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Functional activation features of memory in successful agers across the adult lifespan

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Abstract

Much neuroimaging research has explored the neural mechanisms underlying successful cognitive aging. Two different patterns of functional activation, *maintenance of youth-like activity* and *compensatory novel recruitment*, have been proposed to represent different brain functional features underlying individual differences in cognitive aging. In this study, we investigated the functional features in individuals across the adult lifespan who appeared to resist age-related cognitive decline, in comparison to those with typical age-related declines, over the course of four years. We first implemented latent mixture modeling, a data-driven approach, to classify participants as *successful* and *average* agers in middle-aged, young-old, and very old groups, based on their baseline and longitudinal cognitive performance. Then, using fMRI with a subsequent memory paradigm at the follow-up visit, brain activation specifically related to successful encoding (i.e., subsequent memory effect: subsequently remembered with high confidence > subsequently forgotten) was compared between people who established *successful* cognitive aging versus *average* aging in the three age groups. Several differences in the subsequent memory effect were revealed. First, across core task-related regions commonly used during successful encoding, *successful* agers exhibited high subsequent memory effect, at a level comparable to the young control group, until very old age; in contrast, *average* agers showed reduced subsequent memory effect, compared to *successful* agers, beginning in young-old age when memory performance also reduced in *average* agers, compared to *successful* agers. Second, additional recruitment in prefrontal clusters, distant from the core task-related regions, were identified in the left superior frontal and right orbitofrontal cortices in *successful* agers of young-old age, possibly reflecting functional compensation in successful aging. In summary, *successful* agers demonstrate a pattern of youth-like activation spanning from middle age to young-old age,

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as well as novel frontal recruitment in young-old age. Overall, our study demonstrated evidence of two neural patterns related to successful cognitive aging, offering an integrated view of functional features underlying successful aging, and suggests the importance of studying individuals across the lifespan to understand brain changes occurring in mid and early-late life.

Keywords

Brain maintenance; Compensation; Dedifferentiation; fMRI; Subsequent memory; Successful aging

1. Introduction

Aging has been historically characterized by substantial cognitive decline in many older adults (Park et al., 2002; Salthouse, 2003; Schaie, 1996), but recent literature has recognized the considerable inter-individual variability in the maintenance of cognitive ability throughout the lifespan (Goh et al., 2012; Lindenberger, 2014; Mella et al., 2018; Mungas et al., 2010; Wilson et al., 2002), suggesting that some people are more vulnerable to age-related cognitive decline while others may be more resistant. Recent studies have investigated the neural pathological (Baran et al., 2018; Chen et al., 2021a; Sperling et al., 2019), structural (Gorbach et al., 2017; Webb et al., 2020), and functional connectivity features (Wang et al., 2019; Zhang et al., 2020) related to different cognitive trajectories in aging (Hedden et al., 2014).

Particularly, studies have revealed different functional activation patterns related to successful cognitive aging. Two major views have been proposed to interpret the functional basis of individual differences in aging. Some researchers suggest that successful cognitive aging relies on the maintenance of brain structure and function. This view indicates that “the individual differences in the manifestation of age-related brain changes and pathology allow some people to show little or no age-related cognitive decline” (Nyberg et al., 2012; Nyberg & Pudas, 2018). It suggests that optimal brain function in successful aging is presented as youth-like brain function with a preserved activation pattern similar to young adults. Indeed, studies have shown that older adults, in general, tended to have reduced task-related functional activity, particularly in temporal and occipital regions for memory processing (Li et al., 2015; Maillet and Rajah, 2014), but high-performing older adults showed a comparable functional activation pattern as in younger adults (Duverne et al., 2008; Düzel et al., 2011; Nagel et al., 2009; Persson et al., 2012; Pudas et al., 2018; Samu et al., 2017), supporting the idea that higher similarity to younger brain’s functional activity may be a feature of better brain function underlying successful aging.

On the other hand, studies have also found that older adults may recruit additional brain regions, particularly in the prefrontal lobe, compared to younger adults, likely to compensate for age-related degradation (Cabeza, 2002; Cabeza et al., 2018; Davis et al., 2008; Reuter-Lorenz et al., 1999). This view implies that optimal brain function comprises the ability to *recruit novel* regions that are not commonly utilized for the task. This theory highlights the adaptive and compensatory re-organization in older brains of successful agers and appears to be somewhat contrary to the *brain maintenance* view. It is supported by early evidence

that high-performing older adults exhibited additional recruitment of novel prefrontal areas compared to young adults, which helped them overcome age-related atrophy to meet task demands (Cabeza, 2002). Moreover, later studies have found higher activation in frontal regions in high-performing older adults, and that this activity was negatively correlated with age-related functional decreases in occipital areas. They further posited that successful older adults may shift their functional reliance from posterior regions to anterior regions (Davis et al., 2008), in a way that frontal-regulated top-down processing may increase in high-functioning older people in response to degraded sensory input in the occipital regions.

Although seemingly contrary to each other, these two views of brain aging are not necessarily contradictory: functional compensation may play a role while brain maintenance starts to fail to support cognition in older people, so the two mechanisms may operate concurrently to cope with age-related changes (Cabeza et al., 2018; Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Park, 2014). The present study aims to investigate what neural activity features are present in individuals establishing better cognitive aging trajectories. We used latent mixture modeling, a data-driven approach, to explore subgroups of individuals who represent distinct cognitive aging profiles. We then compared the functional activation between those who established successful cognitive aging to those with typical age-related declines, to characterize the specific neural activity features shared in successful agers.

The operational definition of successful cognitive aging has been controversial (Fiocco and Yaffe, 2010; Rowe and Kahn, 1997). For example, studies have traditionally identified older adults who have comparable memory performance as the young reference sample as successful agers (Habib et al., 2007; Harrison et al., 2012). However, cross-sectional classification is susceptible to confounding factors that are not related to cognitive aging, such as cohort (Salthouse, 2014) and survival (Ronnlund et al., 2005; Singh-Manoux et al., 2012) effects, suggesting the critical need of incorporating longitudinal measures to define successful agers with little cognitive decline. Among the studies with longitudinal data, though, many identified different groups of individuals based on an *a priori* cut-off (Mella et al., 2018; Persson et al., 2005; Yaffe et al., 2009). This cut-off approach heavily relies on researcher's knowledge and is often inconclusive in aging research (Ardila, 2007; Ylikoski et al., 1999). Therefore, we decided to take a data-driven approach, using latent mixture modeling (Muthén, 2001; Nagin, 1999; Ram and Grimm, 2009), to explore the existence of subpopulations who represent statistically different classes of individuals with distinct cognitive aging profiles. Moreover, this approach, as a person-centered analysis rather than a traditional variable-centered analysis (Laursen and Hoff, 2006), recognizes the holistic cognitive profile specific to individuals and incorporates multiple cognitive domains simultaneously, as most research on brain aging only based their classifications on a single domain such as memory (Harrison et al., 2012; Olaya et al., 2017; Pietrzak et al., 2015).

In addition, cognitive aging is a non-linear process throughout the lifespan (Hartshorne & Germine, 2015; Verhaeghen & Salthouse, 1997), but little is known about how brain activity may differ in maintaining and declining individuals across the lifespan, as only a few fMRI investigations examining this specific question included middle-aged adults. For example, (Vidal-Pineiro et al., 2019) found that both high and low performers in middle age, as well as high-performing older individuals, showed similar brain activity as in younger adults,

whereas low-performing older adults showed reduced activation in frontal regions. Further, Park et al., (Park et al., 2013) studied a subset of participants from the Dallas Lifespan Brain Study and found that age-related differences in brain function were most evident in low memory performers beginning in middle age, whereas high memory performers did not show these differences until older age. Both studies used cross-sectional cognitive performance to classify the sample and yielded somewhat different conclusions in middle and late adulthood, suggesting the importance of exploring functional basis of successful aging spanning from middle age to very old age.

Finally, interpretation of the relationship between functional activity and the behavioral outcome is complicated. Increased functional activity in low-performing older adults may be interpreted as inefficient over-recruitment because it was only present in declining individuals (J. Park et al., 2012), whereas the same pattern of activation could also be compensatory in nature: declining individuals are the ones in need of such compensation, but the attempted compensation could not offset the age-related deficits (Cabeza & Dennis, 2012). Careful investigations should not only compare declining and maintaining individuals, but also delineate the functional activation specifically underlying better task outcome (Grady, 1998). Because the subsequent memory paradigm, by design, separates brain activations related to successful and unsuccessful encoding trials, we adopted this paradigm utilizing the subsequent memory contrast, i.e., activation during trials subsequently remembered with high confidence versus trials subsequently forgotten, which represents activation most closely related to memory outcome.

The present study investigated functional activations in middle-aged, young-old, and very old individuals in a large sample of participants from the Dallas Lifespan Brain Study with distinct cognitive aging trajectories, comparing the brain activation underlying successful memory encoding in people with differential cognitive aging profiles in each age group and aimed to identify neural features specifically distinguishing successful agers from average agers across the adult lifespan.

2. Methods

2.1. Participants

The study included all participants from the Dallas Lifespan Brain Study (DLBS), aged 20–89 years old at baseline ($N = 464$). Following a four-year lag, 337 participants returned for a subsequent wave of cognitive testing (72.63% of the initial sample; 84.25% of those who could be contacted). Among these returning participants, 297 participants completed an fMRI scan with a scene-encoding task at the follow-up visit. One participant who had extremely low memory performance (high-confidence false alarm rate = 0.625; high-confidence hit rate = 0.302), and six participants who did not have any forgotten trials were removed from the fMRI analyses. The final sample of 290 participants included 71 middle-aged adults (aged 35–54 at baseline, 39–59 at fMRI scan), 96 young-old adults (aged 55–69 at baseline, 59–74 at fMRI scan), 82 very old adults (aged 70–90 at baseline, 74–93 at fMRI scan), and 41 young adults (aged 20–34 at baseline, 24–38 at fMRI scan) as the reference group. Although we did not presume the healthy young group experiences cognitive decline, we included their data to aid interpretation of findings in other age groups. The average

lag between the follow-up cognitive assessment and the fMRI scan was 16.4 days. The majority completed both within a month (N=251, 86.3%), with a few exceptions (N=8) who went longer than a three-month interval due to hardware difficulties. All participants were recruited locally from the community and were right-handed with normal or corrected to normal vision. Participants were screened for neurological and psychiatric disorders, loss of consciousness for more than ten minutes, a history of drug or alcohol abuse, and a history of major heart surgery or chemotherapy within five years. This study was approved by The University of Texas Southwestern Medical Center and The University of Texas at Dallas institutional review boards. All participants provided written informed consent, were debriefed according to human investigations committee guidelines, and were compensated for their time.

2.2. Cognitive measures

Four cognitive domains in the DLBS cognitive battery were used to identify successful agers. For processing speed (PS), participants completed Digit Comparison (DC) (Salthouse and Babcock, 1991) and Digit Symbol Substitution Test (DS) (Wechsler, 1997) at baseline and follow-up visits, and an additional measure from the NIH Toolbox, Pattern Comparison (NIHPS) (Casaletto et al., 2015) at the follow-up visit. Working memory (WM) was measured by CANTAB Spatial Working Memory (SWM) (Robbins et al., 1994), CANTAB Spatial Recognition Memory (SRM) (Robbins et al., 1994), CANTAB Delayed Match to Sample (DMS) (Robbins et al., 1994), Operation Span (OSPAN) (Turner and Engle, 1989), and Letter Number Sequencing (LNS) (Wechsler, 1997) at baseline, and measured by CANTAB SWM, LNS, and the NIHTB List Sorting Task (NIHLS) (Casaletto et al., 2015) at the follow-up visit. Inductive reasoning was measured by Raven's Progressive Matrices (RAV) (Raven et al., 1998), ETS Letter Sets (ETSLS) (Ekstrom et al., 1976), and CANTAB Stockings of Cambridge (SOC) (Robbins et al., 1994) at both baseline and the follow-up visits. Episodic memory (EM) was measured by CANTAB Verbal Recognition Memory (VRM) (Robbins et al., 1994), and Hopkins Verbal Learning Test with immediate free-recall (HOPF), delayed free-recall (HOPDF), and delayed recognition (HOPDR) (Brandt, 1991) at baseline and at follow-up visit. Woodcock-Johnson III Memory for Names immediate (WJIM) and delayed recognition (WJD) (Woodcock and Johnson, 1989) was added after baseline data collection began, and were available for a subset of participants (N=158) at baseline and for all participants at the follow-up visit.

The internal reliability of all cognitive domains was confirmed based on the Cronbach's α of each domain for each wave. All four domains showed high reliability (processing speed: Cronbach's $\alpha = .865$ for wave 1 and Cronbach's $\alpha = .869$ for wave 2; working memory: Cronbach's $\alpha = .784$ for wave 1 and $.810$ for wave 2; inductive reasoning: Cronbach's $\alpha = .865$ for wave 1 and Cronbach's $\alpha = .869$ for wave 2; episodic memory: standardized Cronbach's α is $.826$ for wave 1 and $.885$ for wave 2).

2.3. MRI acquisition

Participants were scanned using a 3T Philips Achieva scanner with an 8-channel head coil. High-resolution anatomical images were collected with a T1-weighted magnetization-prepared rapid gradient-echo sequence with 160 sagittal slices, field of view (FOV) = $204 \times$

256 × 160 mm; voxel size: 1 × 1 × 1 mm³; time to repetition: 8.1 milliseconds (ms); echo time: 3.7 milliseconds; flip-angle: 12°. Blood Oxygen Level Dependent (BOLD) fMRI data were acquired using a T2* weighted echo-planar imaging sequence with TR/TE/flip-angle = 2000ms/25ms/80° and FOV = 220 × 220 mm². In each volume, 43 interleaved axial slices were acquired parallel to the AC-PC line covering the whole brain, voxel size 3.4 × 3.4 × 3.5 mm³. Five additional volumes collected at the beginning of each run for T1 stabilization were discarded.

2.4. FMRI task

Participants viewed 96 pictures of outdoor scenes and responded whether there was water in the scene by pressing yes/no button in the scanner (Gutchess et al., 2005). Half of the pictures contained water and half did not. Stimuli were presented using E-prime software (Psychology Software Tools, Pittsburgh, PA, USA). Each picture was presented for 3s in an event-related design with jittering range from 4 to 14 seconds (Fig. 1a).

Approximately 20 minutes after the end of the encoding task, a recognition test was administered outside the scanner. Participants were presented with a total of 192 pictures, 96 were target pictures presented in the scanner and 96 lure pictures closely matched to the target pictures for similar content and composition (e.g., both the target and the corresponding lure consisted of a forest and a creek; Fig. 1b). Participants were instructed to indicate whether they remembered seeing the exact picture by making one of three judgments: 1. “high-confidence remember” indicating that the participant was confident the same picture was presented; 2. “low-confidence remember” indicating that the participant remembered seeing the picture but with low confidence; 3. “new item” indicating that the participant judged it as a new picture not previously presented. This recognition task was self-paced with a maximum of 4s for each trial.

2.5. FMRI data processing

Statistical Parametric Mapping (SPM12, University College London, UK) was used for imaging processing and data analysis. For preprocessing, functional images were corrected for motion and realigned to the mean image across all the runs for each participant, which was then used for co-registering the anatomical scan. The anatomical scan was segmented using SPM segment function. All functional images were co-registered to the MNI template via the anatomical image. Finally, spatial smoothing was implemented with a full-width-half-maximum (FWHM) kernel of 8 mm. Artifact Detection Tools (ART) was used to detect outliers due to movement or signal intensity spikes (Mazaika et al., 2005). Time points of movement outliers were dummy coded in the first-level analysis and used to regress out the artifact. Runs containing > 15% outlier volumes (~17 vol) due to intensity shift (>3% deviation from the mean in global intensity) or motion (>2 mm motion displacement) were excluded. No participants had more than one run (out of three) excluded.

A canonical hemodynamic response function was modeled by convolving the signal time course with the stimulus event for each individual. Nuisance regressors included six movement regressors, one artifact regressor, and the difference in the mean signal across runs. An autoregressive model, AR(1), was used to estimate and correct for the temporal

autocorrelation. To study activity specifically related to successful encoding, the contrast of interest was the subsequent memory effect: high-confidence hit (“high-confidence remember” response to old pictures) > miss (“new” response to old pictures).

2.6. Imaging and statistical analyses

2.6.1. Classifying individuals with different cognitive aging profiles—We first specified a measurement model to determine the goodness of fit of the multiple measures of the four cognitive domains simultaneously and to estimate baseline and longitudinal changes to identify successful agers. For each participant, we used latent change score models (McArdle, 2009; Raykov, 1992) that estimated both the initial baseline performance and longitudinal change score for each of the four cognitive domains (episodic memory, inductive reasoning, working memory, speed of processing) simultaneously. This resulted in eight latent scores for each participant (one baseline and one change score for each of the four cognitive domains). The goodness of model fit was examined based on comparative fit index (CFI), Tucker-Lewis Index (TLI), and root-mean-square error of approximation (RMSEA) (Kline, 2015).

The baseline and change latent scores from the measurement model were then used in the mixture models (Muthén, 2001; Muthén & Muthén, 2000). Latent mixture modeling utilizes a person-centered approach that examines the heterogeneity in the sample by classifying individuals into subgroups that display more homogenous profiles (Berlin et al., 2014; Lubke and Muthén, 2005). We used this approach to identify subgroups, or latent *classes*, of individuals showing distinct cognitive aging profiles that were based on the latent scores of cognitive performance and longitudinal change in the four domains. We constructed latent mixture models for three age groups separately so that the classification would not be dominated by age. The final solution with the optimal number of *classes* was iteratively determined based on suggested procedures for implementing mixture modeling analysis (Ram and Grimm, 2009). Specifically, we checked for out-of-bounds parameter estimates, entropy, information criteria, and bootstrapped likelihood ratio test (BLRT) (e.g., Lo-Mendell-Rubin adjusted test), examined the participant number in the smallest class to avoid data over-extraction (Berlin et al., 2014), and ensured that the selected solution could provide empirical interpretation (Ram and Grimm, 2009).

2.6.2. fMRI data analysis—All fMRI analyses were performed using SPM12. Regions of subsequent memory effect were first defined universally in all participants ($N=290$) based on the subsequent memory contrast (subsequently remembered with high confidence > subsequently forgotten). Then, a second-level general linear model (GLM) was created with age as a covariate. The initial activation height threshold was $p < .001$. A voxel-wise multiple comparison correction with family-wise error (FWE) rate at $p < .05$ was applied. The result represents significant activations during successful encoding in all participants regardless of age. The significant clusters were then used as masks in the region of interest (ROI) analyses.

For the ROI analysis, the mean activity estimate within each subsequent-memory-defined cluster was extracted using MarsBar (Brett et al., 2002). We examined whether people with

different *classes* of cognitive aging profiles presented differences in functional activation in these ROIs. We used the analysis of covariance (ANCOVA) to examine the effect of *class*, age (middle-aged, young-old, very old), and their interaction while controlling for sex and education. Then, we examined how activation in individuals with different cognitive aging profiles differed from the young group. We used ANCOVA in each *class* to specifically compare the difference between younger adults and the other age groups, while controlling for sex and education. We applied multiple comparison correction based on false discovery rate (FDR) at the level of 0.05 (Benjamini & Hochberg, 1995; Storey, 2002) and reported the FDR-corrected significance values (*q* values).

In addition to the ROI analyses, we also ran a whole-brain comparison between participants with different cognitive aging profiles in middle-aged, young-old, and very old groups. Using GLM, we compared subsequent memory effect (subsequently remembered with high confidence > subsequently forgotten) between successful and average agers in each age group. This analysis explored any differences in subsequent memory effect between different *classes* of people that may exist outside the core subsequent-memory-defined clusters. The activation height threshold was $p < .001$ and corrected for family-wise error (FWE) rate at $p < .05$. Additional multiple comparison correction based on FDR estimation was applied at the level of 0.05. The FDR-corrected significance values (*q* values) were also reported.

Statistical analyses were conducted using SPSS v25. Statistical significance was determined at $p = .05$, and marginal significance ($p < .1$) was also noted. Multiple comparison correction with FDR was performed using R (v4.1.0) with *qvalue*.

3. Results

Table 1 presents the demographic information of the 290 participants with available fMRI data, separated by age group. There was no difference in sex across age groups, but older groups tended to be less educated, $F(3, 286) = 4.58, p = .004$, and have lower Mini-Mental State Exam (MMSE) scores, $F(3, 286) = 4.29, p = .006$, compared to younger groups.

3.1. Two different aging profiles identified in three age groups

We used latent change score model to estimate the performance and change in all four cognitive domains in all participants (Fig. 2). The model yielded an excellent fit to the data (CFI = 0.95, TLI = 0.94, RMSEA = 0.05), suggesting good quality of cognitive constructs specified to estimate initial baseline performance and longitudinal change. Based on the latent baseline and change scores obtained from the above model, Fig. 3 depicts the longitudinal cognitive change in each individual for the four cognitive domains. Across four cognitive domains, despite the visually overwhelming age-effects on cross-sectional and longitudinal differences, there is great individual variability that permits further investigation of possible heterogeneity using the latent mixture model.

Then, we used latent mixture models to explore possible subpopulations based on the cognitive performance and change across all four domains. The model identified 2 *classes* in all three age groups (middle-aged: entropy = .90, BLRT $p = .57^1$; young-old: entropy =

.93, BLRT $p = .04$; very old: entropy = .93, BLRT $p = .05$): one class (*class 1*) presented typical age-related decline, while the other class (*class 2*) – including 69% middle-aged, 60% young-old, and 51% very old adults – showed superior cognitive performance and better-preserved cognitive function over time across all domains (Fig. 4). This second class with optimal cognitive profiles was defined as representing *successful* agers in this study. The first class was defined as *average* agers who presented typical age-related decline. This grouping reflects their cross-sectional performance at both time points and the change trajectory across all domains. When comparing the two classes (Table 2), class 2, or *successful* agers, tended to be relatively younger ($F(1,69) = 5.298, p = .024$) and more likely to be female ($\chi^2 = 5.973, p = .015$) in the middle-aged group, higher educated ($F(1,94) = 6.887, p = .010$) and more likely to be female ($\chi^2 = 9.293, p = .002$) in the young-old group, and relatively younger ($F(1,80) = 8.073, p = .006$) in the very old group.

3.2. Behavioral performance of subsequent memory task

The mean memory task performance of each age group is presented in Table 3. Overall, this task appears to be sensitive and challenging for all age groups: performance was generally low but above chance level, as shown in previous studies (Gutchess et al., 2005; Park et al., 2013). Participants overall performed similarly in recognizing the old pictures. There was a trend toward significance in the ability to distinguish new pictures: older adults less often correctly identified new pictures as new ($p = .073$) and were more likely to falsely recognize new pictures as old ($p = .077$). Memory discrimination, d' , was calculated from the z-transformed proportion of high-confidence remembered trials minus the proportion of high-confidence false alarms (Park et al., 2013). An analysis of variance (ANOVA) test showed significant differences in d' across age groups, $F(3, 286) = 9.588, p < .001$. Post-hoc analyses revealed that the difference occurred because very old adults differed from the other three groups (p 's $< .001$), despite equivalent performance in the other three age groups (p 's $> .294$). When comparing d' between successful and average agers of each age group, we found the difference began to become significant in the young-old ($t = -2.727, p = .008$) and continued in the very old group ($t = -3.805, p = .001$), as shown in Fig. 5.

3.3. Significant regions for subsequent memory effect

To identify significant regions for successful encoding in all participants, a whole-brain general linear model was fit for the subsequent memory contrast (high-confidence remembered $>$ forgotten) while controlling for age. Four significant clusters were identified, at a height-threshold $p < .001$, FWE corrected $p < .05$, including left and right fusiform/parahippocampal gyrus, and left and right lateral/mid occipital regions (Table 4; Fig. 6).

3.4. Subsequent memory effect differences between successful vs average agers

To compare the subsequent memory effect between *successful* and *average* agers in middle-aged, young-old, and old adults, an ANCOVA was performed predicting BOLD estimate for

¹For the middle-aged group, the two-class model showed adequate fit (entropy = .90) but a non-significant BLRT ($p = .57$), which could suggest that both one-class and two-class models could be appropriate. But when iteratively examined for the best solution, the three-class model yielded a significant BLRT ($p = .04$), indicating significant heterogeneity in the data. Since one of the three classes had only one participant, which invalidated this solution (Berlin et al., 2014), the two-class model was therefore determined as the best solution, following suggested procedures for implementing mixture modeling (Ram & Grimm, 2009).

each cluster to test the effects of age (3-level categorical variable: middle-aged, young-old, very old), class (2-level categorical variable: *successful*, *average*), and their interaction while controlling for sex and education as nuisance variables. As shown in Fig. 7, for left fusiform, there were a significant main effect of *class* ($F(1, 241) = 7.073, p = .008, q = .035$) where *successful* agers had higher activation than *average* agers, and a significant age \times class interaction ($F(2, 241) = 5.026, p = .007, q = .035$) such that the activation difference between *successful* versus *average* agers was most evident in the young-old group. Right fusiform showed a similar but weaker pattern of results with a trend-level interaction between age and class ($F(2, 241) = 2.43, p = .09, q = .17$) such that *successful* agers in young-old age had greater subsequent memory effect than *average* agers. Similarly, in the two occipital clusters, *successful* agers appeared to overall show a stronger subsequent memory effect, despite the age-related reduction. There was a significant age effect in the left lateral/middle occipital cluster, $F(2, 241) = 4.585, p = .011, q = .035$, where older adults had reduced occipital effect, and a marginally significant class effect, $F(1, 241) = 3.337, p = .069, q = .148$, such that *successful* agers had greater subsequent memory effect than *average* agers. There was no significant age \times class interaction ($p = .511$). Right lateral/middle occipital cluster also showed a significant age effect, $F(2, 241) = 4.74, p = .01, q = .035$, with older groups showing decreased subsequent memory effect, and a significant class effect, $F(1, 241) = 6.053, p = .015, q = .039$, where *successful* agers showed greater subsequent memory effect than *average* agers. There was likewise no significant age \times class interaction in the right occipital cluster ($p = .201$). Overall, *successful* agers evidenced higher subsequent memory effect, compared to *average* agers; this difference was particularly evident in young-old adults in the temporal clusters (Fig. 7). All significant effects survived multiple comparison correction for FDR (q 's $< .05$), whereas the marginal age \times class interaction in the right fusiform/parahippocampal cluster and the marginal class effect in the left lateral/middle occipital cluster were no longer approaching significance (q 's $> .15$).

3.5. Subsequent memory effect in successful and average agers relative to younger adults

Next, to examine whether the activation in *successful* and *average* agers is different from younger adults, the subsequent memory effect in middle-aged, young-old, and very old adults was compared to the younger reference group using ANCOVA while controlling for sex and education, for *successful* and *average* agers separately. We specifically focused on the difference relative to the young reference group as it is important for the interpretation of the activation differences found between *successful* and *average* agers. The results showed that *successful* agers demonstrated youth-like activation until very old age, whereas *average* agers showed decreases beginning in young-old age (Fig. 8). Specifically, for the left fusiform/parahippocampal cluster, the analysis revealed, in *successful* agers, only a weak trend of reduced subsequent memory effect ($F(3, 181) = 3.492, p = .062, q = .062$), driven by the only difference in the very old group relative to the young reference group ($p = .097, q = .062$). *Average* agers, however, showed a strong effect of age group, $F(3, 138) = 4.305, p = .006, q = .024$, driven by the significant reduction in both young-old ($p = .001, q = .004$) and very old groups ($p = .026, q = .022$) relative to young adults. A similar pattern was also found in the right fusiform/parahippocampal cluster: in *successful* agers, reduction in subsequent memory effect ($F(3, 181) = 3.000, p = .032, q = .037$) was only found in the

very old group ($p = .008$, $q = .01$), whereas *average* agers showed significantly reduced subsequent memory effect, $F(3, 138) = 3.615$, $p = .015$, $q = .040$, in both young-old ($p = .003$, $q = .008$) and very old adults ($p = .007$, $q = .01$). The two occipital clusters revealed the same pattern: for the left lateral/middle occipital cluster, the analysis of *successful* agers showed that age-related reduction in subsequent memory effect ($F(3, 181) = 2.880$, $p = .037$, $q = .043$) was only significant in the very old group, compared to young ($p = .025$, $q = .022$), but in *average* agers, the age-related reduction ($F(3, 138) = 2.902$, $p = .037$, $q = .043$) started in young-old adults ($p = .056$, $q = .042$) and was more evident in very old adults ($p = .005$, $q = .01$). For the right lateral/middle occipital cluster, in *successful* agers, the age group effect was significant, $F(3, 181) = 3.177$, $p = .025$, $q = .043$, driven by the only difference in the very old group ($p = .016$, $q = .017$), whereas *average* agers showed a significant reduction, $F(3, 138) = 4.595$, $p = .004$, $q = .024$, starting in the young-old group ($p = .008$, $q = .01$) and continuing in the very old group ($p = .001$, $q = .004$). All significant effects survived multiple comparison correction controlling for FDR (q 's $> .05$).

In summary, despite the age-related reduction in subsequent memory effect in older ages, *successful* agers overall had higher subsequent memory effect than *average* agers. Across all core regions supporting successful encoding, we found a consistent pattern that *successful* agers were featured with better preservation of youth-like subsequent memory effect, until very old age, whereas *average* agers showed early reduction starting at a younger age in late adulthood.

3.6. Whole brain exploration of subsequent memory effect differences

To explore activity differences between *successful* and *average* agers that may exist outside the core subsequent memory defined regions, whole-brain analyses were additionally performed in middle-aged, young-old, and very old groups separately, comparing the subsequent memory effect in *successful* and *average* agers. The only group where we observed significant difference was the young-old group, where five cortical clusters showed higher subsequent memory effect in *successful* agers than *average* agers (Fig. 9A): left superior frontal cortex (peak: $[-9, 32, 44]$, $t = 4.40$; cluster: $k = 251$, $p_{\text{FWE-corr}} < .001$); left inferior/middle frontal cortex (peak: $[-42, 32, 5]$, $t = 4.99$; cluster: $k = 552$, $p_{\text{FWE-corr}} < .001$); left lingual/fusiform gyrus (peak: $[-18, -37, -1]$, $t = 5.14$; cluster: $k = 886$, $p_{\text{FWE-corr}} < .001$); bilateral parieto-occipital regions (peak: $[-24, -67, 35]$, $t = 4.52$; cluster: $k = 1389$, $p_{\text{FWE-corr}} < .001$); right orbitofrontal cortex (peak: $[30, 41, -10]$, $t = 4.31$; cluster: $k = 133$, $p_{\text{FWE-corr}} = .01$). These clusters primarily overlap with regions that have been previously associated with subsequent memory or memory processing (Kim, 2011). Some of these clusters were also identified in the ROI analysis (e.g., left and right occipital, left fusiform), and some were new clusters outside the subsequent-memory-defined regions, particularly in prefrontal regions (e.g., left inferior frontal, left superior frontal, right orbitofrontal cortex).

To focus on the activations outside the identified subsequent memory regions, the voxels belonging to the defined ROIs were first masked out. Then, we extracted the mean activity estimate in these clusters and found that *successful* agers showed significant subsequent memory effect in most clusters identified, including left lingual/fusiform ($p < .001$, $q < .001$), left and right occipital ($p < .001$, $q < .001$), left inferior frontal ($p < .001$, $q < .001$),

and left superior frontal regions ($p < .001$, $q < .001$), suggesting a reliance of an expanded network in *successful* agers for successful encoding. *Average* young-old agers, however, showed negative effects (p 's $< .023$, q 's $< .036$) in these regions, possibly suggesting disengagement of these regions during encoding in *average* agers. Interestingly, most of these regions, except the occipital cluster ($p = .021$, $q = .035$), did not show any significant subsequent memory effect in young adults (p 's $> .173$, q 's $> .228$), further suggesting that *successful* young-old agers appeared to have additional recruitment that was not utilized in healthy young adults. Indeed, when comparing to the young reference group using ANCOVA controlling for sex and education, we found the magnitude of the subsequent memory effect in *successful* young-old agers was significantly higher than young adults in left superior frontal ($F(1, 95) = 8.184$, $p = .005$, $q = .009$) and right orbitofrontal cortices ($F(1, 95) = 4.227$, $p = .043$, $q = .063$). These two prefrontal clusters were distant from the subsequent memory clusters identified: we examined the subsequent memory effect in young adults and confirmed that there were no prefrontal clusters utilized in young adults (Fig. 9B), even with no correction, where significant subsequent memory activation was found in *successful* young-old agers (Fig. 9C), suggesting additional frontal recruitment during memory encoding in *successful* agers.

We did not find any region that showed significantly greater activation in *average* agers compared to *successful* agers. And no significant activity differences between *successful* and *average* agers were found in the other two age groups.

4. Discussion

This study attempts to characterize neural activity features in people who showed superior cognitive performance and little longitudinal cognitive decline in aging over four years. Using a data-driven classification that identified successful agers in an across adult lifespan sample, we compared the neural activity supporting successful encoding using a subsequent memory fMRI task. We found that *successful* agers managed to preserve youth-like activation until very old age. The *average* agers, on the other hand, showed an early reduction in subsequent memory effect beginning in young-old age. Additionally, we also found evidence of additional neural recruitment outside the core subsequent-memory-defined ROIs in young-old *successful* agers, particularly in the left superior frontal and right orbitofrontal cortices, likely suggesting adaptive recruitment of novel regions underlying better cognitive aging. Overall, the findings implicated neural features of *brain maintenance* in task-sensitive regions, as well as *adaptive recruitment* in frontal regions, in *successful* agers with less retrospective cognitive decline.

4.1. Fusiform, parahippocampal, and occipital regions in successful encoding

The present study used a subsequent memory task to investigate brain activities that are specific to successful encoding. Some studies have explored functional activity during encoding between older individuals with different cognitive aging trajectories (e.g., Persson et al., 2011; Pudas et al., 2013; Pudas et al., 2018), but those studies did not separate successful encoding from unsuccessful encoding. Activities during unsuccessful encoding may not involve mental processes leading to memory, but reflect general visual-perceptual

processing of the stimuli. As alluded to in the introduction, those studies may be limited in the interpretation of the differences in functional brain activity between individuals. The present study specifically focused on subsequent memory effect that distinguishes successful and unsuccessful encoding. The results, in fact, converge with previous findings of subsequent memory effect and highlight the importance of functional integrity in core memory regions in aging.

The present study found subsequent memory effect in left and right temporal and occipital regions including fusiform, parahippocampal, and lateral/middle occipital clusters, which are essential for successful encoding. The results suggest the higher-order visual processing, particularly involved in occipital regions (Grill-Spector et al., 2001), is essential for successful memory of the pictorial stimuli in this study. Moreover, parahippocampal gyrus and fusiform gyrus have both been linked to successful memory encoding, particularly for colorful visual materials containing environmental and scenery information (Aguirre et al., 1996; Gutchess et al., 2005). It has been frequently reported that fusiform and parahippocampal activation is critical for subsequent memory during the processing of pictorial stimuli in young adults (Kim, 2011). Further, a meta-analysis on subsequent memory effect in young and older adults showed medial temporal lobe and left fusiform gyrus were activated in both young and older adults (Maillet and Rajah, 2014). Overall, our study substantiates prior findings that activity in temporal regions including fusiform and parahippocampal gyrus is critical for successful encoding regardless of age.

4.2. People who aged better have higher subsequent memory activations

The comparison between *successful* and *average* agers revealed that *successful* agers overall had higher activation than *average* agers. Higher task-related neural activity has been found positively correlated with better cognitive aging cross-sectionally (Eyler et al., 2011), and typical aging is often accompanied by age-related loss of neural responses or neural modulation, particularly in temporal and occipital regions during memory encoding (Koen and Rugg, 2019; Li et al., 2001). The present study showed that this age-related neural deterioration may not be universal and that people with less longitudinal cognitive decline had higher activations than those with suboptimal patterns of cognitive aging. Notably, successful agers in our study presented performance increases in some domains. Our tests were presented at long intervals of 4 years and many used non-verbal, abstract items designed to be harder to remember. The better performance at time 2 may thus reflect a general familiarity of being a research participant and being tested in the laboratory environment. Practice effect is common in repeated testing (Bartels et al., 2010), calling for more careful interpretations of the absolute change in longitudinal tests: performance drop may not be the only manifestation of worsening cognition; exhibiting little improvement in tasks where many people show practice effects could also be suboptimal, as suggested in this study.

In this study, the activation pattern difference between successful and average agers was based on a data-driven classification that, as depicted in Fig. 4, reflects both cross-sectional level and longitudinal change in cognition across all domains. Although it was very unlikely that the results were driven by the performance at the follow-up visit when fMRI data

were collected, we conducted a *post hoc* exploration and correlated the subsequent memory activation with the latent factor scores of longitudinal changes and at each time point for each cognitive domain (Fig. 10). We found that the relationship was very similar for baseline, follow-up, and the change scores for all domains and that the effect appears to be primarily driven by the contrast of successful agers versus suboptimal performers (Fig. 10). This may suggest that the higher subsequent memory activation effect reflects a general feature of successful aging across domains.

Typical lower task-related functional activation in old age may reflect age-related adverse effects of accumulated neural depletion factors on functional alterations. For example, gray matter atrophy (Pudas et al., 2018), white matter microstructure (Webb et al., 2020), and decreased dopamine availability (Backman et al., 2010) have all been linked to age-related reduction in brain activity. These factors may also contribute to differences in cognitive aging trajectories, directly or indirectly through brain function (Hedden and Gabrieli, 2004; Nyberg and Pudas, 2018). As a consequence, higher task-related activation may reflect better structural integrity (Nyberg et al. 2012; Cabeza et al., 2018) and is thus an important neural feature prevalent in individuals who present better cognitive aging profiles.

4.3. Maintaining functional activation in successful agers until very old age

By examining fMRI data in a large sample across the adult lifespan, the present study provides evidence that better cognitive aging is associated with better preservation of task-related activations. This conclusion is supported by two interconnected findings. First, *successful* agers demonstrated task-related activations at a similar magnitude as in young adults, until very old age where the activity magnitude became low in both *classes*. On the contrary, *average* agers showed earlier reduction in task-related activation starting in young-old age. This finding suggests that expected age-related functional reduction is delayed in *successful* agers, compared to *average* agers, and that the subsequent memory effect appears to be well preserved throughout most of the adult lifespan in individuals showing better cognitive aging trajectories. Second, *average* young-old agers additionally showed disengagement of subsequent memory activation outside task-related regions. This pattern is also consistent with the suggestion of *brain maintenance* theory (Nyberg et al., 2012; Cabeza et al., 2018) that the inability of recruiting proper activation during task condition is likely a consequence of age-related detrimental changes in the whole brain, not necessarily specific for a particular region.

The importance of preserving high brain functional activation in older individuals has been suggested previously. For example, Pudas et al. (2013) found successful older adults, defined by maintaining high memory performance over 15–20 years, had comparable medial temporal activation during a memory task as in young adults, whereas the average older adults who showed typical memory decline had reduced activation. A longitudinal examination of functional activity change also found that it was the declining older adults with greater memory decline showed greater activation reduction in the hippocampus with age (Persson et al., 2011). The current study further provides evidence of such characteristics by including an adult lifespan sample and specifically focusing on subsequent

memory effect, and presents a clear consistency across task-related regions responsible for successful encoding, as well as the extended clusters outside core task regions.

4.4. Additional frontal recruitment in successful agers at young-old age

The present study also showed evidence of *additional neural recruitment* in frontal regions in *successful* agers at young-old age (55–69 years old at baseline, 59–74 years old at scan). In two prefrontal clusters (left superior frontal, right orbitofrontal), *successful* agers showed significant subsequent memory effect that was not present in young adults. Given the nature of a subsequent memory contrast, *successful* agers utilized this additional recruitment for successful encoding, and this recruitment likely reflects adaptive and compensatory neural response supporting their completion of the task. The critical role of the prefrontal lobe in brain adaptive responses in aging has been well documented. An early review examined 47 neuroimaging studies and found that greater frontal activation was one of the most evident patterns related to better cognitive aging in older adults (Eyler et al., 2011). Prefrontal regions are actively involved in cognitive control processes that contribute to a wide range of cognitive tasks, including memory encoding (Badre and Wagner, 2007). It has been suggested that individuals who showed the least parahippocampal activation recruited the most frontal regions (Gutchess et al., 2005) and the ability to activate prefrontal function may be a mediator of encoding quality in aging (de Chastelaine et al., 2016), as it is one of the particularly vulnerable regions affected by age-related detrimental effects and may limit the neural responses in older brains (Fjell et al., 2014; Rabbitt, 2005). The ability to utilize additional prefrontal regions should be recognized as an important neural feature of desired activation patterns in *successful* agers particularly at the beginning of late adulthood.

4.5. Age as a potential moderator of what functional activity pattern is expected in successful aging

Another important finding of the present study is that it demonstrates the brain activity pattern associated with better cognitive aging in different stages of life. We suspected that functional characteristics related to better cognitive aging may depend on age. The findings suggest that preservation of sufficient functional activation is likely most critical in young-old adults, and the additional frontal recruitment also emerges in the same age.

Middle-aged brains are likely relatively spared from age-related detrimental changes and present high levels of functional brain activity with little need for compensation. But as age increases, the individual difference in preserving proper brain function becomes critical. Studies have suggested that the ability to resist functional and structural decline relies on neural plasticity and cellular repair which may offset age-related pathology (Cabeza et al., 2018). For individuals who can no longer withstand the increasing neural deterioration, there may start to be functional activity deficits in task-related regions. Not coincidentally, this is also when task performance starts to diverge. Meanwhile, additional neural responses in prefrontal regions start to emerge in some individuals, probably to cope with functional deteriorations (Park and Reuter-Lorenz, 2009). The present study suggests that young-old age (55–69 years old at baseline, 59–74 years old at scan in the study) is when this critical brain and behavioral divergence begins. Finally, very old brains likely lose the necessary integrity, regardless of being a *successful* or *average* ager, due to “wear and tear”

at cellular levels at an advanced age (Nyberg et al., 2012). There is little neural resource for preserving high brain activation or recruiting additional activities even in high-performing oldest adults. This pattern of decreased sensitivity of functional signal in very old brain has been previously reported (Chen et al., 2021b; Kennedy et al., 2015; Song et al., 2016), suggesting age as a potential moderator in the brain-behavior relationship as brain degrades.

Previous studies on functional neuroimaging of aging often focus on the contrast between a young and an older group. The present study suggests that brain aging is likely nonlinear and that late middle age to the beginning of late adulthood may be a particularly critical period for maintaining brain function and cognition. Furthermore, functional activity is not exclusively related to one's biological age, but also a reflection of whether one could be considered a *successful* or *average* ager, highlighting the importance of recognizing individual differences in cognitive aging when examining brain function change in aging.

4.6. Limitation and future direction

One limitation of the present study is that the functional inference was based on a cross-sectional comparison. However, older participants in across-lifespan samples may be more selective (Fjell et al., 2014; Rugg, 2016), and the difference could also reflect sample differences in addition to developmental changes. In future studies, we plan to examine the longitudinal relationship between functional and cognitive changes in the same individual for a more definitive inference. Another caveat is that non-neural differences could be a confounding factor, such as neurovascular coupling and vascular dynamics which have been found to affect BOLD signal in older adults (Andrews-Hanna et al., 2007; D'Esposito et al., 2003). This potential influence is a common issue in most studies examining age-related effects on fMRI activation (Grady and Garrett, 2014; Qin and Basak, 2020). Future studies may consider incorporating measures, such as cerebrovascular reactivity (Liu et al., 2013) or the resting-state fluctuation amplitude (Tsvetanov et al., 2015), that correct for its effect on BOLD signal (Liu et al., 2019). It is also important to note that the present study is correlational. The findings illustrate the patterns of brain activation that are present in individuals who have accomplished better cognitive aging retrospectively. It does not directly examine causation between brain and behavior. It is likely that functional activity patterns identified in this study reflect a “snapshot” of neural features, which indeed underlie better cognitive outcomes. It is also possible that cognitive changes over the past years resulted in alterations in strategy, motivation, etc., which could also be reflected in brain activity. Finally, this sample represents a typical longitudinal sample of highly educated individuals with a low minority presence. For this particular reason, we considered those with better cognitive aging in this selective sample as *successful* agers and refrained from labeling the other *class* as “unsuccessful”, given that they stayed cognitively normal and managed to come back for the follow-up cognitive testing. More *classes* may be identified in the general population that represent greater heterogeneity in cognitive aging.

5. Conclusions

The present study used a data-driven, multivariate approach to identify successful agers based on baseline and longitudinal cognitive data of four different cognitive domains,

and provided characterization of functional activation patterns that represent successful cognitive aging. Successful agers showed better preservation of high brain activation until very old age, whereas average agers showed functional reduction starting in young-old age. Moreover, successful agers of young-old age also exhibited additional frontal recruitment outside the core task-related regions, likely reflecting neural compensation in successful aging. We propose that the divergence of brain activation emerges in young-old age and that maintaining youth-like activation and compensatory novel recruitment are likely not competing, but complementary functional mechanisms related to successful aging.

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Data and code availability statement

Data and code in the study is available upon email request.

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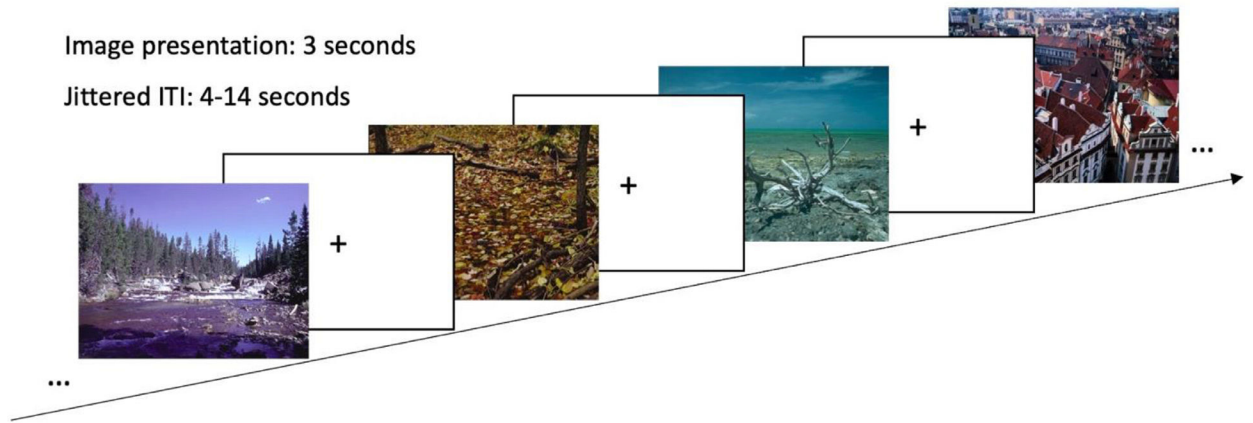
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a. Encoding phase (in scanner)



b. Example of pictures encoded and its matching lure for recognition outside scanner



Fig. 1. (a) Presentation of the scene pictures in the scanner during the encoding phase. (b). Example of encoded and matching lure pictures.

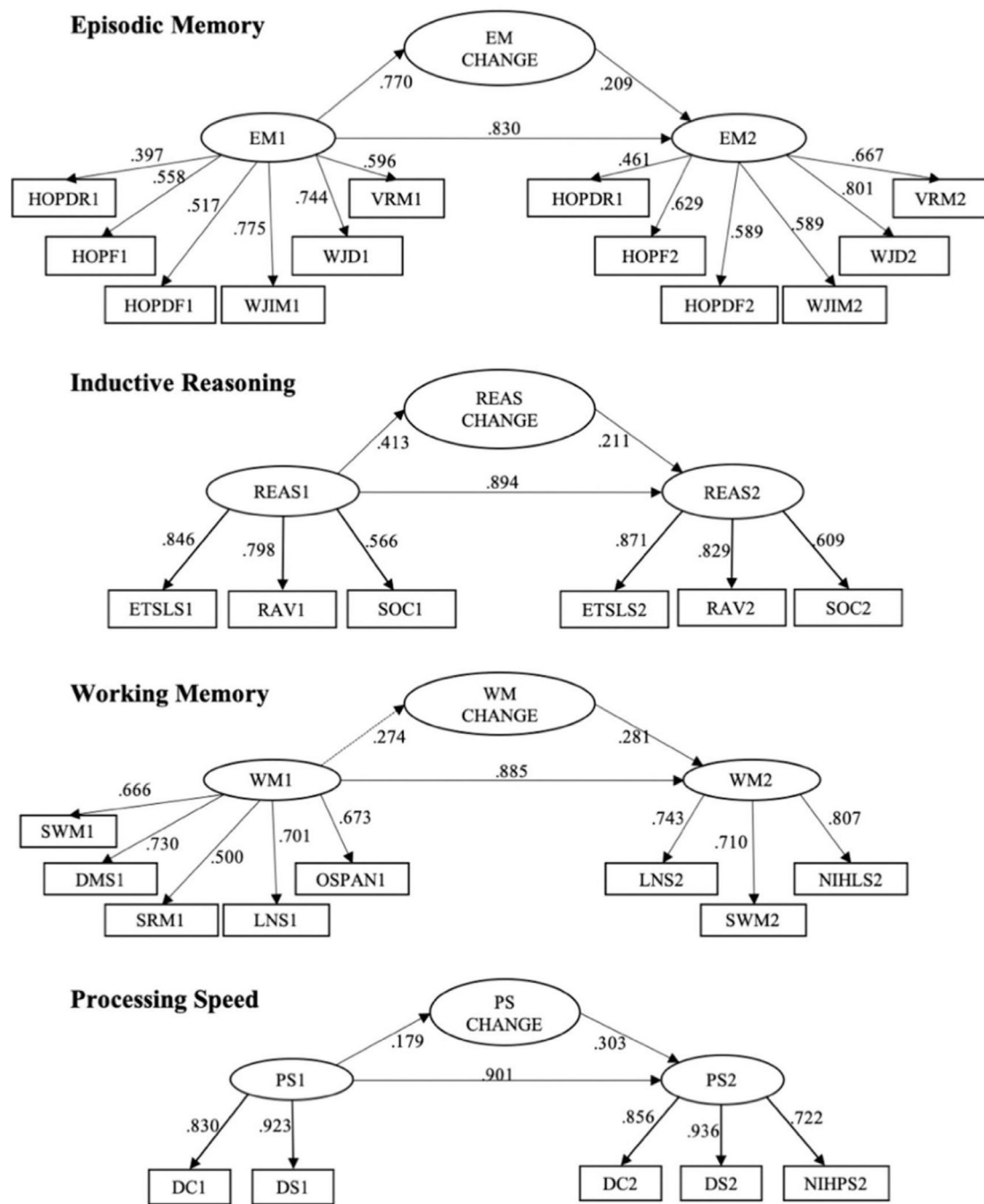


Fig. 2. Latent change score model simultaneously estimates cross-sectional performance and longitudinal change in four cognitive domains. Cross-time residual autocorrelations were allowed for measures from a repeated task but not depicted for simplicity. For measures from the same task, correlations were also specified but not depicted in the diagram. See Cognitive Measures in Methods for abbreviations.

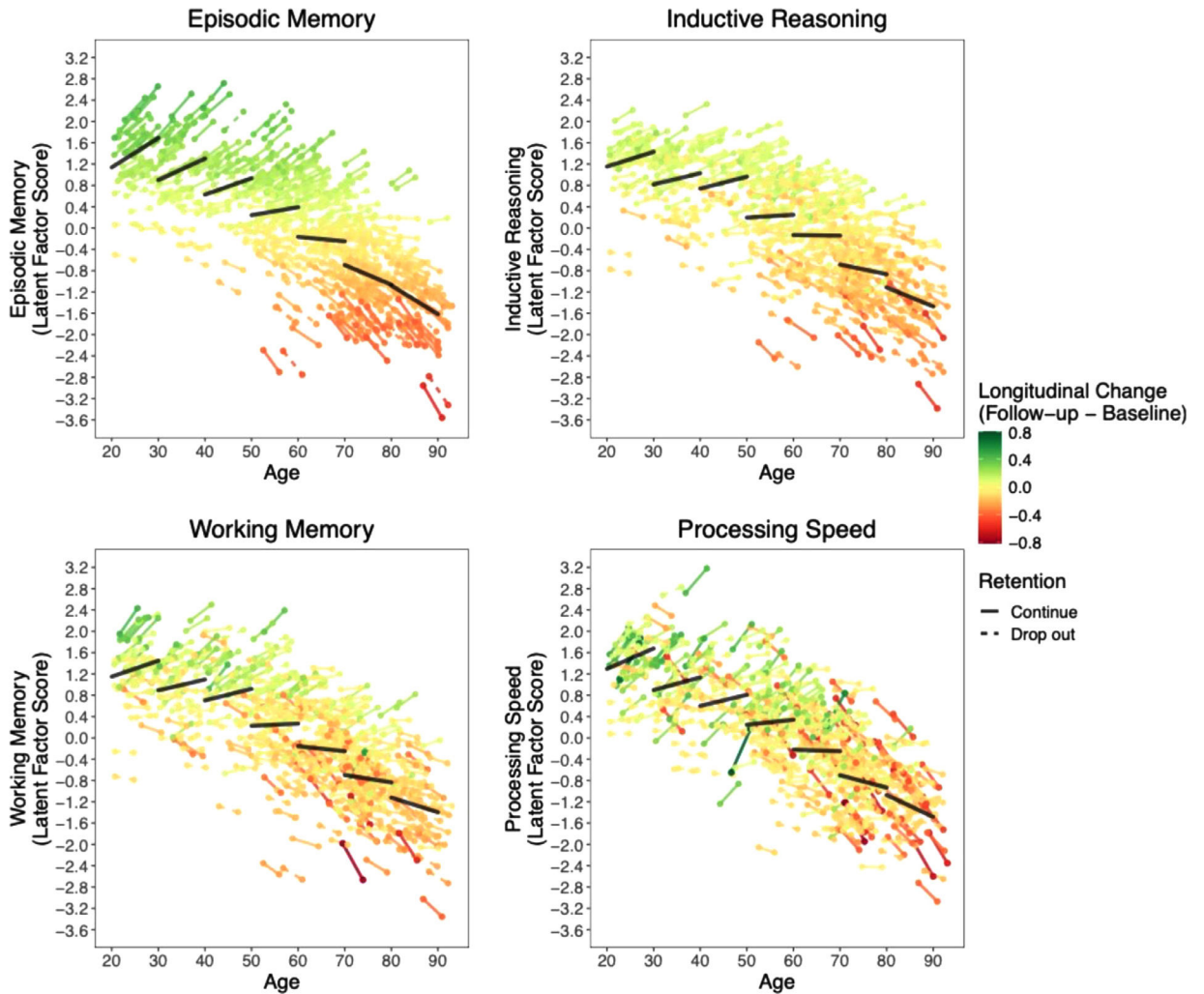


Fig. 3.

Spaghetti plot of longitudinal cognitive change over four years. Each line represents one individual in the study, going from the baseline score to the follow-up performance score. Lines are color-coded based on the longitudinal change: red means decline, yellow means stability, and green means performance increase, likely due to practice effect. The solid lines represent participants who continued to participate, and dashed lines represent participants who dropped out of the study (their scores were estimated using full information maximum likelihood estimation; they were included to aid visual interpretation, but not included in any further analysis). Black lines overlaying individual lines represent the mean level and change of the corresponding age decade.

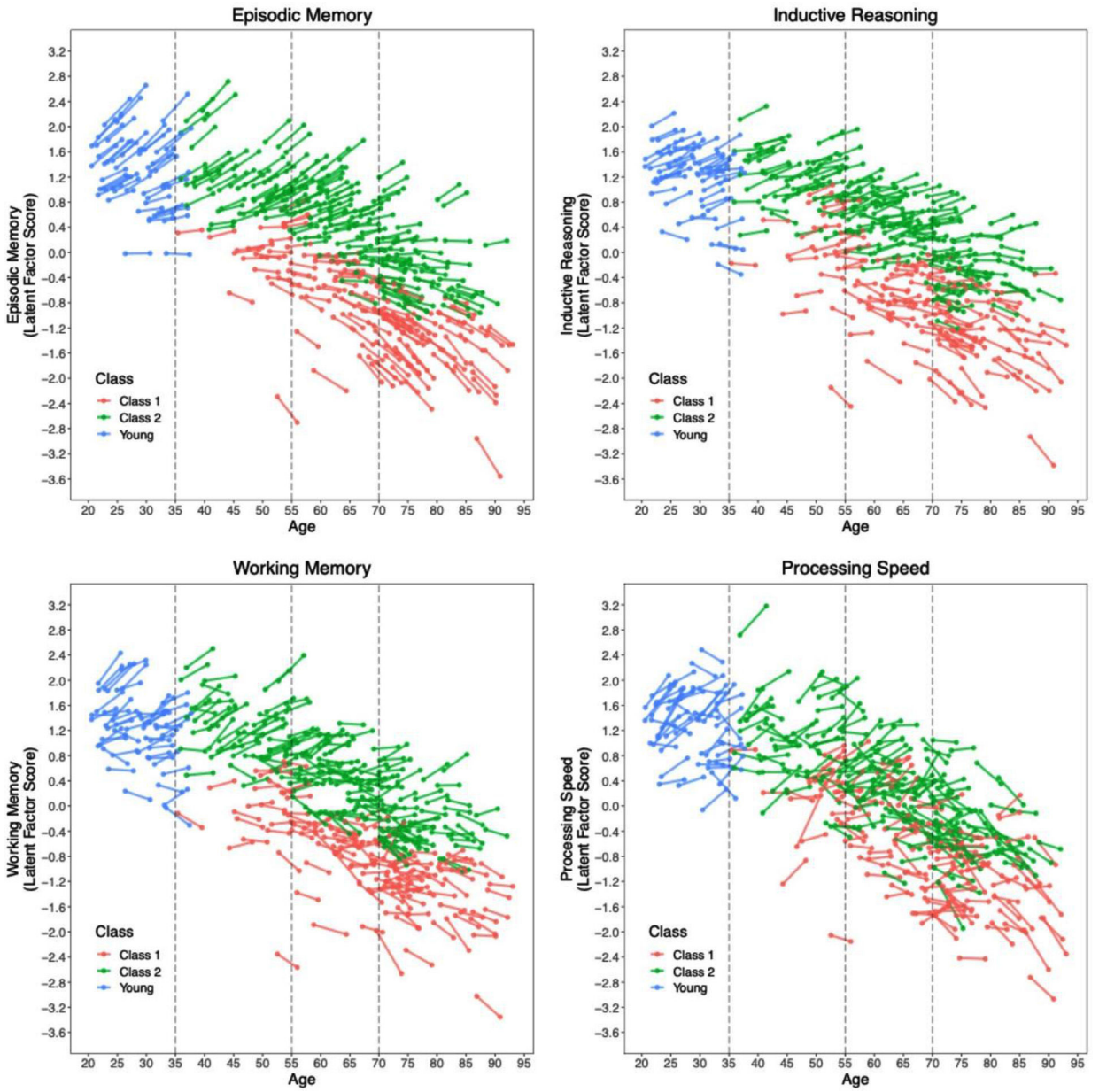


Fig. 4. Longitudinal cognitive change of two *classes* (*average* agers in red, *successful* agers in green) in four cognitive domains over four years. In all three age groups (middle-aged, young-old, very old), two classes of individuals with distinct patterns of cognitive aging profiles were identified using latent mixture modeling, with one class in red and the other class in green. Young adults (in blue) were included for reference visualization.

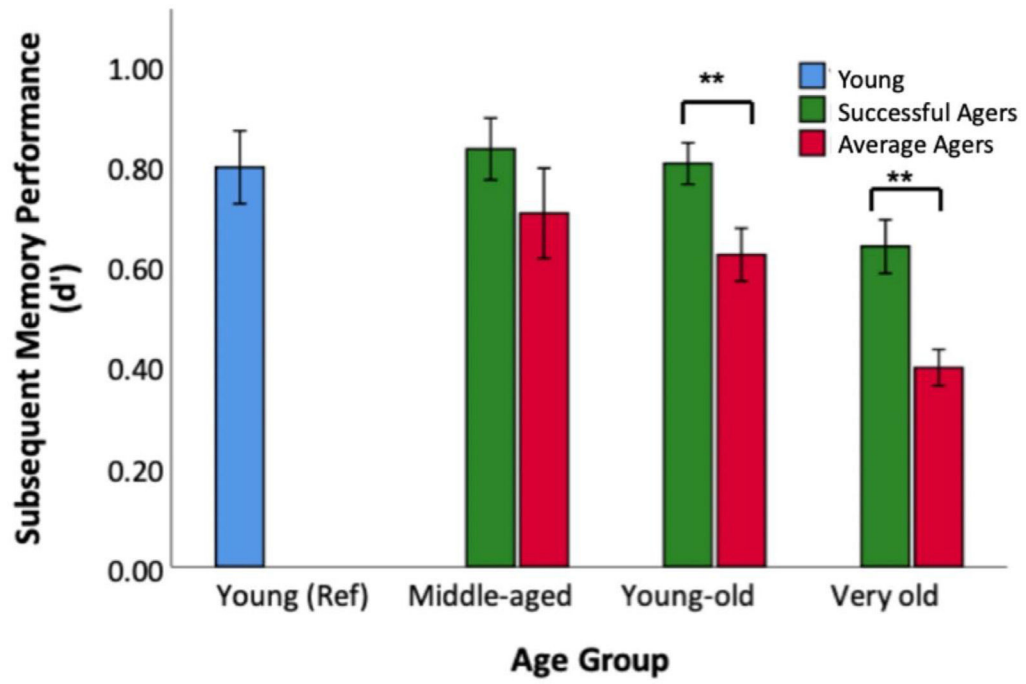


Fig. 5. Subsequent memory performance, indexed by d' ($ZPr(\text{HiC-hit}) - ZPr(\text{HiC-FA})$), separated by *successful* and *average* agers in three age groups. ** $p < .01$

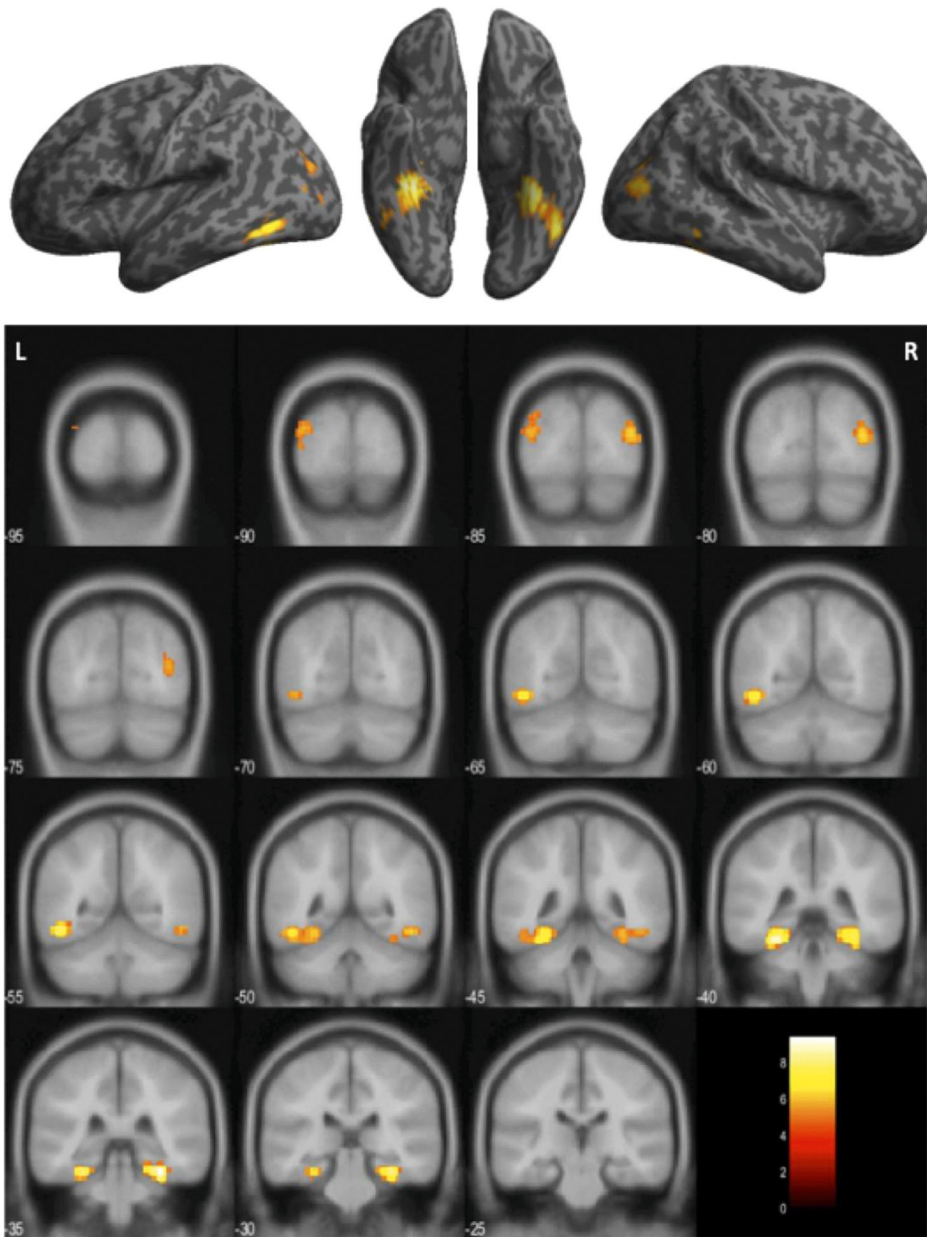


Fig. 6. Significant clusters demonstrating subsequent memory effect (high-confidence remembered > forgotten). Height-threshold at $p < .001$. Voxel-wise family-wise error (FWE) corrected at $p < .05$.

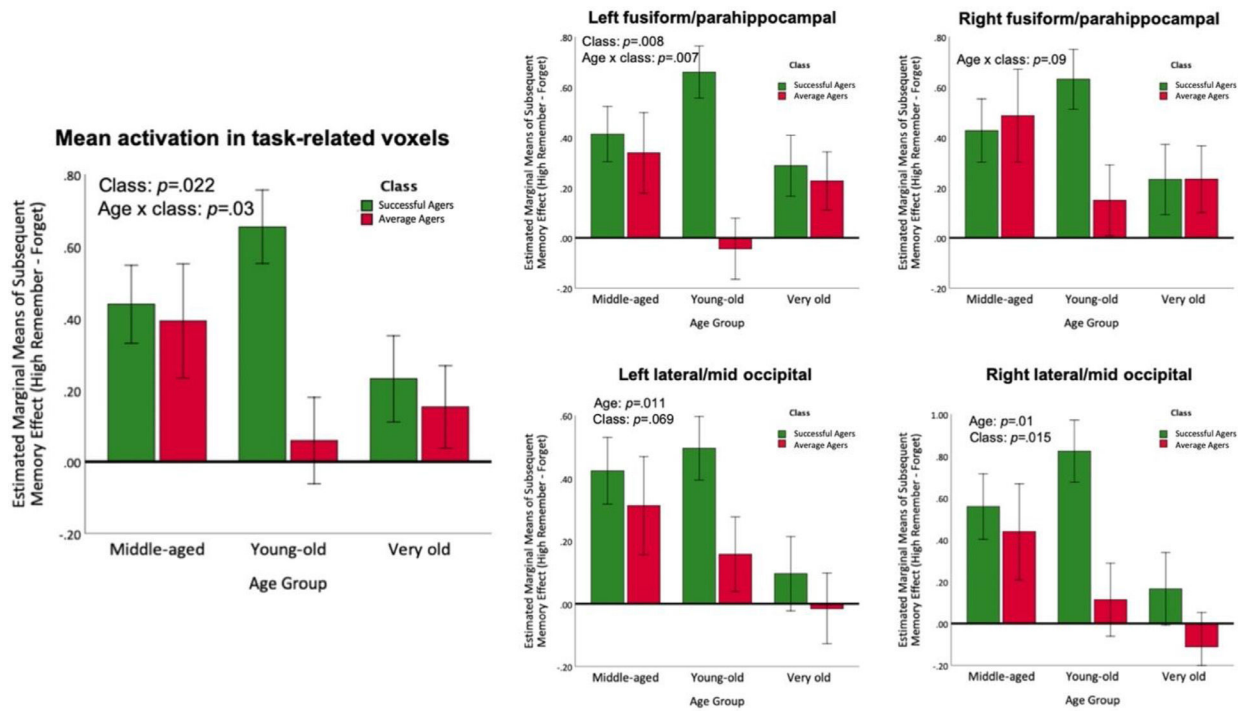


Fig. 7. Estimated marginal means of subsequent memory effect, adjusted for sex and education, in *successful* and *average* agers in middle-aged, young-old and very old adults in four subsequent-memory-defined ROIs. *Successful agers* tended to have higher subsequent memory effect than *average agers*, particularly in the young-old group for the fusiform/parahippocampal regions.

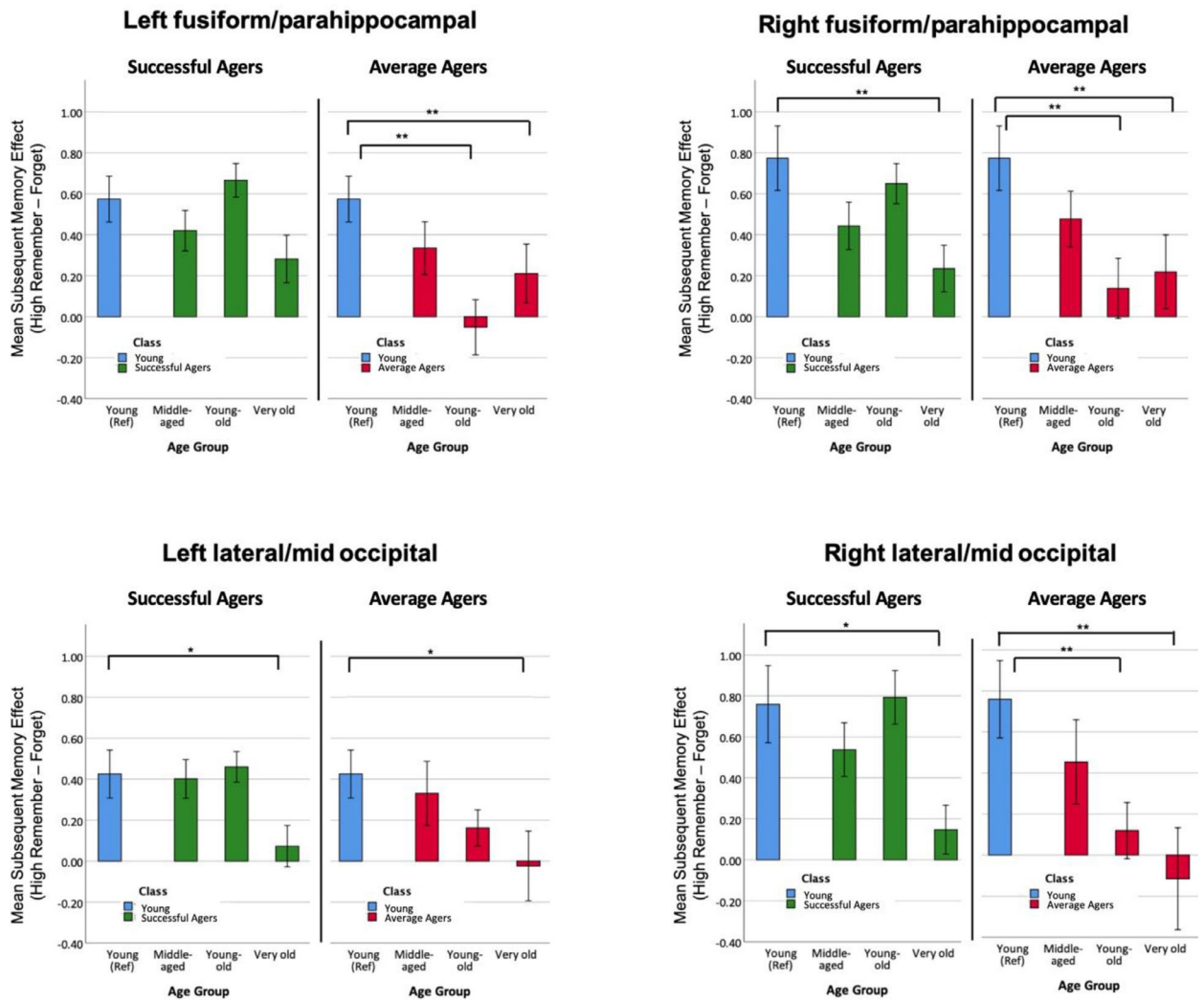


Fig. 8. Mean subsequent memory effect in middle-aged, young-old, and very old adults, compared to the young reference group, separately for *successful* and *average* agers. * $p < .05$. ** $p < .01$. All significant effects survived multiple comparison correction (q 's $> .05$).

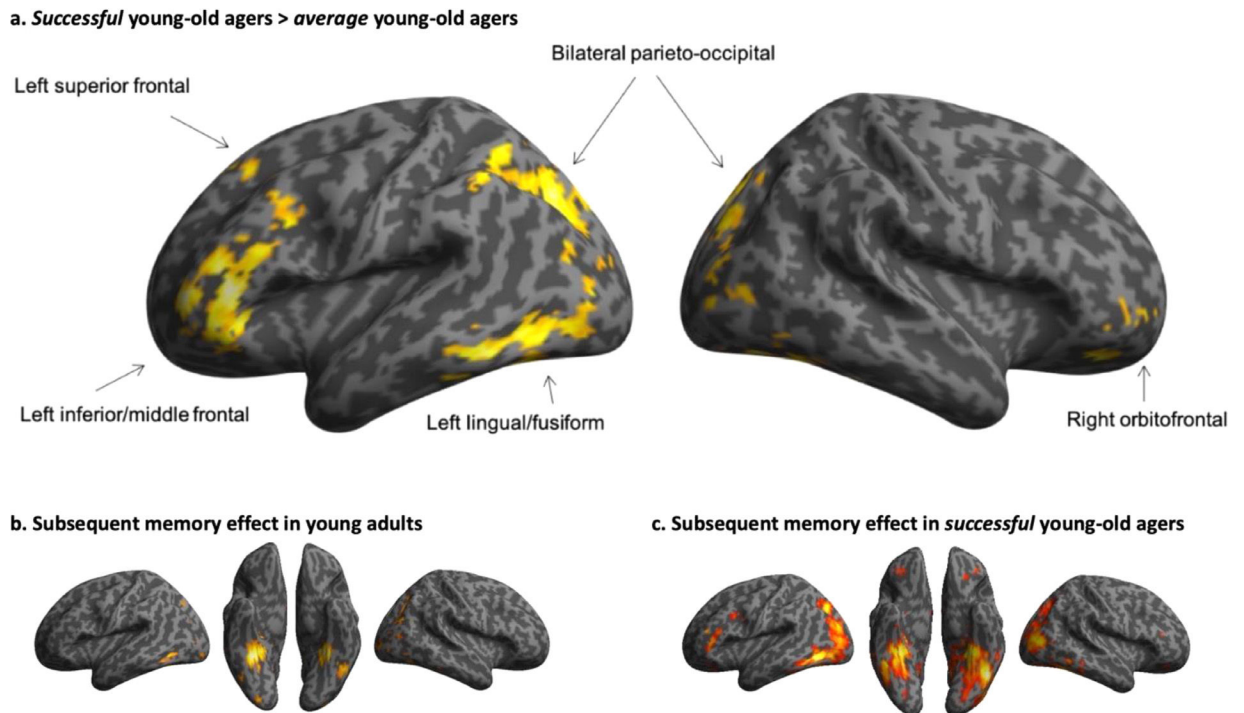


Fig. 9.

(a) Clusters showing significantly higher subsequent memory effect in *successful* agers than *average* agers in young-old age. FWE corrected at $p < .05$. (b) Activation map of subsequent memory effect in young (reference) adults. No correction applied for visualization purpose. (c) Activation map of subsequent memory effect in *successful* young-old agers. No correction applied for visualization purpose.

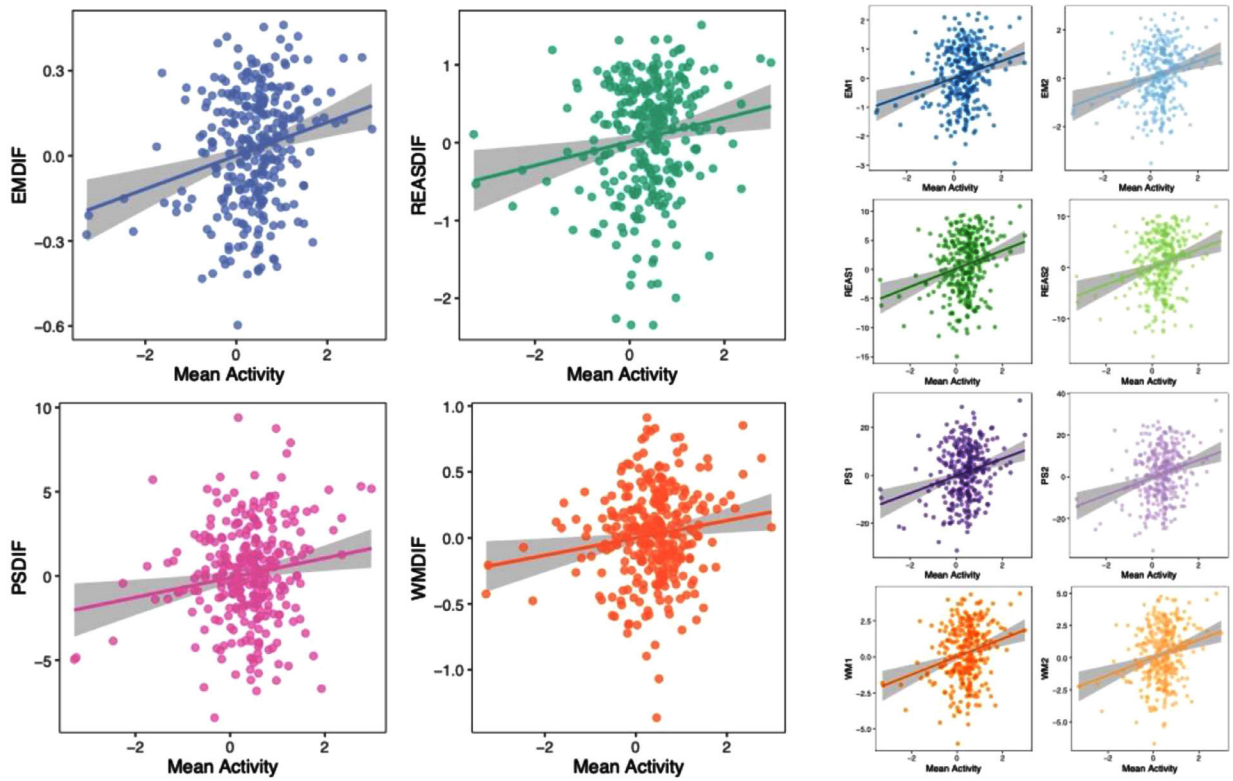


Fig. 10. Higher subsequent memory effect activity associated with better longitudinal cognitive maintenance and higher baseline and follow-up scores. EMDIF: Episodic Memory Change Score. REASDIF: Inductive Reasoning Change Score. PSDIF: Processing Speed Change Score. WMDIF: Working Memory Change Score.

Table 1

Participants' demographic information.

	Young	Middle-aged	Young-old	Very Old
	N = 41	N = 71	N = 96	N = 82
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age range at recruitment	20–34	35–54	55–69	70–89
Age range at fMRI scan	24–38	39–59	59–74	74–93
Mean age at fMRI scan	31.29 (4.29)	51.25 (5.74)	66.73 (4.50)	80.17 (5.49)
Education in years	16.79 (2.04)	16.08 (2.22)	15.90 (2.15)	15.25 (2.47)
Number of women (%)	29 (70.7%)	41 (57.7%)	63 (65.6%)	52 (63.4%)

Table 2

Participants' demographic distribution by class and age group.

	Middle-aged		Young-old		Very Old	
	Class 1 (average)	Class 2 (successful)	Class 1 (average)	Class 2 (successful)	Class 1 (average)	Class 2 (successful)
Mean age at baseline (SD)	49.49 (4.98)	46.09 (6.05)	63.87 (4.37)	62.07 (4.38)	77.85 (5.82)	74.55 (4.55)
Mean years of education (SD)	15.43 (2.05)	16.37 (2.25)	15.21 (2.10)	16.35 (2.08)	14.91 (2.58)	15.63 (2.32)
Number of women (%)	8 (36.4%)	33 (67.3%)	18 (47.4%)	45 (77.6%)	25 (58.1%)	27 (69.2%)

Table 3

Behavioral performance during subsequent memory task.

	Young reference		Middle-aged		Young-old		Very old	
	<i>N</i> = 41	Mean (SD)	<i>N</i> = 71	Mean (SD)	<i>N</i> = 96	Mean (SD)	<i>N</i> = 82	Mean (SD)
Old item								
Total Hits	0.709 (0.154)		0.714 (0.146)		0.719 (0.136)		0.708 (0.145)	.954
High Confidence	0.410 (0.124)		0.502 (0.137)		0.546 (0.152)		0.523 (0.155)	
Low Confidence	0.299 (0.024)		0.212 (0.121)		0.173 (0.123)		0.184 (0.121)	
Misses	0.289 (0.153)		0.282 (0.145)		0.276 (0.136)		0.275 (0.136)	.948
New item								
Correct Rejection	0.473 (0.189)		0.501 (0.166)		0.491 (0.161)		0.441 (0.164)	.073
False Alarm	0.525 (0.188)		0.492 (0.166)		0.494 (0.160)		0.549 (0.163)	.077
<i>d'</i> : ZPr(HIC-hit) – ZPr(HIC-FA)	0.796 (0.465)		0.793 (0.428)		0.731 (0.330)		0.511 (0.310)	<.001

Table 4

Clusters demonstrating significant subsequent memory effect.

Clusters	Peak-level			Cluster-level		
	x y z	$p_{FWE-corr}$	t	$p_{FWE-corr}$	k	k
Left fusiform/parahippocampal gyrus	-30 -40 -19	<.001	9.07	<.001	300	300
Right fusiform/parahippocampal gyrus	33 -34 -22	<.001	9.5	<.001	195	195
Left lateral/mid occipital cortex	-36 -88 20	<.001	6.11	<.001	81	81
Right lateral/mid occipital cortex	39 -82 14	<.001	6.72	<.001	92	92