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An fMRI study of episodic encoding across the lifespan: Changes in subsequent memory effects are evident by middle-age

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Abstract

Although it is well-documented that there are age differences between young and older adults in neural activity associated with successful memory formation (positive subsequent memory effects), little is known about how this activation differs across the lifespan, as few studies have included middle-aged adults. The present study investigated the effect of age on neural activity during episodic encoding using a cross-sectional lifespan sample (20–79 years old, $N=192$) from the Dallas Lifespan Brain Study. We report four major findings. First, in a contrast of remembered vs. forgotten items, a decrease in neural activity occurred with age in bilateral occipito-temporo-parietal regions. Second, when we contrasted forgotten with remembered items (negative subsequent memory), the primary difference was found between middle and older ages. Third, there was evidence for age equivalence in hippocampal regions, congruent with previous studies. Finally, low-memory-performers showed negative subsequent memory differences by middle age, whereas high memory performers did not demonstrate these differences until older age. Taken together, these findings delineate the importance of a lifespan approach to understanding neurocognitive aging and, in particular, the importance of a middle-age sample in revealing different trajectories.

Keywords

aging; episodic memory; encoding; fMRI; lifespan; middle-age

1. Introduction

Previous studies comparing young and older adults have demonstrated age differences in neural activity associated with successful memory formation. However, extreme age group comparisons provide little information about estimates of when in life neural differences begin to occur, and what kinds of neural changes are associated with differences in memory

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formation in different stages of life. These are important issues, as interventions designed to treat cognitive dysfunction may be most effective when age-related memory changes first appear (cf., Smith, Housen, Yaffe, Ruff, Kennison, Mahncke, & Zelinski, 2009). A common fMRI procedure used to study neural activity associated with memory encoding is the subsequent memory procedure, in which encoding items are sorted into remembered items (presented items correctly recognized later) and forgotten items (presented items identified as not presented at recognition). Activation associated with successful encoding is obtained by the contrast of remembered vs. forgotten items. The present study utilizes a subsequent memory fMRI paradigm in a large cross-sectional lifespan sample of adults from age 20–79 to understand how neural activity associated with encoding varies across the lifespan.

Dissociating changes in neural activity from age-related cognitive differences in memory can be difficult. Behavioral memory performance can differ so substantially between younger and older adults that it is hard to interpret age differences in evoked BOLD response. Scene encoding, however, tends to exhibit relatively equivalent memory performance with age because recognition of pictures is largely age-invariant (Park, Puglisi, & Sovacool, 1983; Park, Puglisi, & Smith, 1986; Smith, Park, Cherry, & Berkovsky, 1990; Bartlett & Fulton, 1991; Craik & Jennings, 1992). For that reason, scenes have been used in the memory literature to study neural differences in encoding, with comparisons of children to young adults (Ofen, Kao, Sokol-Hessner, Kim, Gabrieli & Gabrieli, 2007; Chai, Ofen, Jacobs, & Gabrieli, 2010) and young adults to older adults (Gutchess et al., 2005). We adopted the stimuli used in the Gutchess et al. study in order to examine the effect of age on memory across the lifespan.

Early studies employing the subsequent memory paradigm in young adults demonstrated that activity in the prefrontal cortex and the medial temporal lobe predicted the formation of successful memory (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Wagner, Rotte, Koutstaal, Maril, Dale, Rosen, & Buckner, 1998; Kirchoff, Wagner, Maril, & Stern, 2000). Subsequent memory studies on young versus older adults have provided less consistent findings as to the patterns of neural recruitment associated with remembered events. Evidence for enhanced recruitment of bilateral prefrontal activity for remembered events has been reported for both young and older adults on verbal tasks (e.g., Daselaar et al. 2003; Morcom et al. 2003; Duverne, Motamedinia, & Rugg, 2009). A number of other studies that utilized verbal material have also reported decreased subsequent memory effects with age (Grady, McIntosh, Horwitz, Maisog, Ungerleider, Mentis, et al., 1995; Logan et al., 2002; Daselaar et al. 2003), including recent longitudinal work (Nyberg & Backman, 2011). Finally, with the task used in the present research, Gutchess et al. (2005) reported decreased subsequent memory effects with age in the parahippocampus that was related to increases in prefrontal activity.

Positive subsequent memory effects are defined as increased neural activity for remembered compared to forgotten items, and this is one focus of the present research. Additionally, we also investigate negative subsequent memory effects which we define as decreased neural activity for remembered vs. forgotten items. This deactivation typically occurs in the “default mode network”—areas of the brain where young adults show more activation at rest. It has been suggested that activity in the default network regions are associated with off-task processing and that these regions are disengaged or suppressed for optimal performance on cognitive tasks (Gusnard & Raichle, 2001; Greicius et al., 2003). In this framework, negative subsequent memory effects may indicate effective allocation of cognitive resources for successful encoding of a current stimulus by minimizing off-task processing (Daselaar et al., 2004; H. Park & Rugg, 2008; de Chastelaine et al., 2011).

Young adults deactivate these default mode regions when performing a cognitive task (Gusnard & Raichle, 2001; Raichle, MacLeod, Snyder, Power, Gusnard, & Shulman, 2001; Vincent, Snyder, Fox, Shannon, Andrews, Raichle, & Buckner, 2006). Prior studies have consistently shown that older adults show less deactivation and less modulation of the neural activity in response to task demands in these default regions when compared to younger adults (Lustig, Snyder, Bhakta, O'Brien, McAvo, Raichle, et al., 2003; Greicius, Srivastava, Reiss, & Menon, 2004; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007; Park, Polk, Hebrank, & Jenkins, 2010). Subsequent memory studies have consistently shown that areas of deactivation for the contrast of remembered vs. forgotten items (negative subsequent memory effects) occur in the default mode network regions (Otten & Rugg, 2001; Wagner & Davachi, 2001). However, studies with older adults have revealed less deactivation when compared to young adults in this network in response to remembered stimuli (Gutchess et al., 2005; Miller, Celone, DePeau, Diamond, Dickerson, Rentz, Pihlajamaki & Sperling, 2008). Thus, age-related differences in negative subsequent memory effects are associated with a decreased ability to effectively allocate cognitive resources for performing a current encoding task.

The current study investigated how and when differences in positive and negative subsequent memory effects occur across a cross-sectional lifespan sample.¹ By investigating both positive and negative subsequent memory effects together across the lifespan, we aimed to determine whether there were differences in the age at which positive versus negative subsequent memory effects occurred. Although we recognize that the age-related differences found in a cross-sectional study may not convey the precise pattern of age-related changes identified in a longitudinal study (Lindenberger et al., 2011; Nyberg et al., 2010; Raz et al., 2005), this cross-sectional study is an early step for beginning an investigation of lifespan differences. Neuroimaging data on aging and subsequent memory have been available for less than a decade, so it would take decades of research to study the change from young to older adulthood or even from middle to older ages. It has been suggested that functional neuroimaging combined with behavioral tests may provide important information about the bases for age-related memory decline (Bookheimer et al., 2000; Wagner, 2000). Because patterns of neural activity in episodic memory may predict both normal and neurodegenerative memory degradation, middle-age would be the critical time period for detecting preclinical changes in neural function that precede memory declines (Park & Reuter-Lorenz, 2009). Although there are a number of subsequent memory studies that examine neural differences in older and young, we are aware of only one that has examined differences in neural recruitment across a broad age range (e.g., Grady et al., 2006).

Our large sample, distributed evenly from ages 20 to 80, also allows us to explore individual differences relative to general age-related patterns of activation. Previous PET and fMRI studies have shown that individual differences in behavioral memory performance in older adults were related to different patterns of neural activity for episodic memory (Cabeza et al., 2002; Persson et al., 2006; Miller et al., 2006; Duverne et al., 2008), whereas young adults' neural responses were unrelated to behavioral performance. While the comparisons of high- and low-performing older adults provide important clues to understanding individual differences in aging, extreme age group designs cannot address at what age performance differences begin to be associated with varying neural patterns. Furthermore, inconsistencies in this work, such as whether individual differences manifest as positive or negative subsequent memory effects (Miller et al., 2006; Duverne et al., 2008) may be resolved by a more continuous age sample of adults.

¹Findings from a cross-sectional design study may not generalize to findings from a longitudinal study, in that the onset period of age-related changes in the longitudinal study may differ from the onset period in the cross-sectional studies (cf., Rönnlund et al., 2005).

Thus, the present study investigated (1) whether age-related differences are observed in positive and negative neural activity associated with successful encoding; (2) what age-related changes occur specifically before or after middle age; and (3) which brain regions predict successful formation of memory in adulthood; and (4) if and when individual performance differences modulate age-related changes in neural activity.

2. METHODS

2.1. Participant Demographics

A total of 287 individuals were tested for this study. For reasons described below, we present data for 192 individuals (125 female) ranging from age 20 to 79. The 192 participants were distributed equally across each decade of the lifespan ($n = 32$). They were recruited from the Dallas-Fort Worth community for the Dallas Lifespan Brain Study and remunerated for their participation. Informed consent was obtained prior to participation in accordance with the requirements of the Institutional Review Boards of the University of Texas at Dallas, the University of Texas at Arlington, and the University of Texas Southwestern Medical Center, each of which separately reviewed and approved the study protocol.

All participants were right-handed native English speakers with no self-reported history of neurological or psychiatric illness. Participants were well-educated (mean = 16.66 years, $SD = 2.58$) and had high Mini-Mental State Exam (MMSE) scores (mean = 28.35, $SD = 2.4$) (Table 1). There were no significant age differences in years of education, nor age differences in self-reported health ratings. MMSE scores declined as a function of age ($p < .05$), but overall were high and well within the range of normal function. Neuropsychological test scores including Digit Comparison, Letter-Number Sequence, and Operation-Span tasks showed typical age-related decline (all $ps < .001$). Recall scores also declined with age ($p < .001$). However, the Shipley Vocabulary scores revealed the opposite pattern such that middle-aged and older adults showed significantly better performance than young adults, consistent with previous findings in cognitive aging studies (Park et al., 1996; Verhaeghen, 2003; Salthouse, 2004).

Because we had a large number of participants, we made an *a priori* decision to include for analysis only those participants who had at least 13 trials for each event of interest in the subsequent memory analysis (described below) so that there was sufficient power to estimate the BOLD response for each event type. A total of 52 participants had 12 or fewer forgotten trials at recognition and thus were discarded from the sample (13 young; 20 middle-age; 19 older). We also excluded 19 additional participants who performed the encoding task with less than 80% accuracy (5 young; 8 middle-age; 6 older). Discarding these participants resulted in an n for each decade that ranged from 32 to 43. Because we were unaware of any aging and neuroimaging studies in which middle-aged adults were as well-represented as young and older adults, we felt it was important to have an equal number of subjects representing each decade. Thus we randomly discarded a subset of participants within each decade to equate the n per decade. The total discarded for this reason was 24, resulting in 32 subjects per each of six decades for a total sample size of 192. In order to identify age-related changes before or after middle-age, participants were grouped into Young (20–39), Middle (40–59), and Older (60–79) age groups, with 64 participants per group.

2.2. Experimental Materials

Color pictures of outdoor scenes were obtained from Gutchess et al. (2005). Half of them contained water (e.g., a lake, river, ocean, etc.) in the picture and half did not. The encoding

list was comprised of a random ordering of 96 pictures of outdoor scenes. The recognition test list included the 96 encoded pictures and 96 lures, which were counterbalanced across subjects. Each lure was closely matched to a single encoding item with similar content and composition (e.g., both target and lure consisted of an alpine scene with mountains and lake).

2.3. Procedures

All participants underwent three sessions (two neuropsychological assessment sessions and one magnetic resonance imaging session) scheduled approximately within a 2-week interval. Prior to the MR experiment, participants were given the task instructions and practiced for the study task. However, they were not informed about the later memory test. During incidental encoding in the scanner, participants received three runs of 32 pictures each in an event-related, jittered design. During each experimental trial, participants saw a picture for 3s and indicated whether the picture contained water. At the end of each trial, a white fixation cross was presented and stayed on the screen until the next trial began. This interval between trials varied between 4s and 14s. Stimuli were presented via E-prime software (Psychology Software Tools, Pittsburgh, PA, USA) and displayed via a back-projection system. Participants made responses using buttons with the fingers of the right hand.

A surprise recognition test was administered outside of the scanner approximately 20m after the end of the study phase. Participants were presented with 192 pictures consisting of targets and lures, and were instructed to indicate whether they remembered each picture by making one of three judgments: (i) high confidence remembered that the item was presented at study; (ii) low confidence remembered that the item was presented at study; or (iii) new item. The test was self-paced with a maximum time of 4s for each trial.

2.4. Functional Data acquisition

A Philips Intera Achieva 3T MR scanner (Philips Medical Systems, Andover, MA) equipped with an 8-channel head-coil was used to acquire both T_1 -weighted 3D high-resolution anatomical images (MP-RAGE pulse sequence, FOV 205×256 mm, 1mm^3 voxels, axial acquisition) and T_2^* -weighted echo-planar images (EPIs) (SENSE factor of 2, flip angle 80° , FOV 220×220 mm, TR 2000ms, TE 25ms). Each volume comprised 43 slices oriented parallel to the AC-PC line (3.5mm-thick slice without gap, 3mm^3 in-plane) acquired in an interleaved sequence. These slices covered the entire cortex and the cerebellum. Data were acquired during the study phase in 3 runs comprising 171 volumes each. An additional five volumes were collected at the beginning of each run but discarded to allow for T_1 stabilization.

2.5. fMRI Data Analysis

Statistical Parametric Mapping software (SPM8, Wellcome Department of Cognitive Neurology, University College London, London, UK: <http://www.fil.ion.ucl.ac.uk>) running in MATLAB R2008b (Mathworks, Natick, MA) was used for data preprocessing and statistical analyses. For preprocessing, functional images were corrected for slice acquisition order and motion correction and then realigned to the across-run mean image. T_1 -weighted anatomical images were co-registered to each subject's mean functional image and segmented to allow estimation of deformation parameters for different tissue compartments. Both anatomical and functional images were spatially normalized to a study-specific template generated from all subject's anatomical images by the DARTEL algorithm (Ashburner, 2007) and affine-transformed into Montreal Neurological Institute (MNI) stereotactic space. Functional images were then resampled into 3mm^3 voxels. Normalized images were smoothed with an isotropic 8mm full-width half-maximum Gaussian kernel.

Statistical analysis was performed using a mixed-effects GLM. In the first stage, stimulus-elicited neural activity was modeled with 3s boxcar functions spanning the time of each picture presentation. The predicted BOLD response was modeled by convolving these boxcars with a canonical hemodynamic response function (HRF). In addition, seven nuisance regressors were used to model movement-related variance and the difference in mean signal across study runs. Nonsphericity of the error covariance was accommodated by an AR(1) model, in which the temporal autocorrelation was estimated by pooling over suprathreshold voxels (Friston, Penny, Phillips, Kiebel, Hinton, & Ashburner, 2002). The parameters for each covariate and the hyperparameters governing the error covariance were estimated using Restricted Maximum Likelihood.

For analysis of subsequent memory effects, three events of interest were defined: 'remembered-high confidence' (studied pictures that were correctly endorsed as *remembered* on the later test with *high confidence*); 'remembered-low confidence' (studied pictures that were correctly endorsed as *remembered* on the later test but with *low confidence*) and 'forgotten' (studied pictures that were incorrectly judged as *new* on the later test). We contrasted encoding activity of later remembered-high confidence trials (*Hc-hits*) with activity of later forgotten trials (*misses*) in order to identify neural correlates of subsequent memory. The remembered-low confidence trials were not included in the analysis as the low confidence responses tend not to provide a reliable index of memory discrimination between studied items versus similar lures (rf., Wagner et al., 1998; Gutchess et al., 2005).

Contrasts of both positive and negative subsequent memory effects were constructed for each individual, and these contrasts were entered in second-level tests of age effects. To investigate whether age-related differences are observed in positive and negative subsequent memory effects we used a multiple-regression model, in which age was treated as a continuous measure to identify the direction of age-related neural differences with age in adulthood. In order to investigate what age-related changes occur before and after middle-age, post-hoc analyses with age as a three-level factor (Young, Middle, Older) were performed on the clusters identified in the multiple regression model. In addition, a univariate ANOVA model was also constructed to assess effects common across three age groups. Note that age-related differences reported in the Results were based on the clusters identified from the aforementioned multiple-regression model with age as continuous variable, not on the clusters from this ANOVA model. For voxel-wise analyses, the significance level was corrected by a cluster extent of 18 voxels (calculated with a Monte Carlo simulation for cluster threshold $p < .05$) with voxel-wise thresholds of $p < .001$. For post-hoc tests of age effects on the regions identified from these whole-brain contrasts, region-specific parameter estimates were extracted by averaging across activity within a 4mm sphere around local peak voxels for each subject. Significance level for the region-specific parameter estimates was set to $p < .05$.

3. RESULTS

3.1. Behavioral Data

From the recognition test, we calculated the proportion of high confidence hits (*Hc-hits*) and high confidence false alarms (*Hc-FAs*). We utilized the sorted memory data to calculate d' values, a measure of item discriminability in memory. To parallel the approach taken in the fMRI analyses, d' was calculated from *Hc-hits* versus *Hc-FAs*. An analysis of variance (ANOVA) test of d' by three age groups, Young, Middle-age, and Older, did not show a significant main effect of age group ($F[2,189]=0.87$, $p > .4$): Young = .84 (SD = .31), Middle-age = .83 (SD = .37), Older = .77 (SD = .35). Thus, memory discriminability was

equivalent among age groups. Table 2 presents these data as a function of three age groups: Young, Middle-age, and Older.

3.2. fMRI Data

For subsequent memory analyses, encoding activity elicited by pictures that were later correctly endorsed as remembered items with high confidence (*Hc-hits*) was contrasted with activity of encoded pictures receiving an incorrect “new” response (*misses*).

3.2.1. Age-Related Differences in Subsequent Memory—We first treated age as the continuous predictor in a whole brain regression model with the subsequent memory contrast as the dependent measure. The analysis identified both positive subsequent memory regions (greater activation for remembered compared to forgotten items) and negative subsequent memory regions (less activation for remembered items). Figure 1 and Table 3 depict the positive regions with evidence for a significant decrease in activation with age. For these positive regions where activation was associated with remembered items, age-related decreases in activity occurred in the bilateral dorsal and ventral visual streams spanning the occipito-parieto-temporal cortex. In addition we also found significant age differences for negative subsequent memory effects (Figure 2 and Table 4) in bilateral superior to medial parts of the frontal lobe as well as posterior cingulate. These are all regions associated with the default network. These negative subsequent memory regions showed significantly increased (i.e., less negative) activity with age. To summarize, when compared with young adults, older adults had less neural activity in regions associated with successful encoding but at the same time showed an increase (decreased deactivation) in negative regions typically associated with the default mode network.

Because we were particularly interested in how middle-aged adults differed from those older and younger, we conducted post-hoc analyses on the clusters identified from the regression analysis described above (see Tables 3 and 4). For the subsequent memory analysis we extracted parameter estimates (mean activity across 4-mm sphere centered on each cluster’s peak voxel) from the regions identified by the regression analysis. We compared these mean parameter estimates for each region across the three age groups (Young, Middle-aged, Older). Multiple comparison tests of pairwise means shown in Table 5 (Tukey’s Honestly Significant Difference) revealed a pattern indicating that the majority of differences in positive subsequent memory effects occurred between Young and Middle-age. However, the differences in the negative subsequent memory regions were more evident between Middle-age and Older.

Mean parameter estimates collapsed across clusters revealed the same patterns of results². For positive subsequent memory effects, mean differences are most pronounced between Young and Middle-aged groups ($p < .005$) with relatively invariant effects after age 60 ($p > .27$) as displayed in Figure 3A. However, mean parameter estimates collapsed across regions of negative subsequent memory effects exhibit significant difference between Middle-age and Older ($p < .01$), with a marginal difference between Young and Middle-age ($p = .06$) as shown in Figure 3B.

3.2.2. Subsequent Memory Effects common to Young, Middle, and Older groups—In the whole-brain ANOVA model with three age groups, we also looked for neural correlates of subsequent memory common to the age groups. We computed the main effect of subsequent memory (*Hc-hits* > *misses*) across all participants and exclusively

²Our primary analysis is concerned with categorical differences between broad age groups but see Supplemental Figure 1 for the continuous linear effect of age on these mean parameter estimates.

masked out the interaction contrast of Age group $\times$ Subsequent memory (bi-directional $p < .1$). The outcome of this analysis is listed in Table 6. A cluster in the vicinity of the right hippocampus (21 –15–21, $Z = 4.03$, 30 voxels) was identified for encoding activity supporting successful memory as well as bilateral inferior prefrontal cortex (bilateral pars operculum: –45, 9, 7, $Z = 3.97$, 19 voxels; 48, 6, 27, $Z = 4.33$, 24 voxels; Right pars triangularis: 54, 39, 15, $Z = 6.05$, 62 voxels).

3.2.3. Relationship of Neural Activity to Memory Performance—In order to examine whether individual differences in memory performance were related to different patterns of age-related neural changes, we performed ROI (aforementioned regions that exhibited age-related differences in the main regression analysis; Tables 3 and 4) analyses of the three age groups by high and low memory performance. We utilized d' scores as an index of memory performance, and used median performance within each age group to split high and low memory groups for Young, Middle-aged and Older adults. We performed a 3 (Age: Young, Middle, & Older) $\times$ 2 (Memory performance: High, Low) ANOVA on parameter estimates averaged across the clusters showing age-related differences in subsequent memory effects. Neither the main effect of Memory performance nor the interaction of Age group by Memory performance was significant in positive effects whereas the main effect of Memory performance was marginal ($p < .07$) in negative effects.

In order to test the *a priori* hypothesis focused on whether the Young and Older age groups differed from the Middle-aged by memory performance, we further performed pairwise comparisons within each performance group. Pairwise tests on parameter estimates from the clusters showing positive subsequent memory effects showed that neural activity of high-performers and low-performers differed neither between Young and Middle-age nor between Middle-age and Older (Figure 4A). In other words, positive subsequent memory effects differed constantly over the three age groups with little difference by memory performance.

However, parameter estimates averaged across the clusters showing negative subsequent memory effects revealed a different pattern of results (Figure 4B). These showed that neural activity of low-performers did not differ between Young and Middle-age nor between Middle-age and Older. However, neural activity of high-performers differed between Middle-age and Older ($p < .01$) but not between Young and Middle-age. In other words, these data suggest that change in negative subsequent memory effects is distributed across the lifespan for low performers, while high performers did not show change until older age.

4. DISCUSSION

This study was designed to examine the effects of age on neural activity associated with episodic memory formation across the lifespan. By identifying activity that was greater for scenes that were subsequently remembered with high confidence than for scenes that were forgotten, we were able to examine how neural activity supporting successful memory formation differed across Young, Middle, and Older age. We observed age differences for both positive (task-related BOLD increases) and negative (task-related deactivation) subsequent memory effects. Specifically, age-related declines in both positive and negative subsequent memory effects were mostly notable between Young and Middle-aged. However, negative subsequent memory effects exhibited further age-related declines between Middle-aged and Older, but as we have seen, this pattern is differential with memory performance. Age-common subsequent memory effects were evident in the right occipital gyrus and regions demonstrating negative subsequent memory effects, mostly in the parietal lobe. Finally, age-related changes in negative subsequent memory effects between Middle-aged and other age groups were modulated by individual differences in

memory. We note that the interpretation of age-related differences from the current cross-sectional comparisons must be tempered, given that these differences may potentially deviate from within-person change measured by longitudinal designs. Below we discuss these findings in detail.

4.1. Age and Positive Subsequent Memory Effects

Previous studies have reported decreased neural activity for successfully encoded items in older adults compared with young adults (Morcom et al., 2003; Sperling et al., 2003; Gutchess et al., 2005). We also observed age-related decreases associated with successful encoding. The regions where we observed these effects were primarily in occipital-temporo-parietal regions, which are associated with visuo-spatial processing and have been reported by others in subsequent memory studies of pictures (Haxby, Gonnini, Furey, Ishai, Schouten, & Pietrini, 2001; Grill-Spector, Henson, & Martin, 2006). More specifically, our results showed that age-related declines in positive subsequent memory effects were most pronounced between Young and Middle-aged, suggesting that decline occurs relatively early in the lifespan. We are aware of no other studies that explore this trajectory, as previous studies have examined effects only in older and young adults.

4.2. Age and Negative Subsequent Memory Effects

The other direction of age-related differences in subsequent memory revealed in the present study was less deactivation with age in regions typically associated with the default mode network. Young adults show deactivation in the default mode network regions when confronted with a cognitive task (Raichle et al., 2001; Raichle & Snyder, 2007). Unlike young, there is considerable evidence that older individuals exhibit less deactivation under cognitive challenge while performing a cognitive task (Andrews-Hanna et al., 2007; Persson et al., 2007; D. Park et al., 2010).

With respect to subsequent memory effects, there is evidence that higher activity in default network regions is negatively correlated with subsequent memory and thus associated with subsequent forgetting or negative subsequent memory effects (Otten & Rugg, 2001; Wagner & Davachi, 2001). There is also evidence that older individuals differ from young by showing less deactivation in the default mode network area during memory formation (Duverne et al., 2009; Miller et al., 2008). This is consistent with the current findings. Using the theoretical framework that negative subsequent memory effects reflect activity that should be suspended for effective handling of a current task (i.e., encoding), we can speculate that older individuals tended to have more difficulty in disengaging such activity for successful encoding.

4.3. Age-Common Subsequent Memory Effects

We also identified subsequent memory effects common to all ages in the ventral stream associated with visual processing of study stimuli. This finding suggests that visuo-spatial processing of study stimuli (i.e., outdoor scenes) was required for successful memory and it is relatively invariant across the lifespan. We also note that the right MTL and bilateral ventrolateral prefrontal areas showed age-common encoding activity supporting successful memory formation. It has frequently been reported that hippocampal activation is age-invariant in subsequent memory studies, including face-name encoding (Celone et al., 2006; Miller et al., 2008), and word encoding (Morcom et al., 2003; Rand-Giovannetti et al., 2006; Duverne et al., 2009), although other studies suggest decline in hippocampal activity with age (Grady et al., 1995; Salami, et al., 2012). The Salami et al. (2012) study is notable in that it included a very large lifespan sample. The age-related decline of hippocampal activity observed in that study may be due to the complex and effortful encoding task used. Further, the observed age-related decline of hippocampal activity was correlated with hippocampal

atrophy, suggesting a mediating role of pathology in that sample. Overall, our results substantiate prior evidence that hippocampal activation during encoding remains stable with age, but more systematic comparisons that vary the encoding demands of the task and relate activation to brain structure and health are required to resolve this issue.

4.4. Individual Differences and Negative Subsequent Memory Effects

One of the most interesting findings we observed was that the age at which differences in negative subsequent memory emerge is related to individual cognitive performance level. Specifically, low memory performers showed age-related changes across the lifespan—namely during and after middle age. In contrast, high memory performers preserved the ability to suppress default mode activity until older age. Miller et al. (2008) reported that older adults who had low memory performance also showed less suppression of default activity in a subsequent memory study. Our findings suggest that this differential performance-related pattern is evident by middle-age.

The relationship between high memory ability and default network activity is intriguing and suggests that neural and cognitive function are preserved together, although the causality of the relationship cannot be determined from the present cross-sectional data. The few longitudinal investigations of brain changes over time suggest that within-person measurements of brain shrinkage are greater than cross sectional estimates (especially in the prefrontal, hippocampus, cerebellum and parietal cortices, Raz et al., 2005). Consistent with the structural literature, within-person changes in activation across time are also greater in magnitude than cross-sectional estimates and emerge as decreases in activation, at least in the frontal cortex, (Nyberg & Backman, 2011; Nyberg et al., 2010). Planned longitudinal follow-up data for the present sample should provide further insight into this issue. Nevertheless, individual differences in age-related negative subsequent memory effects shed light on the importance of task-related deactivation in episodic memory performance and its sensitivity to age differences, as well as the importance of a middle-age sample in understanding the time-course of those estimated changes.

4.5. Conclusion

In the present study, we found that age-related differences in encoding activity for successful memory formation appeared in both positive and negative aspects of activation across the lifespan. Most age-related differences in subsequent memory effects were evident between Young and Middle-aged groups, although some age-related differences occurred between Middle-age and Older age. Further, individual differences in memory performance modulated at what point in the lifespan age-related differences appeared in negative subsequent memory effects. These results strongly suggest that some of the deleterious effects of aging associated with memory encoding begin at or before middle age, but individual differences in cognitive performance may alter the progression of these changes (or vice-versa). These results make a strong case for the importance of studying a broad age-range of adults, including middle age, to understand the process of neurocognitive aging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We report age-related differences in neural activity of memory across the lifespan.
- Encoding activity differed between middle-age and older in negative subsequent memory effects.
- Individual differences modulated when age-related differences emerged.
- Middle age is the period that critical changes occur in subsequent memory effects.

Figure 1. Brain regions showing age-related decreases in neural activity for the positive subsequent memory effect [High confidence remembered vs. Forgotten items] across the adult lifespan. Activation decreases with age in the bilateral temporal-parietal-occipital areas in the ventral and dorsal visual streams.

Figure 2.

Brain regions showing age-related increases in neural activity for the negative subsequent memory effect [Forgotten vs. High confidence remembered items] across the adult lifespan. There is significant increase in activation with age (i.e., less deactivation) in bilateral superior and medial frontal and bilateral posterior cingulate cortices, all regions associated with the default mode network.

Figure 3.

Average parameter estimates for activation and deactivation for positive subsequent memory contrast (A) and for negative subsequent memory contrast (B), by age group. Parameter estimates are averaged across all regions showing the significant age-related decreases (A) or increases (B). Positive subsequent memory age effects were observed early from young to middle age, whereas negative subsequent memory age effects were most apparent later, from middle to older age.

Figure 4.

Mean parameter estimates for activation for Positive (A) and negative (B) subsequent memory effects, averaged across regions showing age-related differences by age group and memory performance. Middle-aged high performers' activation for negative subsequent memory contrast is similar to young adults' activation, whereas middle-aged low performers' activation is similar to older adults' activation.

Table 1

Participant demographics and neuropsychological assessments (Means and Standard deviations)

	Young	Middle-Age	Older
Education	16.75 (2.43)	16.59 (2.68)	16.62 (2.67)
MMSE	28.67 (1.26)	28.69 (1.09)	27.70 (3.76)
SF-General Health	78.91 (16.07)	81.25 (16.18)	81.56 (16.11)
Shipley Vocabulary	31.80 (3.84)	34.06 (4.22)	35.05 (3.09)
Digit Span	74.89 (11.15)	66.86 (12.78)	59.23 (11.94)
Letter-Number sequence	12.06 (2.58)	12.11 (3.60)	10.44 (2.39)
Operation Span	18.02 (8.70)	17.05 (7.84)	12.81 (5.67)
Memory Recall	8.28 (2.00)	7.55 (2.05)	6.81 (1.69)

Note: Shipley Vocabulary - Young < Middle-age^{***}; Digit Span - Young > Middle-age^{****} > Older^{***}; Letter-Number Sequence - Middle-age > Older^{**}; Operation Span - Middle-age > Older^{**}; Recall - Young > Middle-age^{*} > Older^{*}

Table 2
Mean proportions of test judgments according to age group and study status (Standard deviations in parentheses)

	Studied item		New item	
	Hc-hit	Lc-hit	Hc-FA	Lc-FA
CR				
Young	.42 (.11)	.22 (.13)	.16 (.09)	.26 (.15)
Middle-age	.45 (.13)	.25 (.12)	.19 (.12)	.27 (.14)
Older	.52 (.13)	.18 (.13)	.25 (.10)	.22(.13)

Table 3

Brain regions showing decrease in activity for subsequent memory effects with age

Coordinates (x y z)	<i>p</i> (FDR)	<i>Z</i>	# of voxels	Regions	BA
-33 -51 -15	.007	4.17	228	L fusiform/inferior occipital cortex	18/19/37
27 -45 -12	.02	3.64	26	R fusiform cortex	37
45 -57 -12	.008	4.10	82	R Inferior temporal/ fusiform cortex	20/37
21 -57 15	.02	3.57	25	R precuneus	7
-21 -63 51	.005	4.56	108	L superior parietal lobe	17/18
-42 -84 21	.002	5.34	294	L mid occipito- parietal cortex	17/18/19
39 -78 24	.003	4.81	296	R mid occipito-parietal cortex	17/19/20

Table 4

Brain regions showing age-related increase in activity for subsequent memory

Coordinates (x y z)	<i>p</i> (FDR)	Z	# of voxels	Regions	BA
-15 48 33	.01	3.82	28	L superior frontal lobe	10
6 57 6	.002	5.08	147	Superior medial frontal lobe	11/12
21 45 39	.007	4.14	59	R superior frontal lobe	10
3 -57 39	.004	4.68	375	R precuneus/mid cingulate cortex	23/31/7
-48 -54 27	.02	3.63	41	R angular gyrus	40

Table 5

Age-group comparisons in subsequent memory effects

Coordinates (x y z)	Regions	Pairwise significance ^{1,2} (Tukey-HSD)	
		Young vs. Middle	Middle vs. Older
Positive subsequent memory effects			
-33 -51 -15	L fusiform/ inferior occipital cortex	*	
27 -45 -12	R fusiform cortex		
45 -57 -12	R Inferior temporal/ fusiform cortex	**	
21 -57 15	R precuneus	***	
-21 -63 51	L superior parietal lobe	*	
-42 -84 21	L mid occipito- parietal cortex	**	*
39 -78 24	R mid occipito-parietal cortex		*
Negative subsequent memory effects			
-15 48 33	L superior frontal lobe		**
6 57 6	Superior medial frontal lobe	*	<i>p</i> < .07
21 45 39	R superior frontal lobe		*
3 -57 39	R precuneus/mid cingulate	*	
-48 -54 27	L angular gyrus		*

Note.

¹ $p < .05^*$; $p < .01^{**}$; $p < .05^{***}$

² All comparisons between Young and Older groups were significant at $p < .001$.

Table 6

Subsequent memory effects common to Young, Middle, and Older

Coordinates (x y z)			Z	# voxels	Regions	BA
-45	9	7	3.97	19	L inferior prefrontal cortex	44
48	6	27	4.33	24	R inferior prefrontal gyrus	44/9
54	39	15	6.05	62	R inferior frontal gyrus	46
-33	-39	-12	5.61	69	L posterior parahippocampal cortex	
-48	-51	-15	6.61	81	L inferior temporal lobe/fusiform	20/37
21	-15	-21	4.03	30	R. hippocampus	
12	-51	15	5.18	28	R calcarine sulcus	30
-15	-54	12	5.09	43	L calcarine sulcus	30
39	-78	9	8.18	954	R middle occipito-temporal cortex	19/39/37
-18	-90	54	4.21	18	L superior occipital sulcus	7
-36	-84	0	5.57	53	L inferior occipital gyrus	19
-42	-93	12	6.59	157	L inferior occipital cortex	18/39