unthresholded statistical maps, masks for each ROI, and a 3D image of voxels estimated as outliers during outlier deweighting are provided on github (https://github.com/mwvoss/ProjectChordLearning). An unthresholded statistical map warped to MNI space is also provided on neurovault (https://neurovault.org/collections/2983/).
Key: BSTEM, brain stem; LIFG, left inferior frontal gyrus; LILOC, left inferior lateral occipital cortex; LSLOC, left superior lateral occipital cortex; RILOC, right inferior lateral occipital cortex; RSLOC, right superior lateral occipital cortex.

To further characterize the nature of change within these clusters identified with the overall ANOVA, percent signal change within each task-derived ROI for the FR > baseline contrast was modeled over time by fitting a linear mixed-effects model in *R*. The initial model included fixed effects for age group, fixed and random effects for intercept (centered to the middle session), linear slope (the rate of change over session) and a quadratic slope (the rate of acceleration or deceleration across sessions), and a group × session interaction term to test whether young and old activation level changed differently during training. For each ROI, a series of likelihood-ratio tests were used to determine the maximal random effects structure supported by the data based on a model simplification approach.

Only the LILOC and RILOC were best modeled by the most complex model. The LILOC model showed significant effects of intercept ($t(22) = 10.75$, $p < 0.001$), linear session ($t(22) = -6.03$, $p < 0.001$), and linear session × group ($t(22) = -3.83$, $p < 0.001$). Similarly, the RILOC model showed significant effects of intercept ($t(22) = 13.21$, $p < 0.001$), linear session ($t(22) = -5.80$, $p < 0.001$), and linear session × group ($t(22) = -2.76$, $p = 0.01$). For both regions the session × group interaction was driven by older adults showing greater activation early in training and a steeper activation decline across sessions (Fig. 2B).

The LPHIPP was best modeled with linear and quadratic fixed effects, and random effects for intercept and linear slope. This LPHIPP model showed significant effects of intercept ($t(34.25) = 3.49$, $p = 0.001$), linear session ($t(36.04) = -3.33$, $p = 0.002$), linear session × group ($t(36.04) = -4.83$, $p < 0.001$), and quadratic session × group ($t(212) = 3.4$, $p < 0.001$). Again the linear session × group interaction reflects greater activation during early training and a steeper linear activation decline for older adults. The quadratic session × group interaction was driven by older adults showing linearly decreasing activity that decelerated during the last 3 sessions, whereas young adults showed an inverted U pattern of increasing followed by decreasing activity across the training sessions (Fig. 2B).

The LINS and LSLOC were best modeled with linear and quadratic fixed effects and random intercepts. The LINS model showed significant effects of intercept ($t(27.44) = 5.74$, $p < 0.001$), linear session ($t(212) = -7.04$, $p < 0.001$), quadratic session ($t(212) = 2.82$, $p = 0.005$), and a linear session × group interaction ($t(212) = -2.87$, $p = 0.004$). The LSLOC model showed significant effects of intercept ($t(25.73) = 7.27$, $p < 0.001$), linear session ($t(212) = -5.86$, $p < 0.001$), and quadratic session ($t(212) = 2.29$, $p = 0.02$), reflecting a similar decline in activation over training for young and older adults. Finally, the LIFG, RSLOC, and BSTEM were best modeled with only a linear fixed-effect term and random intercepts. The LIFG model showed significant effects of linear session ($t(214) = -4.88$, $p < 0.001$) and linear session × group ($t(214) = -3.96$, $p < 0.001$), reflecting greater initial activation for older adults followed by linear decline during training. The RSLOC model showed significant effects of intercept ($t(22) = 5.13$, $p < 0.001$) and linear session ($t(214) = -7.02$, $p < 0.001$), reflecting similarly declining activation during training for young and older adults. The BSTEM model showed significant effects of intercept ($t(22) = 5.89$, $p < 0.001$), linear session ($t(214) = -6.17$, $p < 0.001$), group ($t(22) = 2.69$, $p = 0.01$), and a linear session × group interaction ($t(214) = -2.56$, $p = 0.01$), again reflecting greater initial activation for older adults followed by linear decline during training.

In summary, all regions except the LSLOC and RSLOC showed a linear session × group interaction that reflected greater initial activation followed by a steeper decrease over training sessions for older compared to younger adults (Fig. 2B). Only the LPHIPP also showed a quadratic session × group interaction, driven by an early rise in activation for young adults, compared to an early decrease in activation for older adults. These results suggest that younger and older adults activate a similar pattern of brain regions during configural response learning, especially in occipital and temporal cortex. However, older adults show higher initial activation levels, which decline to the level of young adults by the end of training sessions, especially in the ventral visual cortex, left parahippocampus and brain stem, and the left ventrolateral prefrontal cortex (LIFG and LINS). The similarity of the BOLD response between young and older adults during the end of training suggests that the high initial activation from older adults is not due to a general confound of regional differences in the intrinsic nature of the hemodynamic response (Samanez-Larkin and D'Esposito, 2008). Rather, the pattern of age differences suggests greater initial demands on perceptual discrimination of faces (RILOC, LILOC, and LPHIPP) and resolution of conflict while acquiring the rule structure of stimulus-response relationships (LIFG and LINS). We expand on these accounts in the context of cognitive aging and learning in the Discussion.

3.3. Are there age-related differences in how core memory structures interact with cortical regions during and immediately after configural response training?

Here, we evaluate whether young and old adults differ in how core memory structures interact with task-evoked regions during training and consolidation phases. We examined interaction with

the task-evoked network using a repeated measures ANOVA that included memory ROI (HIPP, BDC, BDRP, and BDCP), task-evoked ROI (RILOC, LILOC, BSTEM, LPHIPP, RSLOC, LSLOC, LINS, and LIFG), and session (1, 2, 3, 4, 5) as within-subject factors, and age group as a between-subjects factor. For all models, FC between the memory ROI and task-evoked ROI was the dependent variable. We report only effects not qualified by higher-level interactions in the main text and direct readers to Supplementary Materials with access to analysis notebooks that include code for our statistical models and their corresponding results.

3.3.1. FC during learning

When considering the full model with all ROIs, there was a 3-way interaction between memory ROI, task ROI, and age group ($F(21,462) = 2.31$, $p < 0.001$, $\eta^2 = 0.01$, $\eta_p^2 = 0.10$). Thus, unlike the activation magnitude effects, age groups differed in how memory and task-derived ROIs interact irrespective of training run. In order to focus on age group differences, we break this 3-way interaction down by evaluating group × memory ROI interactions for each task-derived ROI and correct for multiple comparisons across 8 task ROIs ($p < 0.006$). Results from these post hoc tests showed that only the LIFG had a significant group × memory ROI effect ($F(2.43, 53.36) = 7.75$, $p < 0.001$, $\eta^2 = 0.05$, $\eta_p^2 = 0.26$). When evaluating group differences in each memory ROI using a corrected p-value for multiple comparisons across 4 ROIs ($p < 0.01$), we find this interaction is driven by older adults having greater FC between LIFG and BDC ($t(73.26) = -4.36$, $p < 0.001$) with a trend for the same pattern for the BDRP ($t(73.26) = -2.64$, $p = 0.01$).

We also note that in the overall ANOVA, there was a memory ROI × task ROI interaction ($F(21,462) = 24.58$, $p < 0.001$, $\eta^2 = 0.12$, $\eta_p^2 = 0.53$). This result is of theoretical interest because this indicates that the memory ROIs interacted differently with regions showing activation changes over the course of training. To focus on memory system interactions, we break this down by examining memory ROI effects within each task-evoked ROI (corrected significance threshold of $p < 0.006$). The LINS showed an effect of memory ROI ($F(1.98, 43.47) = 9.76$, $p < 0.001$, $\eta^2 = 0.05$, $\eta_p^2 = 0.31$), driven by higher FC with each of the striatal regions compared to the hippocampus [BDC($t(66) = 4.35$, $p < 0.001$), BDCP($t(66) = 4.44$, $p < 0.001$), BDRP($t(66) = 4.46$, $p < 0.001$)]. In addition, the BSTEM showed a main effect of memory ROI ($F(1.57, 34.59) = 24.22$, $p < 0.001$, $\eta^2 = 0.19$, $\eta_p^2 = 0.52$) that was driven by greater FC with the HIPP compared to all striatal ROIs [BDC($t(66) = -7.53$, $p < 0.001$), BDCP($t(66) = -6.64$, $p < 0.001$), BDRP($t(66) = -6.54$, $p < 0.001$)]. The LPHIPP showed the same pattern of main effect of memory ROI ($F(1.60, 35.22) = 100.38$, $p < 0.001$, $\eta^2 = 0.44$, $\eta_p^2 = 0.82$), driven by greater FC with the HIPP compared to all striatal ROIs [BDC($t(66) = -15.72$, $p < 0.001$), BDCP($t(66) = -12.60$, $p < 0.001$), BDRP($t(66) = -13.45$, $p < 0.001$)]. Finally, the RILOC also showed a main effect of memory ROI ($F(1.96, 43.11) = 7.97$, $p = 0.001$, $\eta^2 = 0.06$, $\eta_p^2 = 0.27$), driven by greater FC with the HIPP compared to the BDC ($t(66) = 4.84$, $p < 0.001$). It is worth emphasizing again that the RILOC ROI overlaps with regions associated with face processing and that this right lateralized region has been causally associated with face perception (Rangarajan and Parvizi, 2016).

3.3.2. FC changes during resting state before and after task training

With the same approach, we examined how resting FC of memory systems changed from before to immediately after configural response training. The overall model showed a significant memory ROI × task ROI interaction ($F(7.38, 162.43) = 11.62$, $p < 0.001$, $\eta^2 = 0.11$, $\eta_p^2 = 0.35$). However, post hoc tests showed that this was driven by the LPHIPP and BSTEM having greater FC with the HIPP compared to each striatal ROI (all p's < 0.001; see Supplementary Fig. 2). This is unsurprising given the proximity of these ROIs. There were no main effects or interactions involving age group in the overall ANOVA.

4. Discussion

This study is the first to comprehensively examine age differences in memory system interaction during configural response learning, a task that promotes interaction of hippocampal- and striatal-based memory systems. The task involves processes that have been ascribed to the hippocampal learning system, including rapid associative learning about the relationships between visual-motor associations without interference of overlapping visual or motor elements across relationships. With training, production of more practiced response configurations becomes more fluid and automatic, presumably guided by the striatal-based memory system. The same demands are central to many real-world tasks and to building a vast repertoire of motor skills composed simply of different combinations of effectors. For example, learning how to drive a new car involves learning not only what to do with 1 hand at a time but also how to fluidly combine movements of the left and right hand and each foot into specific postures such as switching turn signals, adjusting speed, and navigating the car. As introduced earlier, configural learning has also been proposed as a model for word learning processes, as we must learn the relations of overlapping phonemes with speech productions for different configurations of words (Wifall et al., 2014). In these ways, configural response learning is a rich model system for both basic and applied investigations of the lifespan development of interacting memory systems.

We first emphasize that the present study replicated our previous behavioral results from an independent sample, showing that older adults can learn a configural response task as well as younger college-age adults despite placing demands on memory systems which are known to degrade with aging (Clark et al., 2015). Because aging is associated with deterioration of both hippocampal and dorsal striatal systems (Raz et al., 2003, 2005), we examined functional brain activation and connectivity patterns to further understand how these memory systems support similar task performance for young and older adults. With respect to neural mechanisms, we aimed to answer 3 overarching questions: (1) what brain regions are involved in configural response learning and how do their spatial and temporal pattern during training compare between young and older adults; (2) does age group impact how hippocampal and striatal memory structures interact with cortical regions during configural response training; and (3) does age group impact how hippocampal and striatal memory structures interact with cortical regions during immediate offline consolidation?

Regarding activation patterns during training, we found that young and older adults engaged in a similar network of regions that were most active during the first session followed by a decline during training (Fig. 2). To empirically characterize component cognitive processes previously linked with the observed activation pattern seen during configural response learning, we compared the spatial pattern of our F-statistic map (Fig. 2A) with the activation patterns found from a large array of different types of perceptual and cognitive tasks (Yeo et al., 2015). The largest overlap was with a network comprised of dorsal ("where") and ventral ("where") visual streams ($r = 0.36$) that was active during visual tracking, action observation, and naming tasks (component C4+). The second largest overlap was with a network active during a variety of language tasks ($r = 0.29$), such as naming, word generation, and syntactic discrimination (component C5). These patterns reflect an integration of visuospatial attention and visual-action mapping with language processing that has previously been proposed (Hazeltine et al., 2007; Wifall et al., 2014) but not formally tested with functional neuroimaging during configural response training.

In particular, the LIFG is proposed to support the resolution of conflict between competing representations during memory and language processes (Musz and Thompson-Schill, 2017), and its functional integration with broader networks during language processing is preserved with healthy aging (Campbell et al., 2016; Shafto and Tyler, 2014). Similarly, the left ventrolateral prefrontal cortex (PFC) has also been proposed to be involved in resolving conflict between competing representations for rules (Bunge, 2004). With this in mind, it is notable that age differences in activation were particularly consistent in the LIFG where young adults showed no activation above baseline during configural response training (Fig. 2B). Moreover, throughout training older adults showed greater coupling of the LIFG with the BDC compared to young adults (Fig. 3). The fact that this interaction for FC was not present during the resting state supports the conclusion that age differences in striatal-cortical coupling were evoked by configural response learning. What could the steep decline in LIFG activation together with the stable pattern of LIFG coupling with the BDC represent with respect to learning mechanisms? One possibility is that the greater earlier coupling with BDC reflected a greater amount of feedback and integrative synaptic coding needed in the LIFG and that the amplitude of the signal received by the LIFG subsided as the system became tuned with training-related strengthening of configural response representations (Kumaran et al., 2016).

We also note that young adults do not show a pattern like that observed for older adults with the LIFG in any ROI in our analyses. In contrast, young adults showed more biased use of the hippocampal system together with the ventral visual stream, without strong evidence of parallel striatal involvement. Indeed, both age groups showed stronger coupling of the right lateralized face-sensitive ventral visual cortex (RILOC) with the HIPP compared to other memory ROIs. Unlike the LIFG, the ventral visual streams showed a pattern of decreasing activation and FC for older adults. Because studies have shown that older adults have poorer specificity for face representations (e.g., Goh et al., 2010; Park et al., 2012), older adults' higher early activation may reflect initially broader tuning curves for face stimuli involved in learning distinct conjunctive configural representations. However, studies have also observed that older adults have a generally weaker signal in ventral visual cortex (Davis et al., 2008), presumed to occur because of poorer perceptual discrimination from weaker dopaminergic modulation of perceptual representations (Li et al., 2009). Although our design limits inferences about the role of perceptual discrimination in age differences in activation, future studies could parametrically manipulate the similarity of cue stimuli and response configurations (e.g., Wifall et al., 2014) to determine the role of different discrimination processes in initial activation levels and corresponding learning performance for older adults.

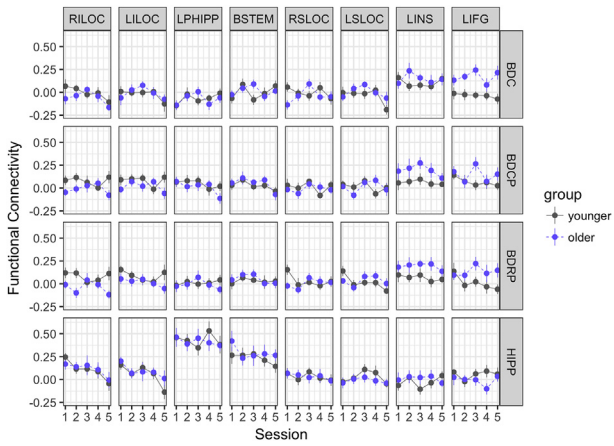

Fig. 3. Changes in FC of core memory system ROIs with cortical regions active during configural response training for young and older adults. See Fig. 2 and Table 1 for details on the cortical regions, including full explanation of acronyms. Error bars represent standard error of the mean. Abbreviations: For memory ROIs, BDC, bilateral dorsal caudate; BDCP, bilateral dorsal caudal putamen; BDRP, bilateral dorsal rostral putamen; FC, functional connectivity; HIPP, hippocampus.

Some have proposed that age group–related increases in cooperation of memory systems may result from less top-down control from PFC cortical structures (e.g., Pereira et al., 2015; Rieckmann and Backman, 2009), which in turn could release competition to allow for more cooperation in guiding behavior. An alternative possibility is that there is greater dedifferentiation (less specificity) in how memory systems become evoked to guide behavior (Dennis and Cabeza, 2011), and this could occur with greater nonselective interaction with the PFC during learning (Rieckmann and Backman, 2009). Although our data support the proposal that older adults showed more parallel involvement of hippocampal and striatal systems during training, we did not find this to be related to a lack of PFC activation or coupling. In contrast, older adults showed greater dorsal striatal coupling with the LIFG throughout training (Fig. 3, movies in Supplementary Fig. 3). Thus, a critical next step is to determine the generality of this pattern to training with similar stimulus-response features but which requires learning a different class of relational rules. Neuromodulation approaches, such as repetitive transcranial magnetic stimulation, would also be helpful to further test the causal role of PFC in the nature of interactions between memory systems for young and older adults.

Finally, with respect to our third question, we examined changes in resting-state FC before and after training, which allowed us to further test the generalizability of age differences in competitive versus cooperative interaction patterns during the immediate consolidation phase when memory processes are ongoing in the absence of task performance. We did not find strong evidence from the resting-state data that age group impacts how memory systems interact during immediate post-training consolidation phases.

As with any study, our results should be viewed in the context of several limitations. First, while our sample sizes are somewhat small, our behavioral results replicate our previous results with an independent sample of young and older adults, which increases our confidence that the configural learning scores are similar for the 2 groups. Our sample size is also similar to previous studies that have detected age differences in the interaction of learning systems during learning (Dennis and Cabeza, 2011; Rieckmann et al., 2010; Simon et al., 2012). Further, a block design is robust for optimizing the detection of regional activation (Amaro and Barker, 2006), and the mixed-effects analysis approach conjointly accounts for individual differences in variance in between-subjects analysis and deweights voxels for individuals that are detected as outliers compared to the rest of the sample (Woolrich, 2008). In turn, our approach for subsequent FC analyses used a targeted ROI approach that included ROIs defined a priori for theoretical interest together with task-derived cluster ROIs, and subsequent ANOVA analyses corrected for multiple comparison for all post hoc tests. Thus, our design and analysis minimized statistical decision errors at the group level. However, we acknowledge that our sample size does not allow investigation of individual differences within age groups and that this will be an important direction for future research to understand the heterogeneity of activation and network profiles related to learning in older adults (e.g., Nyberg et al., 2012). In addition, our cross-sectional design limits inferences about the process of change or adaptations during aging. Longitudinal studies are needed to characterize age-related changes in memory system interaction at a finer temporal resolution over time. Finally, our fMRI-based measures of FC cannot speak to the directionality of the

connectivity between brain regions, they do not exclusively represent direct projections between structures, and they represent synchrony over several minutes. However, fMRI is the only tool that can be used to image functional brain activity throughout the human brain, with relatively good temporal and spatial resolution, and non-invasively such that there can be many repeated measures over time.

In sum, our study provides the first mechanistic insight into how healthy older adults differ from young adults in configural response learning processes. Older adults showed preserved configural response learning compared to young adults. Our results suggest that older adults may learn as well as young adults via increased initial involvement of systems involved in visuospatial-action mapping and resolving conflict for competing memory representations and engagement of these cortical networks with complementary memory systems. These findings have implications for understanding how the brain adapts to deterioration of core memory structures during late adulthood. In this case, similar brain regions were involved in configural response learning but with different localized weights of striatal connectivity with the LIFG. This is broadly consistent with the idea that healthy cognitive aging can in some cases be attained by adaptive increases in overall activation and reconfiguration of neural systems rather than delay of brain aging (Lindenberger, 2014; Pereira et al., 2015).

Disclosure statement

The authors have no actual or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2017.11.001.

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