

ORIGINAL ARTICLE

Reduced Fidelity of Neural Representation Underlies Episodic Memory Decline in Normal Aging

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Abstract

Emerging studies have emphasized the importance of the fidelity of cortical representation in forming enduring episodic memory. No study, however, has examined whether there are age-related reductions in representation fidelity that can explain memory declines in normal aging. Using functional MRI and multivariate pattern analysis, we found that older adults showed reduced representation fidelity in the visual cortex, which accounted for their decreased memory performance even after controlling for the contribution of reduced activation level. This reduced fidelity was specifically due to older adults' poorer item-specific representation, not due to their lower activation level and variance, greater variability in neuro-vascular coupling, or decreased selectivity of categorical representation (i.e., dedifferentiation). Older adults also showed an enhanced subsequent memory effect in the prefrontal cortex based on activation level, and their prefrontal activation was associated with greater fidelity of representation in the visual cortex and better memory performance. The fidelity of cortical representation thus may serve as a promising neural index for better mechanistic understanding of the memory declines and its compensation in normal aging.

Key words: aging, compensation, episodic memory, functional MRI, MVPA

Introduction

Extensive and converging evidence has suggested that normal aging is associated with a decline in episodic memory (Old and Naveh-Benjamin 2008; Koen and Yonelinas 2014). One important characteristic of this decline is that compared with younger adults, older adults remember less specific information but tend to rely more on the abstract/gist-based information to make mnemonic decisions (Koutstaal and Schacter 1997; Aizpurua and Koutstaal 2010; Addis et al. 2015), resulting in a more pronounced age-related decline in recollection memory than in familiarity judgment (Jennings and Jacoby 1997).

Using neuroimaging techniques and the subsequent memory effect (SME) paradigm (Brewer et al. 1998; Wagner et al. 1998), existing studies have found important age-related changes in the neural systems related to episodic memory encoding (Craig and Rose 2012). For example, older adults consistently show decreased activity in the occipital and fusiform gyri (Maillet and Rajah 2014) and medial temporal lobes (Gutchess et al. 2005; Spreng et al. 2010) during memory encoding. Beyond episodic memory, this age-related decrease in activity has been observed in many other cognitive domains, such as attention (Cabeza et al. 2004), visual perception (Madden and Hoffman 1997;

Davis et al. 2008; Reuter et al. 2013; Drag et al. 2016), and working memory (Grossman et al. 2002; Rajah and D'Esposito 2005; Pinal et al. 2015), suggesting a general functional decline in the visual cortex associated normal aging.

The effect of normal aging on structural and functional decline in the frontal cortex is complex and controversial. Meta-analyses suggest that the prefrontal cortex shows the most consistent age-related structural and functional decline (Greenwood 2000; Kaup et al. 2011). On the other hand, using the SME paradigm, older adults have been found to exhibit over-activation in bilateral frontal cortex, precuneus, and left inferior parietal lobes during successful memory encoding (Duverne et al. 2009; Spreng et al. 2010; Mailliet and Rajah 2014). This over-recruitment has been considered as an indication of neural inefficiency in older adults (Morcom et al. 2007; Grady 2008; Mailliet and Rajah 2013). In other words, older adults need greater neural resources to achieve their level of behavioral performance, whether equal to or worse than that of younger adults. Alternatively, the frontal cortex is believed to play a particularly important role in neural compensations (Cabeza et al. 2002; Davis et al. 2008) or scaffolds (Park and Reuter-Lorenz 2009) for the functional declines in the visual cortex. For example, the posterior-anterior shift in aging (PASA) model suggests that the frontal over-recruitment may compensate for functional decline in posterior brain regions, as stronger frontal activity has been found to be correlated with better memory performance in older adults (Davis et al. 2008; Grady 2012). Greater activation in the frontal cortex is also related to better cognitive performance in working memory and face processing among older participants (Reuter-Lorenz et al. 2000; Eyler et al. 2011; Burianova et al. 2013).

Whereas earlier studies (such as those reviewed above) focused on overall activation level, emerging studies have shown that the fidelity of neural representation is also associated with subsequent memory performance (Xue et al. 2010, 2013; Kuhl et al. 2012; Visser et al. 2013; Ward et al. 2013). For example, it has been shown that the neural pattern similarity (PS) across repeated presentations of a stimulus was positively associated with later memory for that stimulus (Xue et al. 2010). This PS reflected the fidelity of item-specific encoding (Xue et al. 2013) and the reinstatement of previously encoded representation (Lu et al. 2015), both of which presumably help to provide unique and consistent input to the hippocampus, and to aid later pattern separation. Similarly, the fidelity of category-specific representation during episodic encoding has been found to predict subsequent memory (Kuhl et al. 2012). Although early behavioral studies have suggested that mental representations are noisier for older than younger adults (Rabbitt 1968; Schneider and Pichora-Fuller 2000), few studies have examined the fidelity of neural representation in older adults and linked it to their memory performance.

Meanwhile, although the frontal cortex has been posited to play a compensatory role in normal aging, the exact mechanisms regarding how the frontal cortex could enhance neural representation and memory are unclear. The frontal cortex is a versatile structure whose functions are flexible and goal-directed (Li et al. 2009; D'Esposito and Postle 2015). It is plausible that the prefrontal cortex might contribute additional neural "space" (Haxby et al. 2014) for the representation of item- or category-specific information when the representation fidelity in the visual cortex is compromised in older adults. In addition, the prefrontal cortex might also compensate by enhancing the fidelity of visual cortex representation (Kuhl et al. 2012; Xue et al. 2013) through top-down modulation (Baldauf and Desimone 2014).

Supporting the top-down mechanism, anodal transcranial direct current stimulation (tDCS) over the frontal cortex has been found to enhance the neural PS and to improve memory (Lu et al. 2015).

The present study examined (1) whether younger and older adults differed in the fidelity of item-specific neural representation in the visual and frontal cortices, (2) whether these differences could account for the memory declines associated with normal aging after controlling for the differences in activation level, and (3) whether and how the frontal cortex's activity could compensate for functional declines in the visual cortex.

Materials and Methods

Participants

Twenty younger adults (ages 17–25; 9 females) and 20 older adults (ages 65–84; 10 females), all college-educated or currently enrolled in college, were recruited from Beijing Normal University and the nearby communities. All participants were right handed, and had normal or corrected-to-normal vision and normal color perception. Based on self-report, all participants were in good health and had no history of neurological or psychiatric disorder, hypertension, diabetes, or the use of certain medications that could affect blood flow. None of the participants was depressed as assessed with the Beck Depression Inventory (younger adults) or the Geriatric Depression Scale (older adults). Older adults were also screened for dementia using the Mini-Mental State Exam (MMSE) and were determined to be qualified for participation if their scores were in the normal range (25–30) (Folstein et al. 1975). Informed written consent was obtained in accordance with the Institutional Review Board of the State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University.

Neuropsychological Testing

Participants were tested on 3 separate days. During the first day (2.5h), they completed a series of standardized tests designed to assess a range of cognitive abilities, including IQ using the Raven's Standard Progressive Matrices (RSPM), short-term memory using the Digit Span Forward and Backward test of the Wechsler Adult Intelligence Scale-Revised (WAIS-R), long-term memory using the Auditory Verbal Learning Test-Huashan version (AVLT-H), verbal comprehension using the Similarities Test of WAIS-R, and spatial visualization ability and motor skill using the Block Design Test of WAIS-R. We also administered the digit symbol substitution test (DSST) of the WAIS-R to screen for possible brain damage, dementia, and depression, and the Rey-Osterrieth Complex Figure (ROCF) test to evaluate visuospatial abilities, memory, attention, planning, and executive functions. Finally, pattern separation was measured by the Behavioral Pattern Separation Task-Object Version (BPS-O) (Stark et al. 2013).

fMRI and Behavioral Task

Experimental Stimuli

The experimental stimuli were 120 colored photographs of the following 3 categories: faces, abstract objects, and scenes (40 pictures per category, Fig. 1). These categories have been used extensively in visual research. We used pictures that were not familiar to the participants (based on the evaluations by a separate sample of 8 subjects) in order to reduce the use of verbal strategies. Half of the pictures (20 in each category) were used

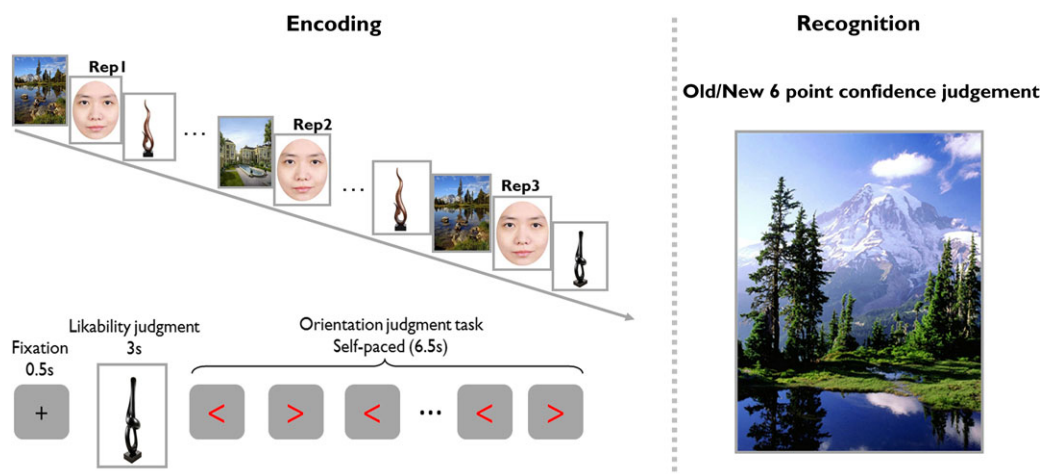


Figure 1. Experiment design and data analysis. A slow event-related design (10 s for each trial) was used to improve the accuracy in the estimation of single-trial responses. Each trial started with 0.5 s fixation. Each picture was presented for 3 s. Participants were asked to make a likability judgment. To prevent further encoding of the picture, a series of angle bracket images were presented during the 6.5 s inter-trial-interval, and subjects were asked to judge the direction of the angle bracket image as quickly and accurately as possible. During the recognition memory test, participants were asked to judge whether they had seen the picture in the scanner on 6-point confidence scale. Each stimulus would remain on the screen for up to 10 s or until a response was made.

for encoding, and the rest served as foils in the recognition memory test. All face pictures have neutral facial expression with the hair and ears digitally removed. The object pictures depict contemporary abstract sculptures, and the scene pictures depict natural scenes. All pictures were normalized to the same size (500 × 650 pixels) and were presented on white background. Ten additional pictures were used in the practice session.

The Encoding Task in the fMRI Scanner

On the second day, participants were asked to complete an incidental memory encoding task in the fMRI scanner. Participants were instructed to view a series of pictures presented on the screen and to indicate how much they liked each picture by pressing one of four buttons with their left or right index finger or middle finger, corresponding to “like it very much,” “like it,” “dislike it,” and “dislike it very much.” The hands for like versus dislike response were counterbalanced across subjects. Each picture was repeated 3 times, with an inter-repetition interval ranging from 8 to 15 trials. A slow event-related design (10 s for each trial) was used in this study to better characterize the activation pattern for each trial (Fig. 1). Each trial started with a 0.5 s fixation, followed by a picture presented for 3 s. Participants were asked to press the button to indicate their response within 3 s. To prevent further encoding of the pictures, participants were asked to perform a visual orientation judgment task for 6.5 s. In this task, an arrow pointing to the left or the right was presented on the screen and subjects were asked to identify the orientation of the arrow by pressing one of the two buttons. A self-paced procedure was used to make this task engaging, and the next arrow would appear 0.2 s after the response. Participants finished 4 runs of the encoding task, each lasting 7.5 min. Before the scan, they finished a practice session to familiarize themselves with the task and key responses. They were not informed of the subsequent memory test.

Postscan Behavioral Test

Approximately 48 h after the scan, subjects were called back for a recognition memory test. During this test, a total of 120 pictures (half old and half new) were randomly mixed together. For each picture, participants were asked to judge whether they

had seen the picture in the scanner on a 6-point confidence scale (1 = “very surely new,” 2 = “surely new,” 3 = “probably new,” 4 = “probably old,” 5 = “surely old,” 6 = “very surely old”). There was no strict time pressure on this task. The stimulus would remain on the screen for up to 10 s or until a response was made (Fig. 1).

MRI Setup and Data Acquisition

Imaging data were acquired using a 3.0 T Siemens MRI scanner in the Brain Imaging Center at Beijing Normal University. Visual stimuli were projected onto a screen behind the scanner, which is made visible to the participant through a mirror attached to the head coil. Stimuli and responses were presented and recorded by MATLAB (MathWorks) and Psychtoolbox on a Windows PC. A single-shot T2*-weighted gradient-echo, EPI sequence was used for the functional scan with the following parameters: time repetition (TR) = 2000 ms; time echo (TE) = 25 ms; flip angle = 90°; FOV = 192 × 192 mm²; 64 × 64 matrix size with a resolution of 3 × 3 mm². Forty-one 3 mm transversal slices parallel to the AC-PC line were obtained to cover the whole cerebrum and partial cerebellum. The anatomical scan was acquired using T1-weighted MPRAGE sequence with the following parameters: T1 = 800 ms; TR/TE/FA = 2530 ms/3.09 ms/10°, FOV = 256 × 256 mm, matrix = 256 × 256, slice thickness = 1.0 mm, 208 sagittal slices.

Data Analysis

Behavioral Data Analysis

For behavioral pattern separation (for objects) score (BPS-O score), we calculated the area under the curve (AUC) across all 7 conditions (repetitions, lure bins 1–5, and new items) (Stark et al. 2013). As to the DSST, the number of correct symbols within the allowed time (90 s) was measured. We summed the digit span forward score and backward score as our digit span score. For the ROCF task, we only reported the memory performance after 30 min delay. In the block design test, we measured the score of the items based on the accuracy in matching the pattern within the defined time. For the similarity test, we calculated the number of correct answers (word pairs).

The AVLT-H total score (the maximum score was 60) was the sum of immediate recall (the maximum score was 36), delayed recall (the maximum score was 12), and delayed recognition (the maximum score was 12).

Studied stimuli recognized with high confidence (scored 5 and 6) were defined as remembered items (R), whereas those scored 4 or lower were defined as forgotten items (F). Items scored 4 (i.e., subjects guessed they were “probably old” items) were considered as forgotten items to achieve comparable numbers of remembered and forgotten trials and to maximize statistical power. New stimuli that were incorrectly judged as old with high confidence (scored as 5 and 6) were defined as false alarm (FA) items. Hit rate, FA rate, and AUC were computed according to signal detection theory. Independent 2-sample *t*-test was conducted to compare the overall memory performance of the 2 age groups, and mixed ANOVA was conducted to examine the interaction between age group and stimulus category.

We also examined the reaction time (RT) and the consistency in how much the participants liked the pictures during encoding (hereafter labeled as likability). Since each stimulus was presented 3 times, the rating inconsistency was indexed by the mean absolute differences of each pair of ratings, with higher values indicating more inconsistent ratings across repetitions. The RT and accuracy data of the orientation judgment task were also collected and compared between the 2 age groups.

fMRI Data Preprocessing Analysis

Image preprocessing analyses were performed by using the FMRI Expert Analysis Tool (version 5.98; part of the FSL package; <http://www.fmrib.ox.ac.uk/fsl>). The first 3 volumes before the task were automatically discarded by the scanner to allow for T1 equilibrium. The remaining images were then realigned to correct for head movements. Data were spatially smoothed by using a 5 mm full width at half maximum Gaussian kernel and filtered in the temporal domain using a nonlinear high-pass filter with a 90 s cutoff. EPI images were first registered to the MPRAGE structural images and then into the standard MNI space, using affine transformations. Registration from MPRAGE structural images to the standard space was further refined using FNIRT nonlinear registration. Statistical analyses were performed in the native image space, with the statistical maps normalized to the standard space before higher level analysis.

Univariate Activation Analysis

We examined the SME using general linear modeling within the FILM module of FSL. During the encoding stage, the recognized (scored 5 and 6) and forgotten (scored 4 and below) pictures were separately modeled. The incorrect trials in the perceptual orientation task were coded as an additional nuisance variable, whereas the correct trials were not coded and thus were treated as an implicit baseline. Events were modeled at the time of the stimulus onset and convolved with canonical hemodynamic response function (double gamma function). The SME was defined as the differences between recognized and forgotten pictures. A higher level analysis was conducted to do cross-run average using a fixed-effects model. These contrasts were then used for group analysis with a random-effects model, using full FMRIB's Local Analysis of Mixed Effect 1 + 2 with automatic outlier detection (Beckmann et al. 2003; Woolrich et al. 2004; Woolrich 2008). Unless otherwise noted, group images were thresholded using cluster detection statistics,

with a height threshold of $z > 2.0$ and a cluster probability of $P < 0.05$, corrected for whole-brain multiple comparisons using Gaussian Random Field Theory.

Single-Item Response Estimation

GLM was performed to estimate the activation pattern for each repetition of the picture during encoding. The same preprocessing procedure as in the univariate analysis was used except that no spatial smoothing was applied. In this single-trial model, each trial was separately modeled and convolved with a canonical hemodynamic response function (double gamma). This voxelwise GLM was used to compute the activation associated with each of the 180 trials in the task. The *t*-map for each trial was used to calculate neural PS. For classification analysis, the 3 presentations of each stimulus were modeled as one regressor, and GLM was performed to compute the *t*-map for each of the 60 unique pictures.

Representation Similarity Analysis

We first identified the SME-sensitive brain regions using a searchlight method (Kriegeskorte et al. 2006). For each voxel, signals were extracted from a cubic regions of interest (ROI) containing 125 surrounding voxels. Pearson correlations on the activation patterns across the 3 repetitions of a given item were calculated and then averaged to represent the PS of that item (within-item PS). These similarity scores were transformed into Fisher's *z*-scores. We compared the differences between remembered (scored 5 and 6) and forgotten pictures (scored 1–4). We also calculated the within-category and between-category PS, separately for remembered and forgotten items, while making sure that the inter-trial interval of the between-item pairs matched that of the within-item pairs (Gilbert et al. 2012). The searchlight analysis was conducted in the standard space, separately for each run, and the results were then concatenated across runs. A random-effects model was used for group analysis. Since no first-level variance was available, an ordinary least square (OLS) model was used.

We defined SME ROIs based on the whole-brain searchlight results, including the bilateral frontal pole (FP), ventral visual cortex (VVC) (including the ventral lateral occipital cortex, vLOC), and inferior temporal gyrus (ITG). They were defined by including all the voxels in each cluster showing suprathreshold effect for the contrast of remembered items versus forgotten items in either of the 2 groups. The mean PS, activation level, and variance for each trial were then extracted and subjected to further analysis.

Correlating Frontal Activity with Cortical PS

We also examined the role of frontal activity in modulating cortical PS. In order not to bias against either age group, the frontal ROI was defined as the frontal region showing common univariate SME for both younger and older adults, that is, the inferior frontal gyrus (IFG). The mean activation (ACT) of each stimulus across 3 repetitions was calculated and correlated with the corresponding PS in the whole brain. Because the frontal activity was associated with the activity level in other brain regions, which was in turn associated with PS, we conducted a partial correlation analysis, with the ACT in each voxel as a covariate, to examine the effect of frontal activity on PS. The resulting correlation coefficients were transformed into Fisher's *z*-scores and then input into a random-effects model for group analysis, using OLS.

Classification Analysis

Classification analyses were conducted using a linear support vector machine (SVM) (Chang and Lin 2011) and custom code implemented in MATLAB (The MathWorks). A penalty parameter of one was used. The fourth run was used as the localizer run to identify the category-sensitive voxels (see below), and the classification analysis was conducted on the first 3 runs using leave-one-run-out cross-validation. For each trial in the testing set, the SVM classifier generated a scalar probability estimate of the trial corresponding to the 2 categories. The category with the higher probability was then set as the classifier's prediction. Classification accuracy thus represented the percentage of trials that were correctly categorized by the classifier.

We selected the category-specific voxels within the anatomically defined regions, that is, the VVC and the frontal cortex, using the Harvard Oxford probabilistic template included in the FSL software (25% probability map). The VVC includes parahippocampal gyrus, ITG, LOC, temporal fusiform cortex, and temporal occipital fusiform cortex. The frontal cortex includes FP, superior frontal gyrus (SFG), middle frontal gyrus (MFG), IFG, medial frontal cortex, frontal orbital cortex, and frontal operculum cortex. To be included as a category-specific voxel, a given voxel should show stronger activation for one category compared with each of the other 2 categories. We then ranked the selectivity by summing up the *t*-values of the 2 contrasts (e.g., category A > category B and category A > category C). We then selected the top 25 voxels from every 250 voxels until reaching 800 (i.e., top 1–25, 251–275, 501–525, 751–775) to examine how the category selectivity based on activation level affected the results from multi-voxel pattern analysis (MVPA).

These category-selective voxels were then used for 3 binary classifications of the 3 categories of stimuli (faces, objects, and scenes). The performance of category-selective voxels in classifying one category (e.g., faces) from other 2 categories (objects and scenes in separate analyses) were averaged to represent self-classification (SC or the difference between a given category and the other 2 categories) performance, which primarily reflects how much information these voxels carried for the selected category. In contrast, the performance of these voxels in classifying the other 2 categories represented the other-classification performance (OC or the difference between the 2 non-selected categories), which reflected how much information these voxels carried for the non-selected categories.

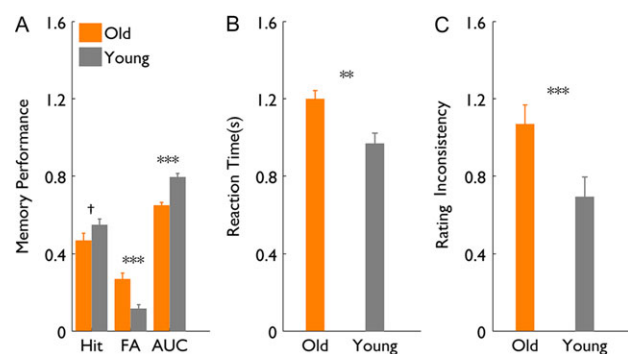


Figure 2. Behavioral results. (A) Mean and standard error of memory performance. (B) Mean and standard error of RT during the likability judgment task and (C) Mean and standard error of rating inconsistency during the likability judgment task. Error bars represent the standardized errors of the means. [†]*P* < 0.10, ^{**}*P* < 0.01, and ^{***}*P* < 0.001.

Mixed-Effects Model

Mixed-effects modeling is a powerful statistical tool that offers many advantages over conventional *t*-test, regression, and ANOVA in sophisticated fMRI designs (Mumford and Poldrack 2007; Ward et al. 2013), especially when the number of trials differs by condition and/or across participants (e.g., in this study, participants remembered different numbers of items). The mixed-effects model was implemented with lme4 in R (Bates et al. 2012). We used the likelihood ratio test (i.e., Chi-Square test) to compare the models (with vs. without the predictor) to determine the effect of the predictor.

Results

Behavioral Results

Older adults were screened for abnormal orientation scores (<27) using MMSE and achieved an average score of 29.50 (standard deviation [SD] = 0.67). The mean score, SD, and age-normed *z*-score (if available) of the neuropsychological tests are presented in Supplementary Table 1. No participant was 1.5 SD below the mean of the age-matched norm (see Supplementary Table 1). The 2 groups were matched on IQ as measured by RSPM. Consistent with previous studies, the score of the BPS-O task was significantly lower for older adults than younger adults (*P* < 0.001).

Figure 2 shows the behavioral performance during postscan memory test. The 2 groups showed only a marginally significant difference in the hit rate ($t(38) = -1.96$, *P* = 0.057), but older adults showed significantly higher FA rate than younger adults ($t(38) = 4.11$, *P* < 0.001), resulting in significantly lower AUC for older adults ($t(38) = -5.81$, *P* < 0.001; Fig. 2). Although older adults made numerically more low-confidence judgment on old items than did younger adults, the difference was not significant (see Supplementary Table 2). Meanwhile, older adults made more high-confidence judgment (i.e., 6) on the new items than did younger adults (*P* < 0.05) (see Supplementary Table 2). When responses to old and new items were pooled together, we did not find significant age differences in terms of high- versus low-confidence judgment (*P* = 0.87). Together, our data suggest that memory decline in older adults was due to reduced memory strength rather than reduced confidence.

To examine the category-specific effect, mixed ANOVA with age group (young vs. old) as a between-subjects variable and stimulus category as a within-subject variable revealed a marginally significant interaction between age and stimulus category in the hit rate ($F_{2,76} = 3.09$, *P* = 0.059). Older adults showed a significantly lower hit rate than younger adults for objects ($t(38) = -2.69$, *P* = 0.011), but not for faces ($t(38) = -0.10$, *P* = 0.919) or scenes ($t(38) = -0.42$, *P* = 0.675). No significant interaction was found for FA rate ($F_{2,76} = 0.43$, *P* = 0.652) or AUC ($F_{2,76} = 2.26$, *P* = 0.111) (see Supplementary Fig. 1). We found no significant age-related difference in the overall RT ($t(38) = -0.20$, *P* = 0.845), or for each response type (Hits: $F_{1,38} = 0.41$, *P* = 0.527; Misses: $F_{1,38} = 0.14$, *P* = 0.716; FAs: $F_{1,23} = 0.002$, *P* = 0.969; CRs: $F_{1,37} = 0.24$, *P* = 0.760) (see Supplementary Table 3). The lack of differences in RT might be because each stimulus would remain on the screen for up to 10 s or until a response was made, and because we emphasized that there was no time pressure on this task.

Compared with younger adults, older adults were slower (1.20 s vs. 0.97 s, $t(38) = 3.33$, *P* = 0.002; Fig. 2B) and less consistent (inconsistency score: 1.07 vs. 0.70, $t(38) = 2.64$, *P* = 0.012; Fig. 2C) in the likability judgment task. Nevertheless, the overall

likability score did not differ between the 2 groups ($t(38) = -1.74, P = 0.090$), and was not correlated with hit rate ($r = 0.12, P = 0.449$). Mixed effect analysis revealed that neither the rating inconsistency ($\chi^2(1) = 0.001, P = 0.980$) nor the overall likability ($\chi^2(1) = 2.88, P = 0.090$) was a significant predictor of memory score for old items. Older adults were also slower (0.68 s vs. 0.40 s, $t(38) = 9.53, P < 0.001$) but more accurate (93.8% vs. 88.6%, $t(38) = 4.15, P < 0.001$) in the orientation judgment task than younger adults, suggesting the former were paying more attention to the task than the latter.

fMRI Results

The SME in Pattern Similarity

We used a searchlight method (Kriegeskorte et al. 2006) to calculate the within-item PS for each item (across 3 repetitions) over the whole brain. PS was significantly greater for subsequently recognized items than for forgotten items in RITG (MNI: 50, -56, -6, $Z = 3.82$), RvLOC (MIN: 58, -64, 4, $Z = 3.80$), and RFP (MNI: 52, 42, 18, $Z = 3.75$) for younger adults, and in the LFP (MNI: 30, 52, 30, $Z = 4.43$) and left inferior parietal lobule (LIPL, MNI: -62, -54, 36, $Z = 4.21$) for older adults (Fig. 3). Direct comparison revealed that older adults showed greater SME of PS in the LIPL (MNI: -60, -48, 36, $Z = 4.18$) and LFP (MNI: -32, 54, 28, $Z = 4.40$).

Focusing on the 4 regions that showed SME of PS for either or both age groups (i.e., the VVC [RvLOC and RITG], LFP, RFP, and LIPL), we further examined whether their PS reflected item-specific representations, that is, stronger within-item similarity than between-item similarity. We performed a 2-way repeated measure analysis of variance, with item specificity (within-item PS/between-item PS) and memory (remembered/forgotten) as within-subjects variables. The results suggest that in all these regions showing PS SME, remembered items showed stronger item-specific representation than did forgotten items (see Supplementary Fig. 2 and Supplementary Results).

In a further analysis, we used the data from 2 runs to define the subsequent memory regions, and data from the remaining 2 runs to examine the item-specificity of representations. This analysis also suggest remembered items showed stronger item-specific representation than did forgotten items (Supplementary Results).

Testing the PASA Hypothesis on Item-Specific Pattern Similarity

The above analysis suggests that item-specific PS underlies subsequent memory for both younger and older adults. We then tested the core hypothesis that older adults showed lower item-specificity in the VVC, but higher item-specificity in the frontal lobe. We included the regions showing SME in PS for

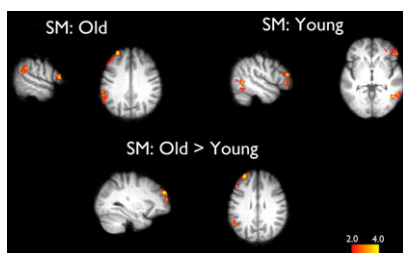


Figure 3. SME of PS for younger and older adults. Results for regions whose PS was greater for subsequently recognized than forgotten items: the RvLOC, RMTG, and RFP for the younger group ($Z > 2.0$, corrected) and the LFP and LIPL for the older group ($Z > 2.0$, corrected). Older adults showed higher PS for SME in LFP and LIPL than younger adults ($Z > 2.0$, corrected).

either older or younger adults and divided them into the VVC (RvLOC/RITG) and the frontoparietal cortex (FPC: LFP and LIPL). We focused on regions showing SME so that the results were specific to memory encoding. For remembered items, a 2-way mixed-effect ANOVA, with age (young/old) as a between-subjects variable and region (VVC/FPC) as a within-subjects variable, showed a significant age-by-region interaction ($F_{1,38} = 23.12, P < 0.001$). Further analysis indicated that younger adults showed significantly higher within-item PS than older adults in the VVC ($F_{1,38} = 7.40, P = 0.01$), whereas older adults showed significantly higher within-item PS than younger adults in the FPC ($F_{1,38} = 5.12, P = 0.029$) (Fig. 4A).

When all items were included, there was only a trend of age-by-region interaction ($F_{1,38} = 3.75, P = 0.06$). Further analysis indicated that younger adults showed significantly higher within-item PS than older adults in the VVC ($F_{1,38} = 9.14, P = 0.004$), whereas no significant difference was found in the FPC ($F_{1,38} = 0.56, P = 0.460$) (Fig. 4B). The same differences between younger and older adults were found when item-specificity was measured by the difference between within-item PS and between-category PS (WI-BC) or by the difference between within-item PS and within-category PS (WI-WC) (see Supplementary Fig. 3 and Supplementary Results).

Because older adults showed a relatively stronger SME in the prefrontal cortex, whereas younger adults showed a stronger SME in the visual cortex, it was possible that our ROI analyses were biased toward one group or the other. In an additional analysis, we defined 2 anatomical ROIs: the VVC and frontal cortex (see Methods). We found that younger adults showed significantly higher within-item PS than older adults in the VVC whereas no significant age difference was found in the frontal cortex. The pattern of the results was the same whether all items or only remembered items were included (Fig. 4C,D and Supplementary Results).

Comparing the Univariate SME Between the 2 Age Groups

Univariate analysis also revealed distributed brain regions that showed stronger activation for recognized items than forgotten items (Fig. 5 and Supplementary Table 4). For older adults, significant SMEs were found in the bilateral SFG, left FP, bilateral temporal occipital fusiform, bilateral ventral LOC, and right occipital fusiform. For younger adults, significant SMEs were found in bilateral IFG, right MFG, bilateral ventral LOC, left ITG, left temporal fusiform, left parahippocampal gyrus, right temporal occipital fusiform, and right occipital fusiform. Direct comparisons revealed that older adults showed greater SMEs in the left ventral medial prefrontal cortex (-10, 50, -14, $Z = 3.55$), SFG (0, 50, 30, $Z = 3.26$), whereas younger adults showed a greater SME in the LvLOC (-28, -90, 2, $Z = 3.47$).

Controlling for the Effect of Univariate Activation Level and Variance

Focusing on the regions showing SME in PS, we used mixed-effect regression models to examine whether the within-item PS was a reliable predictor of memory after controlling for the univariate activation level and variance (Davis et al. 2014). Within a given searchlight, the mean activation and variance of each trial was calculated across 3 presentations and averaged across voxels within that searchlight. This analysis revealed that after controlling for the mean activation level and variance, the within-item PS was still a significant predictor of memory in all ROIs (Younger adults: RvLOC/RITG, $\chi^2(1) = 17.12, P < 0.001$; RFP, $\chi^2(1) = 35.83, P < 0.001$; Older adults: LIPL,

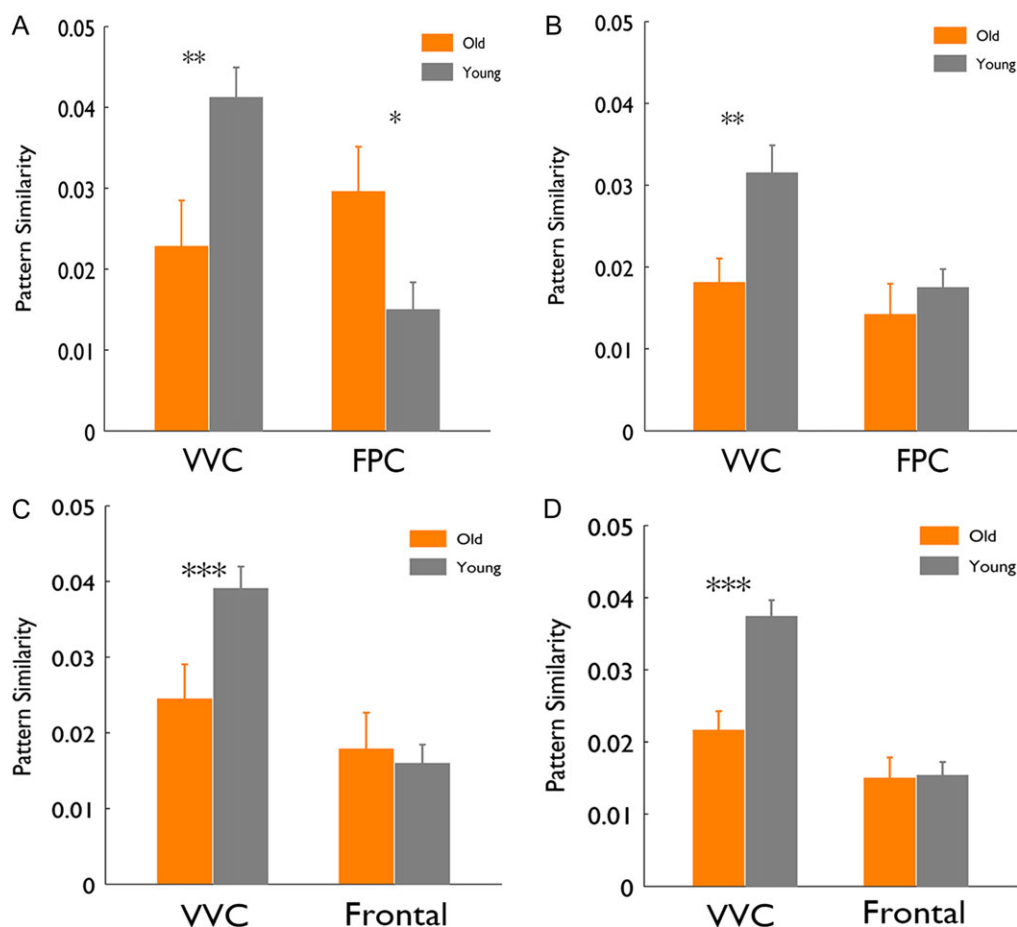


Figure 4. The top row shows the within-item PS in the posterior VVC and the FPC by age group: (A) when only remembered items were included, and (B) when all items were included. The ROIs were defined as the regions showing SME in PS for either the younger or older group. The bottom row shows the results based on anatomically defined ROIs that include the whole VVC and FPC structures (Methods): (C) when only remembered items were included, and (D) when all items were included. Error bars represent standardized errors of the means. * $P < 0.05$, ** $P < 0.01$.

$\chi^2(1) = 13.49$, $P < 0.001$; LFP, $\chi^2(1) = 10.55$, $P < 0.01$; FPC, $\chi^2(1) = 16.62$, $P < 0.001$).

Because the overall activation level was higher for younger adults than for older adults in the VVC and frontal cortex (see Supplementary Fig. 4), we re-examined the age differences in PS after controlling for the activation level and variance using mixed-effect regression models. Since previous studies suggested that the trial-by-trial variability, which reflects neurovascular coupling, increased with aging (D'Esposito et al. 2003) and was associated with reduced neural distinctiveness (Carp et al. 2011), we also calculated and controlled the mean-square error (MSE) of the residuals in the GLM model.

Consistent with previous studies, the MSE of older adults was higher than that of younger adults in a task-independent region, posterior cingulate cortex ($t(38) = 2.28$, $P = 0.028$), as well as in the VVC ($t(38) = 3.48$, $P = 0.001$) and the frontal cortex ($t(38) = 3.83$, $P < 0.001$). Indeed, the MSEs for the 3 regions were highly correlated ($r_s > 0.85$, $p_s < 0.001$). The MSE in the VVC was also correlated with the within-item PS in this region across participants ($r = -0.46$, $P = 0.003$).

For the remembered items, younger adults showed higher within-item similarity than older adults (controlling for the activation level, variance, and MSE) in the VVC regions showing SME in PS (RvLOC/RITG, $\chi^2(1) = 4.43$, $P = 0.035$), but not in the RFP ($\chi^2(1) = 0.41$, $P = 0.524$). In contrast, older adults showed

higher within-item similarity than younger adults in the LIPL ($\chi^2(1) = 9.42$, $P = 0.002$), the LFP ($\chi^2(1) = 5.30$, $P = 0.020$), and the FPC ($\chi^2(1) = 8.14$, $P = 0.004$). When all items were included, younger adults still showed higher within-item similarity than older adults in the VVC (RvLOC/RITG, $\chi^2(1) = 4.66$, $P = 0.030$), but no regions showed greater PS for older adults than younger adults ($p_s > 0.50$). Taken together, these results suggest that younger adults showed higher within-item similarity than older adults, but older adults did not show higher within-item similarity in the frontal cortex than younger adults when all items were considered.

Stronger Association Between Frontal Activation and PS in the VVC for Older Adults than for Younger Adults

To test the hypothesis that the frontal cortex could compensate memory by enhancing the item-specific representation in the visual cortex via top-down modulation (Xue et al. 2013), we calculated partial correlations between activation level in the frontal region that showed common univariate SME for both age groups and PS in each voxel across the brain while controlling for the latter's univariate activation level. We selected the region with SME for both age groups in order to avoid biases toward either group (see Fig. 6A). A direct comparison between the 2 age groups revealed stronger top-down modulation for older adults than younger adults in the LvLOC (MNI: -30, -80, -14,

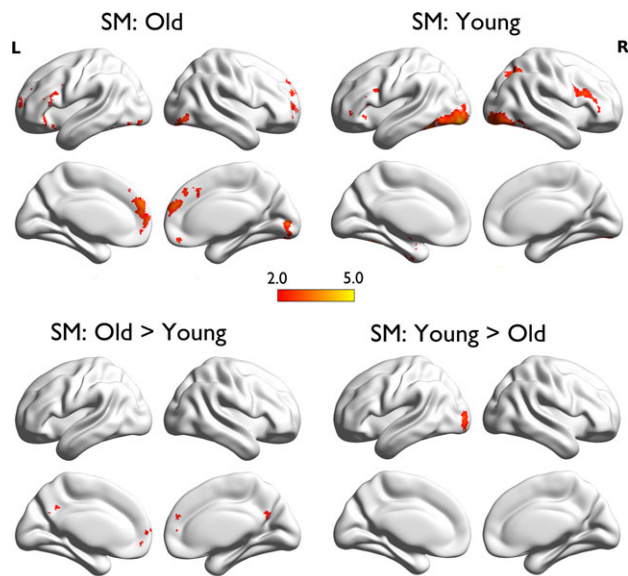


Figure 5. SME at the univariate activation level. Greater activations for the subsequently recognized item than the forgotten items (thresholded at $Z > 2.0$, whole-brain corrected). Results are shown for older and younger adults separately and their direct comparison and are rendered onto a population-averaged surface atlas (Xia et al. 2013).

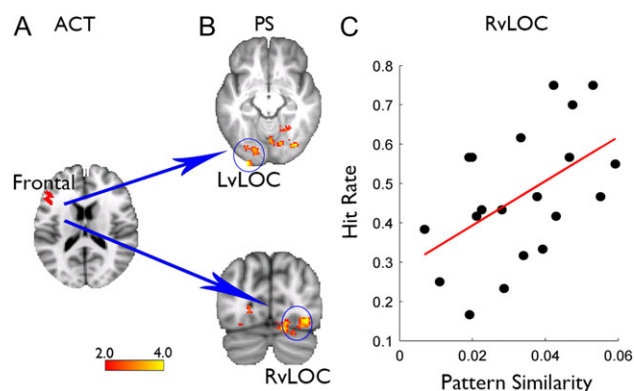


Figure 6. The effect of frontal activity on PS in older adults. (A) The frontal region that showed common univariate SME for both older and younger adults was defined as the ROI. (B) This frontal ROI showed significantly more positive correlations with the PS in the LvLOC and RvLOC for older than for younger adults, after controlling for the activation levels in these regions. (C) The PS in the RvLOC was correlated with older adults' memory performance as measured by hit rate.

$Z = 3.63$) and the RvLOC (MNI: 38, -76, -10, $Z = 4.27$) (Fig. 6B). The within-item PS in the RvLOC was correlated with older adults' memory performance (hit: $r = 0.52$, $P = 0.019$), which was still significant after controlling for the activation level in the RvLOC ($r = 0.57$, $P = 0.012$) (Fig. 6C). These results suggest that the prefrontal cortex might compensate for the older adults' memory decline by enhancing the fidelity of representation in the visual cortex.

Selectivity and Fidelity of Representation Based on Classification Analysis

The above representational similarity analysis (RSA) suggests that older adults showed reduced within-item PS in the visual

cortex, suggesting reduced fidelity of item-level representations. On the other hand, existing studies suggest that normal aging is associated with less functional specificity/selectivity in the VVC (termed dedifferentiation) (Li et al. 2001; Park et al. 2004, 2012; Payer et al. 2006; Voss et al. 2008; Carp et al. 2011; Burianová et al. 2013). Whereas fidelity reflects how much item- or category-level information is contained in the activation pattern, selectivity reflects whether a selected group of voxels carries information for one or multiple visual categories. As a result, the selectivity should be reduced if fidelity is compromised, although one can still have high fidelity in the absence of selectivity. A further question is whether the reduced selectivity found in previous studies could be (partially) explained by reduced fidelity.

Here, we used classification analysis to separate selectivity and fidelity. First, we used univariate analysis to choose voxels showing different levels of selectivity/preference to a certain category. We then used these voxels to classify preferred category from nonpreferred categories (i.e., self classification, SC) and to classify between 2 nonpreferred categories (i.e., other classification, OC). If a region is less selective for the target category, it should show low SC but high OC. This prediction was confirmed by choosing voxels with different levels of selectivity (see below). On the other hand, if these voxels showed reduced fidelity, we should expect overall reductions in SC and OC performance. Taken together, we would predict that if the reduced selectivity was merely due to reduced fidelity in older adults, they would show low SC and OC (a main effect) (Fig. 7A); if only selectivity was reduced in older adults, they would show low SC but high OC (an interaction effect) (Fig. 7B); if both selectivity and fidelity were reduced in older adults, they would show both a main effect and an interaction effect (Fig. 7C).

Focused on the VVC and frontal regions, we first ranked the category-selective voxels within the anatomical boundary, and then used voxels with different levels of category selectivity (from the top 25 selective voxels all the way to the 25 voxels ranked after 800, 4 steps) to do SC and OC. We chose voxels with different levels for 2 aims. First, this could help to confirm whether SC and OC were differentially modulated by the voxel selectivity. Second, we were to examine whether the age differences were robust across voxels with different selectivity. In the VVC, a 3-way ANOVA, with age as a between-subjects variable and voxel-selectivity and classification type as within-subjects variables, revealed a significant interaction between classification type and voxel-selectivity ($F_{3,114} = 14.74$, $P < 0.001$). Further analysis showed that SC performance decreased with decreasing voxel selectivity ($F_{3,114} = 21.54$, $P < 0.001$) (Fig. 7D), whereas OC performance increased with decreasing voxel selectivity ($F_{3,114} = 2.79$, $P = 0.044$) (Fig. 7E), suggesting that our method was able to identify category-selective voxels.

Because there was no significant interaction between voxel-selectivity and age for SC ($F_{3,114} = 0.11$, $P = 0.953$) and OC ($F_{3,114} = 1.42$, $P = 0.240$), we averaged the SC and OC accuracy across voxels with different selectivity levels for the following analysis. To examine the selectivity versus fidelity hypothesis, we conducted a 2-way ANCOVA, with age as a between-subjects variable, classification type (SC vs. OC) as a within-subjects variable, and MSE as a covariate. This analysis revealed a significant interaction between age and classification type ($F_{1,111} = 4.69$, $P = 0.037$), as well as a significant main effect of age ($F_{1,37} = 30.03$, $P < 0.001$), suggesting that older adults were impaired in both fidelity and selectivity (Fig. 7F). Further simple effect analysis revealed that younger adults showed significantly greater SC than did older adults ($F_{1,37} = 28.96$, $P < 0.001$),

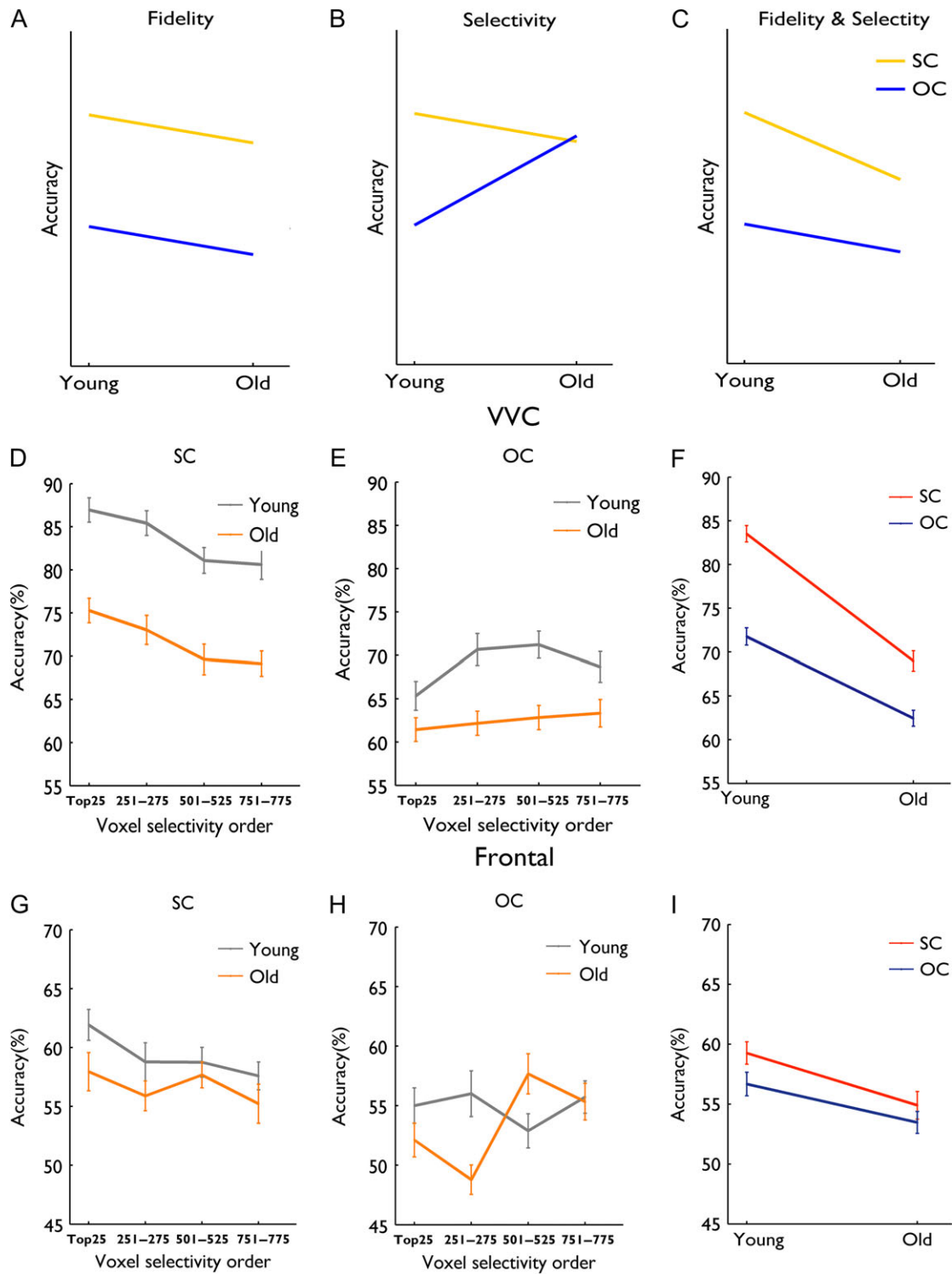


Figure 7. Classification results. The hypothesized pattern of classification accuracy if the fidelity (A), selectivity (B), or both (C) are affected by aging. The classification results are plotted as a function of voxel selectivity, age, and classification type and brain regions (D, E, G, H). To examine the overall pattern of fidelity and selectivity across voxels showing different levels of selectivity, the classification performances were averaged across voxels (F, I). Error bars represent standardized errors of the means.

and the effect was similar but weaker for OC ($F_{1,37} = 18.71, P < 0.001$). Robust age effect was found when each stimulus category was examined separately (see Supplementary Fig. 5 and Supplementary Results).

In the PFC, ANOVA revealed a significant 3-way interaction among classification type, voxel-selectivity, and age ($F_{3,114} = 3.73, P = 0.013$). Two-way ANOVAs were conducted separately by classification type. For SC, voxel selectivity had a

main effect ($F_{3,114} = 3.31$, $P = 0.023$), suggesting that the SC accuracy decreased with decreasing voxel selectivity (Fig. 7G). We found no age-by-voxel-selectivity interaction ($F_{3,114} = 0.53$, $P = 0.663$), and only a marginal main effect of age ($F_{1,38} = 3.60$, $P = 0.065$). For OC, voxel-selectivity also had a main effect ($F_{3,114} = 2.69$, $P = 0.050$), but the main effect of age was not significant ($F_{1,38} = 0.94$, $P = 0.340$). There was a significant interaction between voxel-selectivity and age ($F_{3,114} = 7.65$, $P < 0.001$). Further analysis suggested that older adults showed increased OC accuracy with decreasing voxel selectivity ($F_{3,114} = 9.13$, $P < 0.001$), but this effect was not significant for younger adults ($F_{3,114} = 1.21$, $P = 0.310$) (Fig. 7H). After averaging the SC and OC accuracy rates across voxels showing different levels of selectivity, we found no significant age effect ($F_{1,37} = 2.06$, $P = 0.160$) or age-by-classification-type interaction ($F_{1,111} = 0.024$, $P = 0.878$), suggesting the 2 groups showed similar fidelity and selectivity in the frontal cortex (Fig. 7I). No age effect was found when each stimulus category was examined separately (see Supplementary Fig. 5 and Supplementary Results). We further examined age differences at each level of voxel selectivity. The results revealed that only at 251–275, younger adults showed greater OC than did older adults ($P = 0.024$, after Bonferroni correction for 8 comparisons). These results again suggest no robust age differences in the PFC.

Discussion

The current study investigated age-related differences in the fidelity of neural representation and its role in episodic memory declines in older adults. Our study found that the VVC showed less functional specificity (termed dedifferentiation) during normal aging. This result is consistent with many previous observations (Li et al. 2001; Park et al. 2004, 2012; Payer et al. 2006; Voss et al. 2008; Carp et al. 2011; Burianová et al. 2013). For example, using multiple voxel pattern analysis, one study showed that neural activation patterns within the VVC were less distinctive among older adults than among younger adults (Carp et al. 2011). More recently, it has been further suggested that this age-related dedifferentiation is more salient during mental replay, and that age differences in perception could not account for older adults' reduced neural reactivation specificity (St-Laurent et al. 2014).

In addition to the reduced selectivity of category-level representation, we examined for the first time the reproducibility of item-level representation (termed fidelity). Our results revealed that normal aging was associated with reduced fidelity of visual cortical representation, even after controlling for the reduced activation level. Since the reduced selectivity could be due to the overall reduced fidelity of neural representation, we used classification analysis to separate the effect of selectivity and fidelity on cortical representation. Our results provided strong evidence that older adults showed reduced selectivity as well as reduced fidelity of representation in the VVC. It should be noted that older adults have also been found to show a shift from pattern separation to pattern completion, which is associated with CA3 hyperactivity in older rats (Wilson et al. 2003, 2005) and older humans (Yassa et al. 2011a). Nevertheless, we did not find higher within-category PS for older adults, perhaps due to their overall low fidelity of representation. Future studies should use high-resolution fMRI to directly examine the relationship between CA3 activity and cortical PS in both younger and older adults.

We further linked the fidelity of cortical representation to successful memory encoding. Compared with univariate

activation level, the analysis of distributed activation pattern could provide a deeper mechanistic understanding of memory encoding (Rissman and Wagner 2012). In particular, it is suggested that greater fidelity of cortical representation, which reflects unique and reproducible neural representations during learning, benefits memory encoding (Xue et al. 2010, 2013; Lu et al. 2015). The current study extends these observations and further suggests that the reduced representational fidelity in older adults underlies their memory decline. Consistent with previous studies (Yassa et al. 2011b; Daselaar and Cabeza 2013; Maillet and Rajah 2014), we also found age differences in univariate activations. Further mixed-effect model suggested that PS could account for additional variance of memory performance after controlling for univariate activation level.

One potential confounding factor of age differences is the variability of BOLD response, which reflects the vasculo-neural coupling (Shaw et al. 1984; D'Esposito et al. 2003; Liu et al. 2013). In the current study, participants were screened for hypertension, diabetes, cerebrovascular disease, and the use of certain medications that could affect blood flow. In addition, other variations such as greater head motion in older adults could also contribute higher MSE of the residuals (Johnstone et al. 2006). Consistently, the current study also found greater framewise displacement for older adults than younger adults ($t(38) = 4.15$, $P = 0.001$). Older adults showed higher MSE of the residuals, which were correlated with PS. Age differences in PS, however, were still significant after controlling for the MSE, the mean activity level, and the variance of the activation. Future studies should examine the fidelity of cortical representation after controlling for cerebrovascular reactivity or by performing calibrated fMRI (Liu et al. 2013).

Although older adults showed overall reduced fidelity of cortical representation, they were minimally impaired in recognizing the studied items as measured by the hit rate. This might reflect an overall shift of cognitive strategies to compensate for the neurofunctional declines. Older adults have been shown to remember less specific information but rely more on gist-based information to make mnemonic decisions (Koutstaal and Schacter 1997; Aizpurua and Koutstaal 2010; Addis et al. 2015). Consistently, we found that although older adults showed nearly comparable hit rate as younger adults, the former's FA rate was significantly higher, especially for the nonsense objects, resulting in significantly lower AUC. Furthermore, consistent with previous observations (Yassa et al. 2011a; Stark et al. 2013), we also found that older adults had difficulty in distinguishing the lure items from the old items in the BPS-O task.

Consistent with the meta-analysis results (Greenwood 2000; Kaup et al. 2011), we found that the frontal cortex showed overall reduced activity for older adults than for younger adults based on the task versus baseline contrast. However, when examining the SME, our univariate analysis and RSA results consistently showed frontal over-recruitment in older adults. Many studies have suggested that this increased frontal SME was a means of compensating for functional declines in the visual cortex (Cabeza et al. 2002, 2004; Grady et al. 2005; Davis et al. 2008). Other studies, however, suggest that this over-recruitment reflects a prefrontal dysfunction rather than compensation (Grady 2008, 2012; Morcom and Friston 2012; Maillet and Rajah 2013). Still other studies suggest that the over-recruitment of the frontal cortex may reflect a shift of cognitive focus from perceptual details to personal thoughts and feelings during memory tasks, which is associated with worse memory performance (Maillet and Rajah 2014).

The current study examined 2 potential mechanisms of the compensation hypothesis. First, we examined whether the frontal cortex showed enhanced item- and category-level representation when the representation in the visual cortex was impaired in older adults. We found limited support for this mechanism. Overall, the frontal lobe carried less category- or item-level information, as compared with the visual cortex, which is consistent with the accumulating evidence that information representation in the frontal cortex is more abstract and goal-directed (D'Esposito and Postle 2015). Although the within-item PS of remembered items in the frontal cortex was higher for older adults than younger adults, this difference was no longer significant when all items were included or when the whole prefrontal cortex was considered. One possibility is that a certain prefrontal region could contribute additional neural representational space (Haxby et al. 2014), when attention was effectively allocated and the items were effectively encoded. It could also be argued that older adults might compensate by changing their encoding strategy, that is, verbalizing the material. This seems to be unlikely in the current study since we used unfamiliar faces, objects, and scenes that could not be verbalized easily. In particular, the novel objects were abstract sculptures that were difficult to name, yet the age difference was consistent across 3 categories of stimuli ($F_{2,76} = 0.16$, $P = 0.85$), suggesting that verbal strategies did not confound the results.

Second, we examined whether the association between frontal activity and PS in the VVC was stronger in older adults than in younger adults. We found a stronger association between frontal activity and the PS in the bilateral vLOC for older adults than for younger adults. The PS in the RvLOC was positively correlated with older adults' memory performance (hit rate), even after controlling for overall activation level, suggesting the prefrontal cortex might compensate by increasing the top-down modulation. It should be noted that our result did not suggest that older adults would necessarily show intrinsically stronger top-down modulation in all situations. Our finding might be specific to the experimental conditions where top-down modulation was likely to be more demanding for older adults than for younger adults. When the task becomes more difficult, for example, under noise or distractor condition (Gazzaley et al. 2005), younger adults might show more effective top-down modulation.

These results provided further evidence for the frontal cortex's role in enhancing cortical representation (Jehee et al. 2011; Xue et al. 2013; Baldauf and Desimone 2014; Lu et al. 2015). It has been suggested that the frontal cortex's activity, which reflects goal-directed processing such as selection and attention, can enhance task-relevant feature representations (Jehee et al. 2011; Baldauf and Desimone 2014), reduce noise and interference (Lu et al. 2011), increase the reliability of neuronal responses (Mitchell et al. 2007), and lead to greater PS across repetitions (Moore et al. 2013; Xue et al. 2013). Consistently, enhancing the prefrontal function with anodal tDCS has been found to enhance PS (Lu et al. 2015).

The exact mechanisms underlying the age-related decline in the fidelity of cortical representation need further examination. Here, we outlined several potential factors. First, age-related reductions in PS in the VVC could be attributed to sensory impairment in older adults (Rabbitt 1968; Murphy et al. 2000), which could result in worse fidelity of representation and impoverished memory trace (Schneider and Pichora-Fuller 2000) and general cognitive performance (Lindenberger and Baltes 1994). Second, older adults showed structural and

functional declines in the frontal cortex (Greenwood 2000; Kaup et al. 2011), resulting in reduced attention control or top-down modulation during encoding and thus reduced fidelity of representation. Third, according to the computational model developed by Li et al. (2001), age differences in the fidelity of neural representations could be due to the impaired dopaminergic function and thus reduced neural signal-to-noise ratio in older adults (Backman et al. 2000; Abdulrahman et al. 2017). Fourth, other factors, such as head motion (Power et al. 2014), vasculo-neural coupling (Shaw et al. 1984; D'Esposito et al. 2003; Liu et al. 2013), and variability in brain structure (Poldrack et al. 2011), could also affect image processing and modeling, resulting in worse estimation of brain activity pattern in older adults than younger adults. Fifth, younger and older adults might use different cognitive strategies, depending on the task requirement. For example, the incidental memory encoding paradigm used in the present study might reduce task engagement in the older group. Finally, within-item PS could be associated with the study-phase retrieval, which is accompanied by the reactivation of early neural activation pattern (Kuhl et al. 2010; Xue et al. 2013; Lu et al. 2015). This study-phase retrieval is supported by the hippocampal function (Kuhl et al. 2010; van den Honert et al. 2016). Many studies have shown structural and functional declines in the hippocampus (e.g., A β -induced hippocampal atrophy) as a result of normal aging (Schuff et al. 1999; Driscoll et al. 2003; Raz et al. 2005; Malykhin et al. 2008; Mormino et al. 2009; Jack et al. 2010), which would have impaired study-phase retrieval. In our study, older adults showed lower rating consistency across repetitions, suggesting that they might have difficulties in retrieving previous ratings of the same item.

The present study focused on the neural representations during encoding that were associated with subsequent memory. Our finding of older adults' reduced fidelity of representations in the visual cortex during encoding and poorer memory performance corroborates a previous finding that older adults showed reduced reactivation in the perceptual regions during the retrieval of visual details in a verbally cued recall task (McDonough et al. 2014). Interestingly, it also has been found that even for young adults, retrieval-induced reactivation is less item-specific in the visual cortex than in the higher level cortices, such as the frontoparietal cortices (Xiao et al. 2017). Furthermore, there is emerging evidence that retrieval is not just a faithful replay of encoded representation, but also involves systematic transformation of representation (Chen et al. 2017; Xiao et al. 2017). Future research should examine the fidelity and nature of memory representation during retrieval in older adults.

In conclusion, our study suggests that memory declines during normal aging may be explained by the reduced fidelity of representation in the visual cortex. The frontal cortex seems to play a compensatory role to enhance the fidelity of visual representation via top-down modulation. These results emphasize the critical role of information representation in successful memory encoding, and provide a novel mechanistic understanding of memory functions in older adults. Future studies should further examine the role of sensory processing, top-down attention control, study-phase retrieval, and dopaminergic functions in the fidelity of cortical representations in healthy older adults, as well as in older adults with mild cognitive impairment and Alzheimer's disease. Findings from these lines of research may help to provide novel biomarkers for diagnosis and targets for interventions for age-related memory declines.

Authors' Contributions

G.X. and L.Z. designed the experiment. L.Z. and Z.G. performed the study. L.Z., Z.G., X.X., Z.Y., and G.X. analyzed the data. G.X., L.Z., and C.C. wrote the manuscript.

Supplementary Material

Supplementary material is available at *Cerebral Cortex* online.

Funding

The National Natural Science Foundation of China (31130025), the 973 Program (2014CB846102), the 111 Project (B07008), and the NSFC Project (31521063).

Notes

Conflict of Interest: None declared.

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