Sensitivity of Negative Subsequent Memory and Task-Negative Effects to Age and Associative Memory Performance

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Abstract

The present fMRI experiment employed associative recognition to investigate the relationships between age and encoding-related negative subsequent memory effects and task-negative effects. Young, middle-aged and older adults (total n = 136) were scanned while they made relational judgments on visually presented word pairs. In a later memory test, the participants made associative recognition judgments on studied, rearranged (items studied on different trials) and new pairs. Several regions, mostly localized to the default mode network, demonstrated negative subsequent memory effects in an across age-group analysis. All but one of these regions also demonstrated task-negative effects, although there was no correlation between the size of the respective effects. Whereas negative subsequent memory effects demonstrated a graded attenuation with age, task-negative effects declined markedly between the young and the middle-aged group, but showed no further reduction in the older group. Negative subsequent memory effects did not correlate with memory performance within any age group. By contrast, in the older group only, task-negative effects predicted later memory performance. The findings demonstrate that negative subsequent memory and task-negative effects depend on dissociable neural mechanisms and likely reflect distinct cognitive processes. The relationship between task-negative effects and memory performance in the older group might reflect the sensitivity of these effects to variations in amount of age-related neuropathology.

Keywords

fMRI; aging; associative recognition; memory encoding; recollection

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1. Introduction

Episodic memory – memory for unique events – declines across the adult lifespan (e.g., Nilsson, 2003; Park et al., 2002; Salthouse, 2009). fMRI studies investigating the cognitive and neural bases of age-related episodic memory decline have focused on the neural correlates of both encoding and retrieval operations. Studies that have investigated age-related differences in the neural correlates of encoding (the focus of the present study) have typically utilized the subsequent memory procedure (e.g., de Chastelaine et al., 2011; Duverne et al., 2009; Gutchess et al., 2005; Mattson et al., in press; Miller et al., 2008; Morcom et al., 2003; Mormino et al., 2012; Park et al., 2013). In this procedure (Paller and Wagner, 2002), blood oxygenation level dependent (BOLD) activity elicited by study items is contrasted according to performance on a later memory test. The most commonly reported subsequent memory effects are 'positive', taking the form of greater activity for study items attracting accurate rather than inaccurate memory judgments. Recently, however, there has been increased interest in the effects of age on 'negative' subsequent memory effects, that is, effects taking the form of relative decrements in study activity for items that go on to receive accurate as opposed to inaccurate judgments. Across studies employing a variety of different study tasks and memory tests, negative subsequent memory effects have consistently been reported to be attenuated (and sometimes reversed) in healthy older individuals (e.g., de Chastelaine et al. 2011; Duverne et al., 2009; Gutchess et al., 2005; Mattson et al., in press; Miller et al. 2008; Mormino et al. 2012; Park et al., 2013). Furthermore, the magnitude of negative subsequent memory effects in older adults has been reported to correlate positively with their memory performance (de Chastelaine et al., 2011; Mattson et al., in press; Miller et al., 2008; Mormino et al., 2012; see de Chastelaine and Rugg, 2014, for similar findings in young individuals), suggesting that the effects reflect the engagement of processes that are of functional significance for memory encoding.

The earliest studies to describe negative subsequent memory effects (Otten and Rugg, 2001; Wagner and Davachi, 2001; Wagner et al., 1998) identified them in inferior and medial parietal cortex, posterior cingulate and dorsolateral PFC. The effects were interpreted as reflecting allocation of attentional resources to processes unconnected with or, perhaps, detrimental to successful encoding (e.g., attention to response selection, or task-irrelevant stimulus features or thoughts). Subsequently, it was noted that several of the brain regions identified by negative subsequent memory contrasts fall within the 'default mode network' (Daselaar et al., 2004). This network comprises a set of regions that exhibit greater activity during 'rest' than during task engagement ('task-negative' activity), and demonstrate strong inter-regional 'resting-state' connectivity (see Buckner et al., 2008, for a review). Task-negative activity has been consistently reported to be attenuated in older relative to younger individuals (e.g., Grady et al., 2006; Lustig et al., 2003; Persson et al., 2007; Persson et al., 2014; Park et al., 2013; Sambataro et al., 2010). Whereas the default-mode network is reportedly functionally heterogeneous (e.g., Andrews-Hanna et al., 2010; Gilbert et al., 2012; Leech et al., 2011; Lin et al., 2011), in general terms the network is held to support internally-directed processes that must be disengaged to permit optimal allocation of processing resources to an external event such as a study item (e.g., McKiernan et al., 2003; Raichle et al., 2001). From this perspective, it is natural to conceive of negative subsequent

memory effects as reflecting the extent to which a study event elicits the reallocation of processing resources away from internally directed 'default mode processes' to those supporting successful encoding (e.g., de Chastelaine et al., 2011; Daselaar et al., 2004; Duverne et al., 2009; Miller et al., 2008). This raises the possibility that age-related attenuation of negative subsequent memory and task-negative effects have a common origin, namely, the tendency with increasing age to fail to fully disengage the default mode network when attention must be directed toward an external event.

Negative subsequent memory effects do not, however, simply reflect modulation of task-negative activity within the default-mode network, as the foregoing discussion might be taken to imply. Notably, the effects are typically found in only a small subset of task-negative regions (e.g., de Chastelaine & Rugg, 2014). Moreover, negative subsequent memory effects can also be identified in 'task-positive' regions that are not part of the default mode network. For example, Daselaar et al. (2004) and Mattson et al. (in press) both described robust negative subsequent memory effects in the anterior insula, despite the fact that the region exhibited a marked task-positive response with respect to baseline (see also Reynolds et al., 2004, Wagner and Davachi, 2001). Furthermore, it was recently reported that task-negative and negative subsequent memory effects can be dissociated by manipulation of the difficulty of the study task (de Chastelaine & Rugg, 2014): Whereas the former effects were enhanced in the more difficult condition, difficulty had no effect on the magnitude of the negative subsequent memory effects elicited in the same brain regions. Together, these findings suggest that negative subsequent memory effects reflect processes additional to those reflected in task-induced modulations of the default mode network.

The aim of the present study was to build on prior studies from our group in which we reported both that negative subsequent memory effects were attenuated in older relative to young individuals, and that the magnitude of the effects was positively correlated with memory performance (de Chastelaine et al., 2011; Duverne et al., 2009). We employed the same combination of study task and subsequent associative recognition test that was used by de Chastelaine et al., (2011). This and similar experimental procedures have consistently been reported to elicit robust and widespread negative subsequent memory effects in young adults (e.g., de Chastelaine and Rugg, 2014; de Chastelaine et al., 2011; Daselaar et al., 2004; Park and Rugg, 2008) and are highly sensitive to increasing age (e.g., Bender et al., 2010; Salthouse, 2009). Here, we went beyond our prior study (de Chastelaine et al., 2011) in two ways. First, in addition to investigating new samples of young and older adults, we also included a middle-aged sample. To date, almost no investigations of age-differences in the neural correlates of episodic memory encoding (or, indeed, of cognitive processing more generally) have included middle-aged individuals. One important exception is the study of Park et al. (2013) in which subsequent memory effects for visually presented scenes were contrasted in a large sample that spanned the adult lifespan. As we describe in more detail in the Discussion, these authors reported that the effects of age on negative subsequent memory effects were most apparent in older adults, with relatively little difference evident between young and middle-aged individuals. The present study affords the opportunity to assess whether this pattern generalizes to associative memory.

In addition to the inclusion of a middle-aged sample, here we investigated the effects of age and memory performance on both negative subsequent memory effects and, also, task-negative effects. As was discussed previously, despite their shared sensitivity to increasing age, there are grounds for thinking that the two classes of effects reflect dissociable processes. Thus, it was of interest to determine whether there was any relationship between the magnitudes of the two effects (cf. de Chastelaine and Rugg, 2014), and whether they were similarly sensitive to increasing age.

2. Results

2.1. Neuropsychological data

Demographic and neuropsychological data for the 3 age groups are summarized in Table 1. One-way ANOVAs were conducted for each test, and followed up with t-tests as appropriate. As can be seen from the table, the older adults showed a typical pattern of age-related reduction and preservation of scores on the neuropsychological test battery (Salthouse 2010).

2.2. Behavior

2.2.1. Study phase—Accuracy on the study task was indexed by the proportion of study pairs attracting the response judged the most plausible by the consensus of three experimenters. These judgments had been made, prior to any data collection, in the context of our previous experiment that used the same word pair pool (de Chastelaine et al., 2011). Accuracy was high in all 3 age groups, with means (standard deviations [SDs]) of 0.81 (0.09), 0.82 (0.07) and 0.80 (0.09) for the young, middle-aged and older groups, respectively. Neither accuracy nor reaction time (RT: 1913 (290) ms, 1805 (310) ms and 1849 (243) ms for young, middle-aged and older adults, respectively) differed significantly between the groups.

To parallel the fMRI negative subsequent memory analyses described later, study RTs for word pairs presented in the same pairing at test (intact pairs) were segregated according to later memory performance (subsequent associative hits versus subsequent associative misses). ANOVA revealed a main effect of subsequent memory ($F_{1, 133} = 38.25$, $p < 0.001$). The effect reflected faster study RTs for subsequent misses than for subsequent hits (collapsed across age-group, 1835 (279) ms and 1883 (285) ms respectively). There was no effect of age, and no evidence of an age group by subsequent memory interaction.

2.2.2 Test phase—Accuracy on the associative recognition test is summarized in Table 2. Associative recognition accuracy (pR) was indexed as the difference between the proportion of intact test pairs correctly endorsed as intact (associative hits) and the proportion of rearranged test pairs incorrectly judged intact (associative false alarms). Accuracy showed a graded decline with age, with means (SDs) of 0.48 (0.19), 0.39 (0.14) and 0.31 (0.15) for the young, middle-aged and older groups, respectively ($F_{2, 135} = 12.80$, $p < 0.001$). Pair-wise contrasts (t-tests, equal variances not assumed) revealed that young participants had higher pRs than both middle-aged ($t_{64} = 2.25$, $p < 0.05$) and older participants ($t_{59} = 4.50$, $p <$

0.001), and that middle-aged participants were more accurate than the older participants (t76 = 2.60, p < 0.025).

2.3. fMRI data

2.3.1. Across-group main negative subsequent memory effect—To assess the influence of age on negative subsequent memory effects, we first identified regions showing the unbiased, across-group main effect of negative subsequent memory (associative misses > associative hits). Table 3 summarizes the outcome of this contrast, which revealed negative subsequent memory effects in right dorsolateral and superior frontal cortex, medial frontal cortex, left posterior cingulate / precuneus, right inferior temporal gyrus, right lateral parietal cortex, and the right insula (see Fig. 1a). Other than one cluster located in the cerebellum, we found no evidence for a group by subsequent memory interaction with a whole brain analysis thresholded at our pre-experimentally determined significance level of p < .001. We extracted mean parameter estimates for the BOLD responses elicited by items that went on to become associative hits and misses across all voxels within a 5 mm radius of each peak in the 8 regions identified by the negative subsequent memory contrast (see Table 3), along with an additional sub-peak in the precuneus. Figure 1b shows the means of these parameter estimates for 4 representative regions according to age- group. All but one of the regions demonstrating negative subsequent memory effects also demonstrated below-baseline task effects (i.e., task-negative effects), the one exception being the anterior insula, where negative subsequent memory effects co-existed with task-positive effects (see Fig. 1b). To directly assess group differences in the magnitude of both negative subsequent memory and the task effects, each class of effect was subjected to a two-way mixed design ANOVA, with levels of group (3) and region (9). The data collapsed across region are illustrated in Figure 2.

ANOVA of the negative subsequent memory effects revealed a main effect of region (F6, 822 = 5.01, p <0.001, Greenhouse-Geisser corrected for non-sphericity), indicating differences in the size of negative subsequent memory effects across regions (largest in the left precuneus, smallest in the left medial frontal cortex). There was no group by region interaction (F < 1). A main effect of group (F2, 133 = 4.55, p <0.025) reflected a decline in the size of negative subsequent memory effects with age (young > middle > older; see Fig. 2). T-tests (equal variances not assumed) revealed that there was a significant difference in the size of the effects between the young and older groups (t59 = 2.62, p < 0.025), the effects in the middle-aged group differing from neither of the other two groups. Additional t-tests revealed that, collapsed across regions, negative subsequent memory effects were independently reliable in each age group (all ps < 0.01).

ANOVA of the task effects revealed a main effect of region (F7, 880 = 77.04, p <0.001, Greenhouse-Geisser corrected for non-sphericity), indicative of differences in the size (and direction) of the effects across regions (task-negative effects were largest in right medial frontal cortex, smallest in right inferior temporal gyrus and, as already noted, a task-positive effect was evident in right anterior insula). There was also a main effect of group (F2, 133 = 5.45, p<0.01), but no group by region interaction (F < 1.1). Follow-up analyses (t-tests, equal variances not assumed) revealed that task-negative effects (see Fig. 2) decreased in

magnitude from the young to the middle-aged and older groups (young vs middle-aged: t70 = 3.31, p = 0.001; young vs older group: t87 = 2.99, p < 0.005), but did not differ between the middle-aged and older groups (t < 1). One-sample t-tests indicated that, collapsed across regions, the effects were significantly negative-going in each group, despite the inclusion of data from the insula (all ps < 0.001).

2.3.2. Relationship between negative subsequent memory and task effects—

We investigated the relationship between the magnitudes of negative subsequent memory and task effects using the data collapsed across the 9 regions that were identified by the across-group main effect of negative subsequent memory. We found no relationship between the size of negative subsequent memory and task effects across all participants (partial correlation, controlling for age (entered as a continuous variable) and memory performance, of .03), and this remained the case when the correlation was computed for each group separately, and also for the simple rather than the partial correlation. Re-running the correlations using data derived only from the 8 task-negative regions did not change the results. We also re-ran the above analyses for each region separately (across and within group). No significant correlations were identified.

2.3.3. Relationship of negative subsequent memory and task effects with memory performance—

In light of prior reports that the magnitude of negative subsequent memory effects covaries with memory performance (de Chastelaine and Rugg, 2014; Duverne et al., 2009; Mattson et al., in press; Miller et al., 2008; Mormino et al., 2012), we computed the across-participant partial correlation (controlling for age) between pR (associative recognition performance) and the magnitude of the negative subsequent memory effects (collapsed across the 9 regions described previously). The correlation was far from significant (r = .04), and the correlations remained non-significant when computed for each age group separately (all rs < 0.19). We re-ran the correlations for each of the 9 regions individually (across and within age-groups). In the young group only, associative memory performance was positively correlated with the size of the negative subsequent memory effects in the inferior temporal gyrus (r = .47, p < 0.005). No other region showed a significant correlation between negative subsequent memory effects and associative memory performance after Bonferroni correction.

In a second correlational analysis we addressed the question of whether the relationship between age and the magnitude of negative subsequent memory effects was independent of memory performance. The partial correlation (controlling for pR) between age and negative subsequent memory effects (collapsed across regions) was significant (r = −.233, p < .01), as would be expected given the lack of correlation between pR and the effects.

We then addressed the question of whether the magnitude of task effects in the regions demonstrating negative subsequent memory effects correlated with memory performance. The partial correlation (controlling for age) between task effects and memory performance was not significant when computed across all participants (r = 0.06). Within age groups, the partial correlation (controlling for within-group age differences) was significant in the older group (r = 0.307, p < 0.025), indicating that increased task-negative activity predicted better memory performance in these participants (see Fig. 3). Removing the data from the insula

did not alter any of the foregoing results. We conducted analogous analyses separately for each of the 9 regions demonstrating negative subsequent memory effects. For the older group only, task effects in one region - the supramarginal gyrus - demonstrated a correlation with Pr that survived Bonferroni correction (r = 0.362, p < 0.005).

In light of the finding of a reliable correlation between task effects and associative memory performance in the older, but not the young or middle-aged groups, we employed multiple regression analysis to directly assess the relative contributions of the variables of age, task effects, and their interaction to explaining variance in associative memory performance. The regression model accounted for a significant proportion of the variance in performance (F3, 135 = 13.12, p < 0.001, R^2 = 0.230). As is evident from Table 4, age was a significant predictor. Confirming the impression derived from the correlational analyses conducted on the separate age groups, the task effect was not a reliable predictor, but its interaction with age group was. Thus, the regression coefficients for the relationship between memory performance and task negative effects differed reliably across the age groups.

Finally, we addressed the question of whether the age-related differences in task-negative effects were mediated by differences between the age groups in memory performance. This was not the case: the partial correlation (controlling for pR) between age and the across-region mean of the task-negative effects was reliable (r = .211, p < .025), indicating that the influence of age on these effects cannot be explained by the relationship between age and memory performance.

2.3.4. Whole brain analysis of task negative effects—The foregoing analyses indicate that task-negative effects were attenuated with age and, among older participants only, correlated reliably with later associative recognition performance. We extended these findings by performing a series of whole brain analyses that identified task-negative effects and investigated their relationship with age and performance. As is evident from Fig. 4A, task-negative effects were widespread throughout the brain, encompassing but extending well beyond regions typically identified within the default mode network. We investigated whether these effects varied across age groups by inclusively masking the main task-negative effect (thresholded at p < .001; Fig. 4A) with the pair-wise contrasts identifying where effects were greater in the young group relative to the middle-aged or older groups, and where effects were greater in the middle-aged than the older participants (each contrast was thresholded at p < .01, and preserved the 21 voxel cluster extent threshold). As is illustrated in Figures 4B and 4C, larger task-negative effects were evident in the young than in either of the other two groups in numerous task-negative regions. Moreover, the patterning of the group-wise differences was very similar in each case. By contrast, differences between the middle-aged and older participants were limited to a single small cluster (25 voxels) in right posterior lateral temporal cortex.

In light of the findings reported above of a relationship in the older group between task-negative effects and memory performance, we performed whole-brain analyses to identify where task-negative effects correlated with memory performance at the voxel-wise level. For each age group, we generated a second-level GLM in which task-negative effects were regressed against memory performance and inclusively masked with the outcome of the

across-participants task-negative main effect (thresholded at p<.001). The GLM was height thresholded at p < .005 with a cluster extent threshold of 47 voxels to give a cluster-wise corrected significance level of p < .05. This height threshold corresponds to a correlation coefficient of approximately .46 for the young and middle-aged groups, and to a correlation of about .35 for the analysis of the older group's data. No clusters were identified where task-negative effects co-varied with behavior in either the young or middle-aged group (this remained the case when the threshold was reduced to p<.01, corresponding to a correlation of about .41). By contrast, 4 clusters were identified where the effects correlated with performance in the older group (see Table 5 and Fig. 5).

Together, these whole-brain findings complement those obtained from the analysis of the negative subsequent memory effects in demonstrating first, that task-negative effects declined substantially in magnitude between the young and middle-aged groups, but showed little further decline in the older group, and second, that the magnitude of these effects positively co-varied with later memory performance, but in the older group only.

3. Discussion

We used an associative recognition task to investigate the relationships between age, negative subsequent memory effects and task-negative effects in young, middle-aged and older participants. While most regions demonstrating negative subsequent memory effects also demonstrated task-negative effects (the exception being a task-positive region of the anterior insula), negative subsequent memory effects were identified in only a small subset of all task-sensitive voxels. We found no correlation between the magnitude of negative subsequent memory and task-negative effects, despite finding that both classes of effects were attenuated with age. The magnitude of negative subsequent memory effects was not associated with memory performance in the older or middle-aged groups, and existed for only one region in the young. In contrast, task-negative effects correlated positively with associative memory performance only in the older group.

3.1. Behavioral findings

As expected, associative recognition performance was higher in the young than in the older group. Performance in the middle-aged group also exceeded that of the older individuals, but was significantly worse than that of the young. This graded decline in associative memory performance with age is consistent with previous reports that associative memory declines continuously across the adult age-range (Bender et al., 2010; Salthouse, 2009; see for example Nilsson, 2003, and Park et al., 2002, for additional evidence that episodic memory declines continuously with age). The sensitivity of the present associative recognition test to increasing age stands in contrast to the null effects of age on one of our standardized memory tests (WMS), and to its modest effects on the other test (the CVLT). The findings are well accommodated by the proposal that the ability to encode and retrieve associative information is especially sensitive to increasing age (Naveh-Benjamin, 2000).

In contrast to the findings for associative recognition performance, there were no differences between the age groups in the accuracy or speed with which the study task was performed, or in the relationship between study RT and subsequent memory performance. Therefore,

any between-group differences in fMRI subsequent memory or task effects are unlikely to be accounted for by gross differences between the groups in the efficiency with which study pairs were processed. Of potential importance, study RTs differed according to later associative memory performance (items going on to become associative hits were responded to more slowly than those that became associative misses) regardless of age group. As we elaborate below, analogous differences were not evident in our earlier study that employed the same experimental materials and very similar study and test procedures (de Chastelaine et al., 2011; see Introduction).

3.2. fMRI findings

Negative subsequent associative memory effects were evident in several of the cortical regions where such effects have been reported previously (e.g., Chua et al., 2007; de Chastelaine and Rugg, 2014; de Chastelaine et al., 2011; Daselaar et al., 2004; Miller et al.. 2008; Park and Rugg, 2008; see also Mattson et al., in press). The effects were restricted mainly to regions that also demonstrated task-negative effects, consistent with the proposal that negative subsequent memory effects primarily reflect modulation of task-negative activity (Daselaar et al., 2004; de Chastelaine and Rugg, 2014). As was also reported by de Chastelaine and Rugg (2014), negative subsequent memory effects were evident in only a subset of task-negative regions (compare Figs. 1 and 4a). Notably, among the task-negative regions that failed to show negative subsequent memory effects were some core members of the default mode network, such as bilateral angular gyrus. Thus, the present findings add to the evidence that associative encoding benefits from the disengagement of only some default-mode processes (de Chastelaine and Rugg, 2014). Additionally, we found no correlation between the magnitudes of negative subsequent memory and task-negative effects (despite the fact that the two effects were derived from the same voxels). This result is consistent with prior findings suggesting that the factors modulating subsequent memory and task-negative effects are at least partially independent (de Chastelaine and Rugg, 2014).

As has been reported in numerous prior studies of the encoding of both single study items (Duverne et al., 2009; Gutchess et al., 2005; Morcom et al., 2003; Mormino et al., 2012; Park et al., 2013) and inter-item associations (de Chastelaine et al., 2011; Miller et al., 2008), the present negative subsequent memory effects were significantly smaller in the older than in the young age group. By contrast, the effects in the middle-aged group did not significantly differ from those of the young. However, since the effects in this group also failed to differ from those of the older group, it is not possible to draw a strong conclusion about the profile of age-related differences in negative subsequent memory effects. In this respect, the findings are reminiscent of those reported by Park et al. (2013), who investigated subsequent memory effects elicited by later recognized and forgotten visually presented scenes in young, middle-aged and older participants. In this study too, negative subsequent memory effects were graded in magnitude as a function of age-group. Unlike in the present case, however, the effects in the middle-aged group differed reliably from those of both young and older participants, albeit in only two of the five regions where effects were identified.

While the majority of previous studies have reported age-related declines in negative subsequent memory effects, a recent study by Mattson et al. (in press) reported that negative subsequent source memory effects (differences in the activity elicited by later recognized study items according to whether the items attracted incorrect or correct source memory judgments) did not differ in magnitude between young and older individuals. In light of these findings, it might seem puzzling that the magnitude of negative subsequent memory effects declined with age in the present and our prior studies since, in both cases, a memory test held to be strongly dependent on recollection was employed. Importantly, though, in the study of Mattson et al. (in press) the subsequent memory contrast only included items that went on to receive correct and highly confident 'old' judgments. These items were segregated according to whether they also received a correct and highly confident source judgment or an inaccurate judgment (correct source judgments made with low confidence were excluded). Therefore, the subsequent source memory effects were generated from items that differed little between the two age groups with respect to the strength of the memory signal supporting the source judgments (cf. Wixted and Mickes, 2010). In discussing the findings from our prior experiment (de Chastelaine et al., 2011), Mattson et al. (in press) suggested that, had the strength of associative recognition been equated across age groups by restricting the subsequent memory contrast to associative hits made with high confidence, the resulting negative subsequent memory effects might have been age-invariant. By this view, therefore, the age-related reduction in the magnitude of negative subsequent associative memory effects in both our present and prior studies might be a consequence not of age *per se*, but of an age-associated reduction in the strength of the recollection signal supporting accurate associative recognition judgments.

Whereas this proposal cannot be ruled out, it sits uncomfortably with the present failure to identify a relationship between the magnitude of negative subsequent memory effects and associative recognition performance. If negative subsequent associative memory effects reflect the strength of the recollection signal elicited at test, and if in turn recollection strength is associated with overall associative recognition performance, then a relationship between negative subsequent memory effects and performance should have been evident. Such a relationship was reported in our prior study (de Chastelaine et al., 2011), however, and it is unclear why that finding was not replicated here. One possibility is that this disparity between the two studies reflects subtle differences between the respective samples of older adults, although there is little evidence to support this possibility in respect of either patterns of performance on the neuropsychological test battery, or performance on the experimental task. A more likely possibility is that the disparity reflects differences between the studies in the nature of the study processing associated with successful encoding. Unlike in our prior study, here study RTs demonstrated a sizeable (ca. 50 ms) and statistically robust subsequent memory effect, such that study items that went on to become associative hits were responded to more slowly than those destined to become associative misses. Why this effect should have been evident in the present but not the prior study is unclear, although one possible explanation might lie in the very different test conditions of the two studies (outside versus inside the scanner, and unpaced versus paced retrieval tests, in the prior and present studies respectively). Whatever the reason, we conjecture that the additional processing time accorded later remembered versus later forgotten items in the

present study modulated or added variance to the resulting subsequent memory effects in a manner that over-shadowed any relationship with overall memory performance.

As already noted, the present negative subsequent memory effects were not localized exclusively to regions demonstrating task-negative effects, but were evident also in the anterior insula, where task effects were positive. Similar findings were reported in a previous study that employed associative recognition (Daselaar et al., 2004), and negative subsequent memory effects in the insula have also been reported in studies employing other types of memory test (Kukolja et al., 2009; Mattson et al., in press; Otten and Rugg 2001; Reynolds et al., 2004; Wagner and Davachi 2001). The anterior insula is held to be a component of the 'salience network', and is thought to be important for the initiation of cognitive control in response to salient events (Ham et al., 2013; Seeley et al., 2007). Thus, negative subsequent memory effects in this region might reflect the allocation of processing resources to salient but mnemonically irrelevant aspects of a study event or the experimental environment (Mattson et al., in press; see also Uncapher and Wagner, 2009, for a similar suggestion with respect to negative subsequent memory effects in the temporoparietal junction). This proposal highlights the possibility that, whether found in task-negative or task-positive regions, negative subsequent memory effects reflect processes that compete or interfere with those supporting successful encoding. The more these processes are disengaged (in the case of regions belonging to the default mode network) or are not engaged (in the case, for example, of the insula) during the study event, the greater the probability of successful encoding.

In contrast to the effects of age on negative subsequent memory effects, there was considerably less ambiguity with respect to task-negative effects. Whether the effects were defined only for the regions where negative subsequent memory effects were evident, or at the whole brain level, the influence of age demonstrated a clear step-function. While reliable in each age group separately, task-negative effects were greater in the young than the middle-aged group, but showed no further decline in the older group[1]. The difference between young and older individuals in the magnitudes of their task-negative effects replicates numerous prior findings (e.g., Grady et al., 2006; Lustig et al., 2003; Persson et al., 2007; see Hafkemeijer et al., 2012, for a review). Additionally, a reduction in task-negative effects from young to middle-aged individuals during memory encoding has also been reported previously (Grady et al., 2006). In that study, however, the effects demonstrated a graded decline with increasing age.

While our findings of a decline in task-negative effects indicated a clear step-function with age (young > middle-age = older), associative memory performance showed a graded decline with increasing age. Given that the decline in the magnitude of task-negative effects (relative to the young) was as great for the middle-aged group as it was for the older group, the relationship between task-negative effects and memory performance does not appear to be straightforward. Indeed, task-negative effects and associative memory performance were

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[1] It is worth noting that the contrast we employed to identify task negative effects gave equal weight to study items that went on to receive accurate or inaccurate associative recognition judgments. Therefore, the impact of age on these effects is not confounded with the influence of age that was evident in negative subsequent memory effects.

significantly correlated across participants in the older group only. This difference between the age groups in the strength of the relationship between task negative effects and performance was confirmed statistically in a multiple regression analysis (see Table 4).

What might account for the age-specificity of this relationship? A possible clue comes from reports that task-negative effects are reduced in healthy older adults in whom there is evidence of beta-amyloid deposition as assessed by Positron Emission Tomography (e.g., Kennedy et al., 2012; Sperling et al. 2009; Vannini et al., 2012), along with evidence that amyloid deposition is also associated with episodic memory decline (e.g., Ellis et al., 2013; Hedden et al., 2012, 2013; Lim et al., 2014). In light of these observations, one speculative account of the present correlation between task-negative effects and memory performance in our older group is that the correlation was mediated by individual differences in amyloid deposition among the members of this group.

The foregoing account does not however address the more general question of why task-negative effects decline with increasing age. Such declines are evident in older individuals with no evidence of amyloid deposition (e.g., Sperling et al., 2009) and, at least in the present case, are already present by middle-age. These age-related differences in the magnitude of task-negative effects were independent of the accuracy and speed of the study judgments and, as was noted above, of subsequent memory performance. Addtionally, there were no correlations between the effects and any of the scores on the neuropsychological test battery, either within or across groups. Thus the functional significance of age-related decline in task-negative effects remains elusive.

4. Experimental procedure

4.1. Participants

Participants included 36 young adults (17 female) aged 18–29 yrs (M = 22 yrs; SD = 3.0 yrs), 36 middle-aged adults (19 female) aged 43–55 yrs (M = 49 yrs; SD = 3.4 yrs) and 64 older adults (35 female) aged 63–76 yrs (M = 68 yrs; SD = 3.6 yrs). Data collected from 12 additional individuals were excluded because of inadequate behavioral performance either at study or test (2 young, 1 middle-aged and 2 older), abnormalities in their anatomical scan (2 older), technical problems during scanning (1 middle-aged) or insufficient trial numbers (i.e., less than 10 trials) for fMRI analysis in one of the critical conditions (3 young and 1older). When participants did not provide sufficient numbers of trials for the fMRI analysis, this was always because of too few associative misses. For those who were excluded due to insufficient associative miss trials, the memory performance of three of these participants was above the mean for their group (2 young and 1 older), whereas for one young participant performance was below the mean.

Participants were recruited from the University of Texas at Dallas and surrounding communities. All were healthy, right-handed, had normal or corrected-to-normal vision and had learned English before age 5. They had no history of cardiovascular, neurological, or psychiatric disease and were not taking central nervous system-active medication. Exclusion criteria based on neuropsychological test scores are described below. All participants gave

informed consent according to the procedures approved by the UT Dallas and University of Texas Southwestern Institutional Review Boards. They were compensated at $30 per hour.

4.2. Neuropsychological testing

A battery of standardized neuropsychological tests was administered to all participants in a separate experimental session. The battery assessed a range of cognitive functions known to either decline or be maintained with age. The Mini-Mental State Examination was employed to screen participants for dementia – a cutoff score of 27/30 was adopted. The remainder of the battery comprised the California Verbal Learning Test-II (CVLT; Delis et al. 2000), the Wechsler Memory Scale (WMS-IV), the Digit Span Forward and Backward test of the Wechsler Adult Intelligence Scale Revised (WAIS-R) (Wechsler 2001), the Digit/Symbol Coding test of the WAIS-R, Trail Making Tests A and B, letter and category fluency tests, the Wechsler Test of Adult Reading (WTAR; Wechsler 2001) and the Raven's Progressive Matrices (short version). Potential participants were excluded if they scored 1.5 standard deviations (SD) below their age-appropriate norm on the CVLT or the WMS, below an estimated full-scale IQ of 100 as given by performance on the WTAR, or more than 1.5 SD below the age-appropriate norm on any 2 of the other neuropsychological tests. As CVLT recall scores were highly correlated with each other, a composite CVLT score was calculated by averaging across the 4 tests (immediate and delayed free and cued recall) and was used for all further analysis (see Results). For the same reason, a composite WMS score was also computed by averaging the scores on WMS 1 and WMS 2.

4.3. Experimental materials

Experimental items comprised 320 semantically unrelated, visually-presented word pairs. The words were selected from the word association norms compiled by Nelson et al. (2004) – each was a concrete noun and ranged in length from 3 to 9 letters. The items were randomly divided into 4 lists of 80 word pairs. Lists were rotated so that, across each set of yoked participants (1 young, 1 middle-aged and 1 or 2 older participants), each list provided the items for all 3 of the experimental word-pair categories: intact, rearranged, and new (see below). For each set of yoked participants, word pairs from 3 of the lists were pseudo-randomly ordered to form the study list. Critical study pairs were intermixed with 80 null trials. The test list included 320 critical word pairs – 160 of the test pairs had been presented at study (intact pairs), 80 of the pairs were studied items that had been repaired from study (rearranged pairs) and 80 were unstudied pairs (new pairs). Critical test pairs were intermixed with 106 null trials. Two buffer pairs were placed at the start and 2 in the middle of each of the 2 study blocks and 3 test blocks (see below). The different categories of word pairs in the study and test lists were pseudo-randomly ordered such that the same category did not occur more than 3 times in succession. Practice study and test lists were formed from items additional to those used to create the experimental lists.

4.4. Procedure

Prior to scanning, participants were given instructions and practice sessions for both the study task and the memory test and were therefore aware that their memory for the study items would be tested. The experimental study and test phases were run in separate scanning sessions. During the first scanning session, participants made judgments about each of the

study pairs, which were presented in 2 consecutive blocks separated by a short rest interval. The study task was to indicate with a button press which of the 2 objects denoted by the words was more likely to fit into the other. After completion of the study task, participants exited the scanner for 15 min. They returned to the scanner to complete an associative memory test in 3 consecutively administered blocks. One of 3 key press responses was required to indicate whether each test pair was intact, rearranged, or new. Participants were required to respond 'intact' when they recognized both words and had a specific memory of the 2 words having been presented together at study. A 'rearranged' response was required when both words were recognized from the study phase but there was no specific memory of the words being paired together previously. A 'new' response was required when neither or only one word was recognized. The test phase concluded with DTI and structural scans. Participants were instructed to respond 'intact' only when they were confident that the words had been studied together.

At both study and test, the words were presented for a duration of 2 s just above and below fixation in white uppercase Helvetica 30 point font against a black background. The word pairs subtended an approximate vertical visual angle of 1.8 deg. and a maximum horizontal visual angle of 5.1 deg. at a 56.6 cm viewing distance. Participants viewed the experimental items via a mirror placed directly above their eyes. Each pair was preceded by a red fixation cross for 0.5 s and replaced with a white fixation cross for 1 s at study, and for 2 s at test. Null trials consisted of the presentation of a white fixation cross against a black background for 3.5 s and 4.5 s at study and test respectively. A 30 s break occurred halfway through each study and test block, while inter-block intervals were approximately 2 min in duration. Experimental control, including stimulus display, was implemented in the 'Cogent' software package (http://www.vislab.ucl.ac.uk/cogent.php).

Study and test instructions emphasized the need for both accuracy and speed.

4.5. MRI data acquisition

Functional and anatomical images were acquired with a Philips Achieva 3T MR scanner (Philips Medical System, Andover, MA USA) equipped with a 32 channel parallel imaging head coil. A T1-weighted anatomical image was acquired with a 3D magnetization-prepared rapid gradient echo (MP-RAGE) pulse sequence (FOV= 256×224, voxel size 1×1×1 mm, 160 slices, sagittal acquisition). Functional scans were acquired with a T_2^*–weighted echo-planar image (EPI) (TR 2 s, TE 30 ms, flip angle 70°, FOV 240×240, matrix size 80×78). Each EPI volume comprised 33×3 mm slices (1 mm inter-slice gap) with an in-plane resolution of 3×3 mm. Slices were acquired in ascending order, oriented parallel to the AC–PC line and positioned for full coverage of the cerebrum and most of the cerebellum. The functional data were acquired using a sensitivity encoding (SENSE) reduction factor of 2. fMRI data were acquired during both study and test phases (311 and 351 volumes for each study and test block, respectively). The first 5 volumes of each block were discarded to allow tissue magnetization to achieve a steady state. For the GLM analyses, study sessions were concatenated to form a single time-series.

4.6. MRI data processing

Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK), run under Matlab R2008a (MathWorks) was employed for MRI data analysis. Functional images were motion and slice-time corrected, realigned, and spatially normalized using a sample-specific template. The template was created by first normalizing (Ashburner and Friston 1999) the mean volume of each participant's functional time series (separately for study and test) with reference to a standard EPI template based on the Montreal Neurological Institute (MNI) reference brain (Cocosco et al. 1997). The normalized mean images were separately averaged within each age group and the resulting 3 mean images were then averaged to generate a template that was equally weighted with respect to the 3 age groups. This template was used to normalize all other volumes, which were also resampled into 3 mm isotropic voxels and smoothed with an isotropic 8 mm full-width half-maximum Gaussian kernel. T1 anatomical images were normalized with a procedure analogous to that applied to the functional images, but using as an initial template the standard T1-weighted MNI reference brain.

For each participant, item-elicited neural activity was modeled by a delta function and convolved with 2 hemodynamic response functions (HRFs) using a GLM. These functions consisted of a canonical (Friston et al. 1998) and an orthogonalized, delayed HRF (Andrade et al. 1999), the latter generated by shifting the canonical HRF one TR (2 s) later in time. As results from the late HRF did not add anything of theoretical significance to the present findings, we report only the effects detected with the canonical HRF.

As noted in the Introduction, we focus here on fMRI findings from the study phase pertaining to negative subsequent memory and stimulus-elicited effects. The fMRI data were analyzed in two stages. In the first stage, separate GLMs were constructed for each participant. Two events of interest were included in the design matrix: study pairs that went on to be correctly endorsed as intact (*subsequent associative hits*) and pairs that were later incorrectly identified as rearranged (*subsequent associative misses*) on the subsequent associative recognition test. The average number (and range) of trials included as subsequent associative hits and misses were, respectively, 100 (42–144) and 41 (12–85) for the young adults, 99 (30–134) and 42 (14–78) for the middle-aged adults, and 89 (25–142) and 46 (11–97) for the older adults. Study pairs later incorrectly identified as new, buffer pairs and the two 30 s breaks interposed during the study list were also modeled, along with 6 regressors representing motion-related variance and 2 constants representing means across each scan session. The time series in each voxel were high-pass filtered to 1/128 Hz to remove low-frequency noise and scaled within session to a grand mean of 100 across voxels and scans.

In the second stage of the analysis, the participant-specific parameter estimates for subsequent hits and misses were taken forward to a 3×2 mixed-design analysis of variance (ANOVA) with factors of age group (young, middle-aged, older) and subsequent memory (associative hits, associative misses) using an ANOVA model implemented within SPM8 (and hence employing a single pooled error term). Negative subsequent memory effects were identified in a manner unbiased with respect to age group by using the across-group pairwise directional contrast (subsequent misses > subsequent hits) derived from the

ANOVA model. Effects exceeding a height threshold of p < 0.001 (one-sided) and comprising clusters of 21 or more contiguous voxels were considered reliable. The cluster extent threshold was determined by a Monte Carlo simulation implemented in AlphaSim (http://afni.nimh.nih.gov/afni) to give a corrected cluster-wise significance level of p < 0.05. Parameter estimates extracted from regions demonstrating negative subsequent memory effects were interrogated in order to identify any differences in the magnitude of these effects due to age. We also investigated the effects of age on the magnitude of task-negative effects; these effects were identified by contrasting the activity elicited by all studied pairs (i.e. subsequent hits and misses) with respect to the implicit baseline of the GLM (contrast weights of −1 −1 0)[2].

For the purposes of visualizing the fMRI findings, Caret software (Van Essen et al., 2001) was used to map fMRI effects of interest onto inflated fiducial brains derived from the PALS-B12 atlas (Van Essen 2002, 2005) in SPM5 space. Results were also visualized using sections from the across-group averaged T1 structural image.

Acknowledgements

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[2]The '0' in this contrast refers to the GLM's implicit baseline measure (as opposed to a regressor specified in the GLM). If we had included rest blocks as a regressor in the GLM, for example, we would have used contrast weights of −1 −1 2.

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Associative memory performance declined across young, middle-aged and older adults.

Negative subsequent memory effects showed a graded decline with age.

Task-negative effects declined markedly from the young to the middle-aged group.

Task-negative effects predicted associative recognition in older individuals.
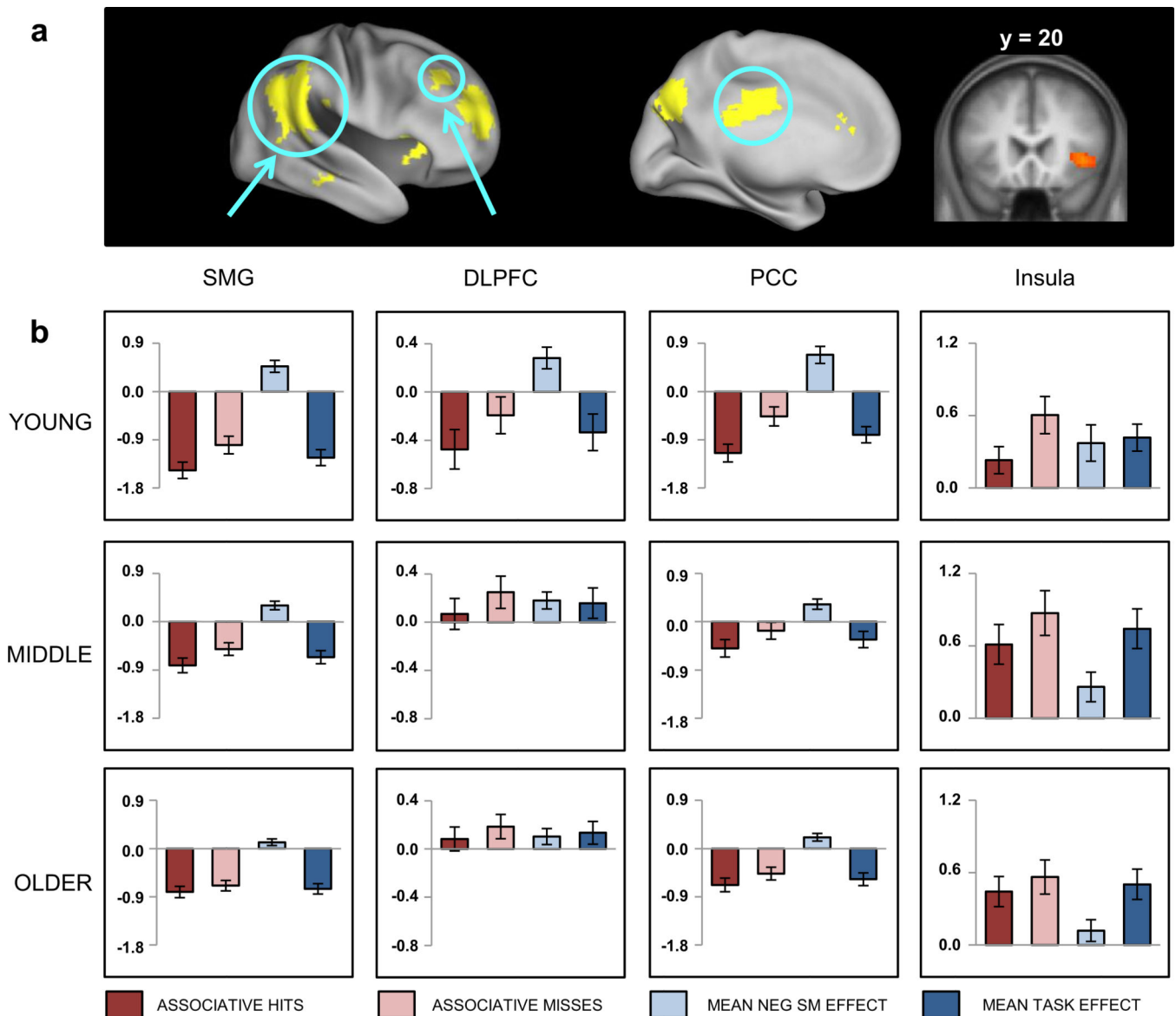
Figure 1.
Regions demonstrating negative subsequent memory effects across age groups. (A) Effects displayed on the right lateral and left medial surfaces of a standardized brain (PALS-B12) atlas using Caret 5, and on a coronal section of the across-groups mean T1-weighted structural image; (B) Parameter estimates (arbitrary units) and standard errors for associative hits, associative misses, mean negative subsequent memory effect, and mean task effect by group and region.
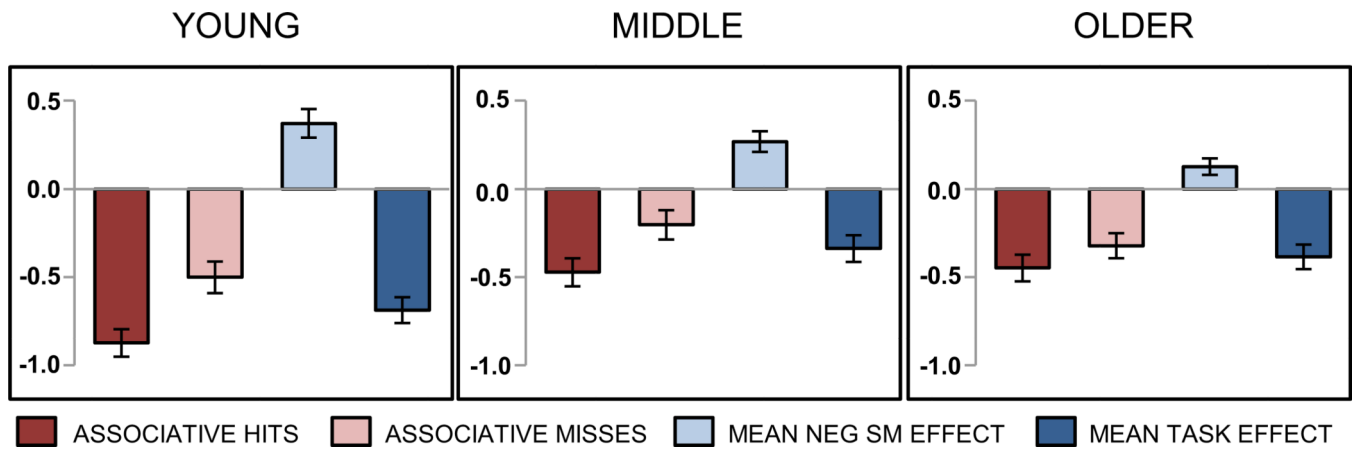
Figure 2.
Parameter estimates (arbitrary units) and standard errors for associative hits, associative misses, mean negative subsequent memory effect, and mean task effect, averaged across all voxels within a 5 mm radius of each peak in 9 regions identified by the across-group main effect of negative subsequent memory.
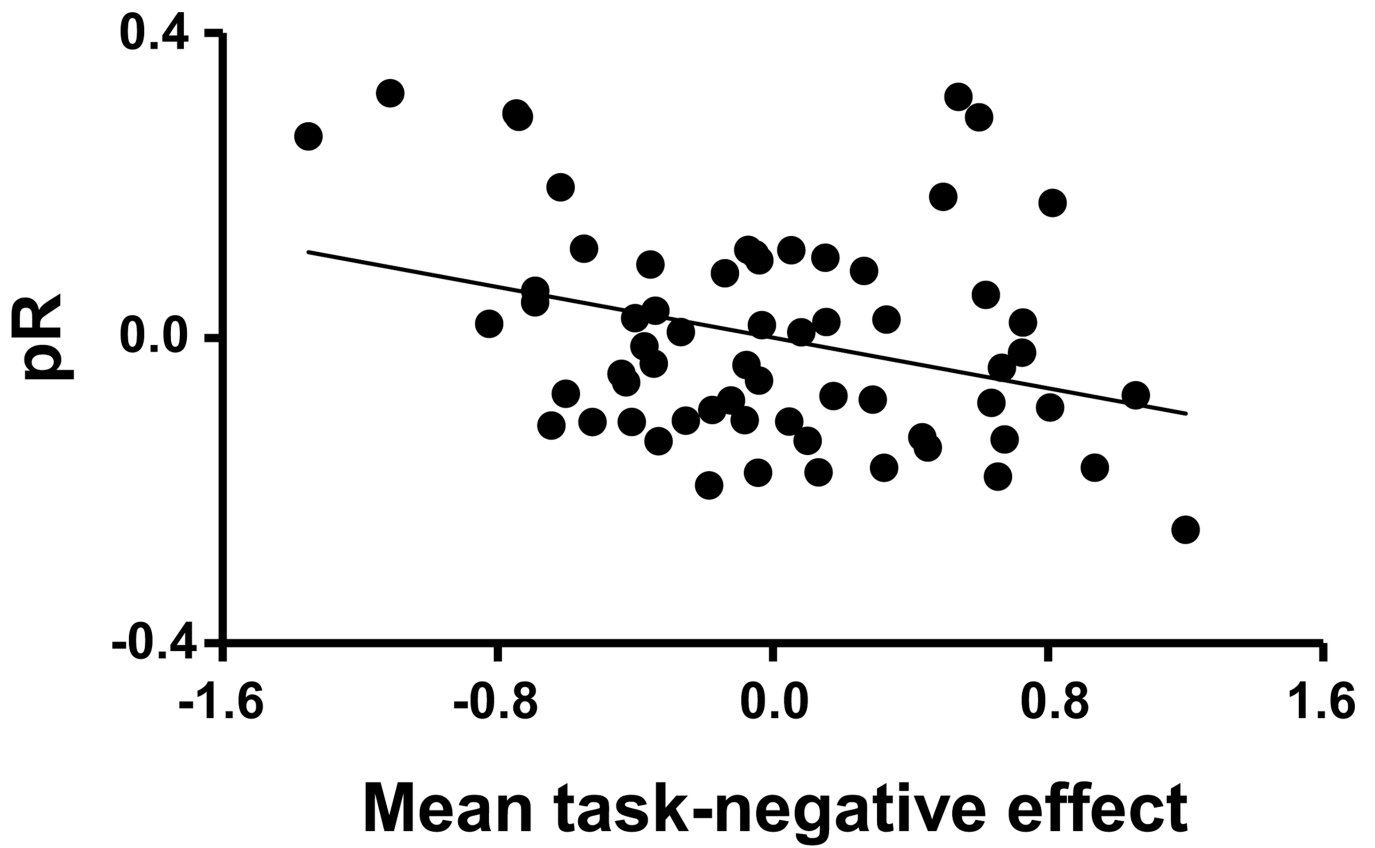
Figure 3.
Partial plot showing the relationship between the across-region mean task-negative effect and associative memory performance across older participants after controlling for age.
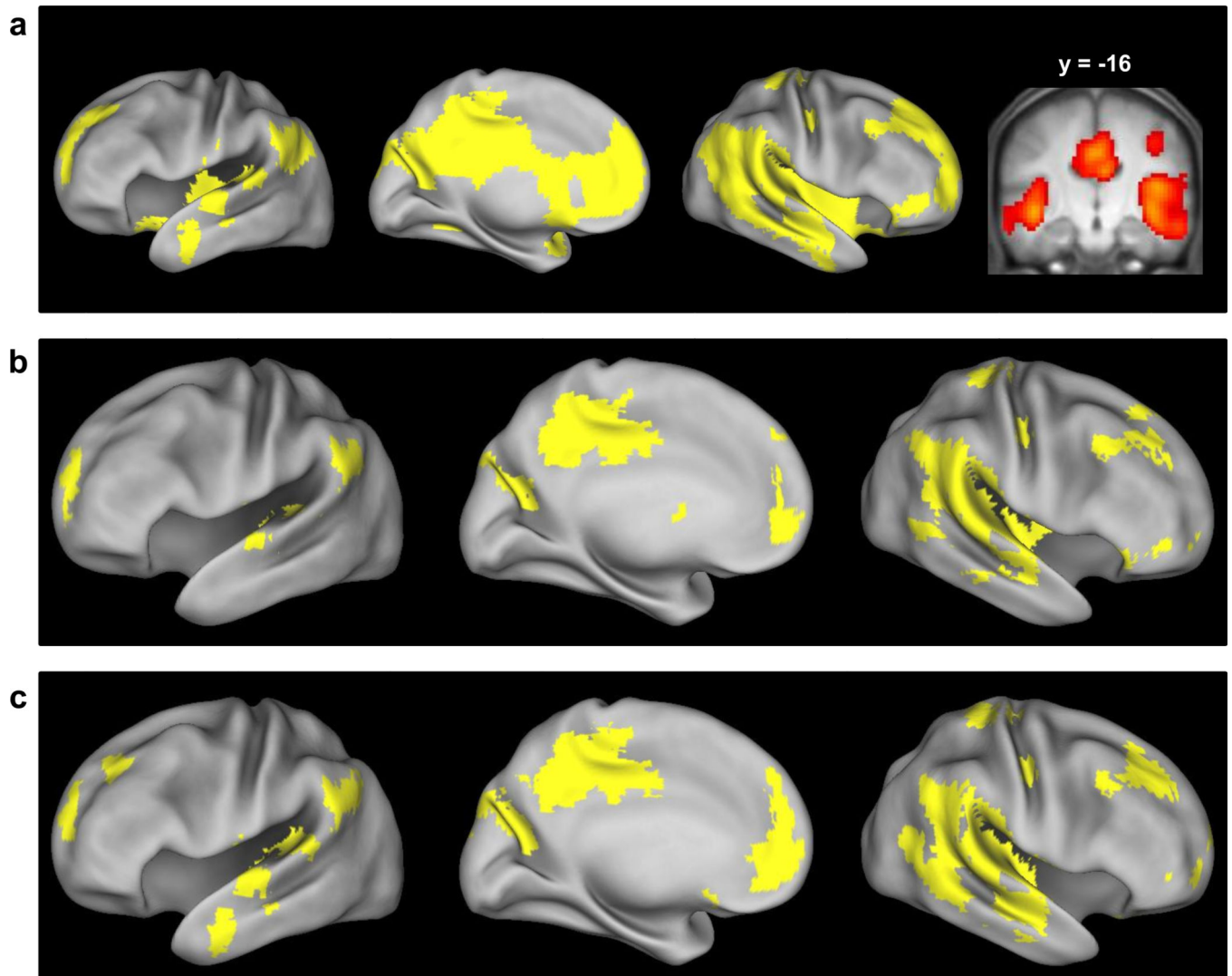
Figure 4.
(A) Regions demonstrating task-negative effects across age groups. The effects are displayed on the left and right lateral surfaces and left medial surface of a standardized brain (PALS-B12) atlas using Caret 5, and on a coronal section of the across-group mean T1-weighted structural image; (B) Regions where young adults displayed greater task-negative effects than middle-aged adults; (C) Regions where young adults displayed greater task-negative effects than older adults.

Figure 5.
Regions where task-negative effects covaried with pR in older adults. Effects are displayed on sagittal sections of the across-group mean T1-weighted structural image and on the right lateral surface of a standardized brain (PALS-B12) atlas using Caret 5.
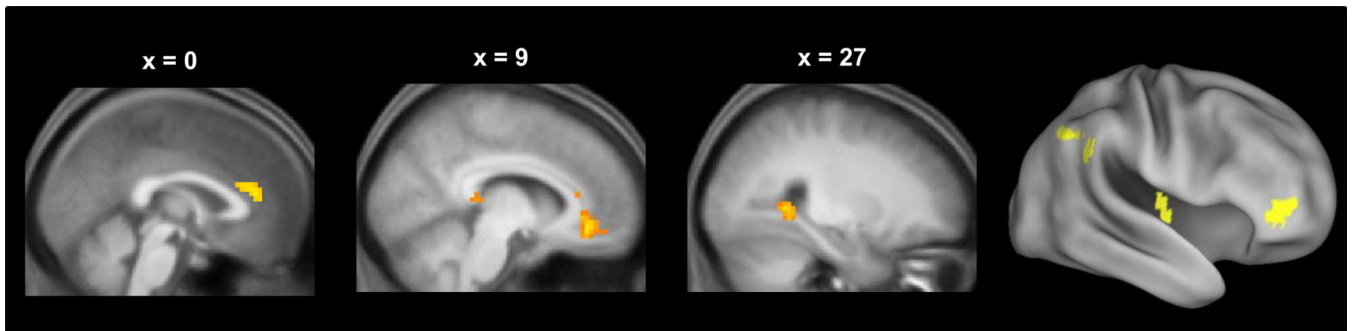
Table 1

Demographic and neuropsychological data (mean, SD, and range) for young, middle-aged, and older adults.

	Young adults			Middle-aged adults			Older adults		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Age	22.2	3.0	18–29	49.4	3.4	43–55	68.4	3.6	63–76
Years of Education[a†]	15.5	2.4	11–22	16.3	2.6	10–22	17.1	2.3	12–22
Mini Mental State Exam	29.6	0.6	28–30	29.3	0.8	28–30	29.3	0.8	27–30
CVLT[1] Composite Recall[a†]	13.3	1.9	9.3–16	12.4	2.0	9–16	12.0	2.5	5.5–16
CVLT[1] Recognition[a‡, b*]	15.6	0.6	14–16	15.2	0.9	13–16	14.8	1.3	12–16
CVLT[1] False Positives[a†, b*]	0.9	1.0	0–4	1.9	2.2	0–8	1.9	2.2	0–10
WMS[2] Composite Score	29.0	6.6	15.5–41	27.1	6.2	14–44.5	27.5	5.3	18.5–39.5
Forward/Backward Digit Span	18.0	3.9	11–26	18.2	3.5	13–26	18.3	4.4	12–27
Digit Symbol Substitution[a‡, b†, c†]	61.4	10.1	39–83	55.2	7.8	41–70	49.7	8.5	31–74
Trail A[a‡, c‡]	20.9	7.3	11–47	24.1	6.7	14–39	32.5	11.4	15–88
Trail B[a‡, c‡]	46.7	17.3	23–108	51.7	16.9	27–95	74.8	46.7	31–360
Letter Fluency	43.6	11.8	23–65	47.5	12.0	28–69	45.3	12.6	21–81
Category Fluency	24.8	5.9	16–42	24.0	5.9	13–36	22.3	5.5	12–40
WTAR[3] Raw Score	112.3	5.0	102–119	111.1	5.1	101–118	112.5	5.5	101–119
Raven's Prog. Matrices[4 a‡, b**]	11.2	1.0	8–12	10.4	1.5	7–12	9.7	2.0	3–12

[1] California Verbal Learning Test

[2] Wechsler Memory Scale (WMS-IV)

[3] Wechsler Test of Adult Reading Full Scale Intellectual Quotient

[4] Short version of Raven's Progressive Matrices

Note: Statistically significant difference between a) young and older adults, b) young and middle-aged adults, c) middle-aged and older adults.

*
P < .05,

**
P < .01,

†
P < .005,

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Table 2

Mean associative recognition memory (±SD) for young, middle-aged, and older adults.

	Young	Middle-aged	Older
Intact responses			
Intact pairs	**0.63 (0.17)**	**0.63 (0.14)**	**0.56 (0.16)**
Rearranged pairs	0.15 (0.11)	0.24 (0.12)	0.25 (0.13)
New pairs	0.03 (0.06)	0.06 (0.07)	0.07 (0.07)
Rearranged responses			
Intact pairs	0.26 (0.12)	0.27 (0.11)	0.29 (0.13)
Rearranged pairs	**0.64 (0.16)**	**0.55 (0.15)**	**0.49 (0.16)**
New pairs	0.29 (0.15)	0.30 (0.16)	0.30 (0.16)
New responses			
Intact pairs	0.11 (0.09)	0.10 (0.09)	0.14 (0.09)
Rearranged pairs	0.20 (0.11)	0.21 (0.13)	0.26 (0.12)
New pairs	**0.68 (0.17)**	**0.64 (0.19)**	**0.63 (0.18)**

Note: The table shows the proportion of intact, rearranged, and new pairs given intact, rearranged, and new responses. Correct responses are highlighted in bold.

Table 3

Peak voxels of the across-group main effect of negative subsequent memory.

Coordinates			Peak Z	No. of above-threshold voxels	Region
x	y	z			
−6	29	16	3.94	23	Left anterior cingulate cortex
−3	−28	28	6.85	1297	Left posterior cingulate cortex
24	56	19	4.72	293	Right superior frontal gyrus
9	47	4	4.11	143	Right anterior cingulate cortex
36	35	34	4.08	70	Right dorsolateral prefrontal cortex
42	20	−2	3.98	66	Right insula
57	−22	−20	4.34	55	Right inferior temporal gyrus
60	−49	37	5.99	567	Right supramarginal gyrus

Table 4

Results of the across-group regression model investigating variables that predict pR.

Model	b	SE b	β	P value
(Constant)	.691	.062		< .001
Age	−.006	.001	−.680	< .001
Mean task effect	.019	.029	.058	n.s.
Age group × mean task effect	−.102	.032	−.373	< .005

Note: *b*, unstandardized coefficient; SE *b*, standard error of the unstandardized coefficient; and β, standardized coefficient.

Table 5

Peak voxels of task-negative effects that covaried with pR in older adults.

Coordinates			Peak Z	No. of above-threshold voxels	Region
x	y	z			
−6	29	19	3.27	50	Left anterior cingulate cortex
12	38	−5	3.27	53	Right medial frontal cortex
15	−37	7	3.25	52	Right caudate (tail)
66	−46	37	4.44	72	Right supramarginal gyrus