Neuron, Vol. 42, 865–875, June 10, 2004, Copyright ©2004 by Cell Press

Preserved Neural Correlates of Priming in Old Age and Dementia

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Summary

Implicit memory, including priming, can be preserved in aging and dementia despite impairment of explicit memory. To explore the neural correlates of preserved memory ability, whole-brain functional MRI (fMRI) was used during a repetition priming paradigm to study 34 young adults, 33 older adults without dementia, and 24 older adults in the early stages of dementia of the Alzheimer type (DAT). Both older adult groups showed repetition-based response time benefits (priming) and changes in activation along inferior frontal gyrus similar to those shown by young adults. Across all three groups, repetition-related response time reductions correlated with prefrontal activity reductions, demonstrating a direct relation between priming and fMRI-measured activity change. These results suggest that despite difficulties with deliberate memory, both older adults without dementia and those with early-stage DAT can modify behavior mediated by prefrontal contributions, making these preserved abilities an attractive target for cognitive training and rehabilitation.

Introduction

Difficulties with deliberate, explicit memory are among the chief complaints of healthy older adults and are the hallmark of dementia of the Alzheimer type (DAT) (see reviews by Craik and Jennings, 1992; Fleischman and Gabrieli, 1999; Kausler et al., 1988; Light, 1991; Zacks et al., 2000). In contrast, older adults without dementia and those with DAT often show performance benefits on nondeliberate, or implicit, memory tasks that are as great or nearly as great as those shown by young adults (e.g., Gabrieli et al., 1999; Light et al., 2000a; see reviews by Fleischman and Gabrieli, 1998; LaVoie and Light, 1994; Light et al., 2000b; Rybash, 1996). Implicit memory relies on brain systems independent from those supporting the explicit memory forms that may decline with aging and that are devastated by DAT (Squire, 1992; Tulving and Schacter, 1990). To explore the neural correlates of preserved memory abilities, we studied repetition priming, a form of implicit retrieval, in young adults, older adults without dementia, and older adults with early-stage DAT using functional MRI (fMRI).

Event-related fMRI measurements were taken while participants performed a meaning-based word classification task, with new and repeated items intermixed. Similar classification and production tasks consistently activate a network of regions including left prefrontal cortex along inferior frontal gyrus (e.g., Bokde et al., 2001; Demb et al., 1995; Gabrieli et al., 1998; Gold and Buckner, 2002; Kapur et al., 1994; Petersen et al., 1989). In young adults, items repeated within these tasks are associated with reduced response times compared to new items (repetition priming) and with reduced left prefrontal activity (e.g., Buckner et al., 1995, 2000a; Demb et al., 1995; Gabrieli et al., 1996; Raichle et al., 1994; Wagner et al., 1997, 2000; for reviews see Henson, 2003; Schacter and Buckner, 1998).

Activity modulation in these frontal regions occurs when lexical or semantic representations must be elaborated upon in a controlled fashion (e.g., Thompson-Schill et al., 1997; Wagner et al., 2001; see Buckner, 2003 for a recent review). In contrast, these regions participate minimally when responding does not require such control but can instead be based on overlearned stimulus-to-representation mappings, as in single-word reading or even temporally extended tasks that require phonological comparisons among overlearned mappings from letters to sounds (e.g., Demb et al., 1995; Gold and Buckner, 2002). Furthermore, priming-related activity reductions in these frontal regions are sensitive to whether items are repeated within the same task or a different one (Demb et al., 1995; Dobbins et al., 2004; Wagner et al., 2000), but occur regardless of whether stimuli are read or heard (e.g., Buckner et al., 2000a). Such characteristics indicate that these regions reflect the controlled retrieval of relatively high-level, task-specific, modality-independent information about an item.

Older adults, including those with DAT, often show left frontal activity patterns similar to young adults' during controlled verbal processing, and may also show activity in additional brain regions where young adults do not (e.g., Cabeza et al., 1997; Grady et al., 2003; Logan et al., 2002; see reviews by Cabeza, 2002; Park et al., 2001; Reuter-Lorenz et al., 2001). Behaviorally, the three groups also show similar repetition-related response time benefits, or priming effects (e.g., Gabrieli et al., 1999; Lazzara et al., 2002; Light et al., 2000a; but see Lazzara et al. 2001). The main goal of the current study was to determine whether older adults without dementia and those with DAT show repetition-related changes in brain activity similar to those shown by young adults, especially in left frontal regions involved in controlled verbal processing.

Results

Repetition-Related Response Time Priming Is Preserved in Old Age and DAT

All three groups correctly classified the words at rates significantly above chance, all $p < 0.0001$. There were group differences in classification accuracy, $F(2, 88) = 11.88$, $MSE = 0.06$, $p < 0.0001$, with DAT participants (85% correct) less accurate than the older adults without

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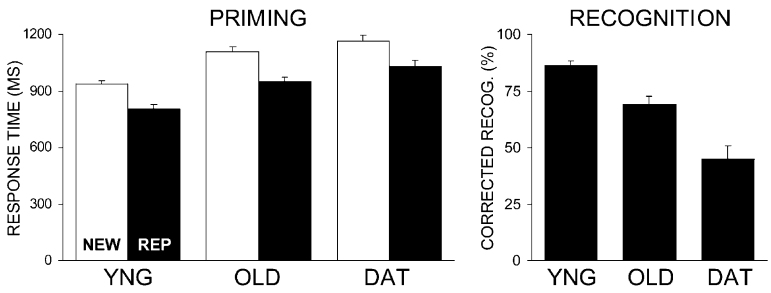

Figure 1. Repetition Priming, but Not Recognition Memory, Is Preserved in Old Age and Early Dementia

The left panel (priming) shows mean response times for new and repeated items. All groups showed a significant decrease in response time for repeated compared to new items, all $p < 0.0001$. The right panel (recognition) shows corrected recognition (hits minus false alarms), with large age- and DAT-related differences. Error bars represent standard error of the mean.

dementia (91%), $t(55) = 2.24$, $p < 0.01$, who in turn were marginally less accurate than were the young adults, (94%), $t(65) = 1.78$, $p = 0.08$. The response time data (Figure 1, left) suggest that the two older adult groups were somewhat slower overall, $F(2, 88) = 22.07$, $MSE = 802{,}322.89$, $p < 0.0001$, but priming effects were robust across all three groups, $F(1, 88) = 464.50$, $MSE = 871{,}404.07$, $p < 0.0001$. Numerically, there was a trend toward slightly smaller priming effects for the older adult groups, but the repetition X group interaction was not significant, $F(1, 88) = 2.04$, $MSE = 3832.89$, $p = 0.14$, and post hoc tests revealed robust priming effects for all three groups, all $p < 0.0001$.

The similar priming effects across all three groups stand in stark contrast to the large group differences in recognition memory (Figure 1, right). Recognition performance showed a main effect of group, $F(2, 87) = 27.05$, $MSE = 1.19$, $p < 0.0001$. The DAT group performed markedly worse than did the older adults without dementia, $t(55) = 3.64$, $p < 0.001$, who in turn performed worse than the young, $t(64) = 4.06$, $p < 0.001$. These data strongly suggest that the preservation of priming, a form of implicit memory, in the older adult groups occurred despite large age- and dementia-related differences in deliberate, explicit recognition memory.

Repetition-Related Activity Reductions Are Preserved in Old Age and DAT

The primary question was whether older adults without dementia and those with DAT would show repetition-related changes in brain activity comparable to those shown by young adults. Of particular interest were regions in left frontal cortex that are associated with controlled verbal processing (e.g., Demb et al., 1995; Gold and Buckner, 2002; Kapur et al., 1994; Poldrack et al., 1999). To that end, we compared activity for repeated and new words in all three groups, with analyses focusing on two predefined regions along left inferior frontal gyrus roughly corresponding to BA 45/47 and BA 44/6. These predefined regions have previously been used to study controlled processing during semantic classification of new words in young and older adults (Logan et al., 2002) and are consistent with the left frontal regions in which young adults show repetition-related activity reductions (Buckner et al., 2000a; Demb et al., 1995; Gabrieli et al., 1996; Raichle et al., 1994; Wagner et al., 2000).

The predefined regions, along with the time courses of activation for each group, are displayed in Figure 2. Exploratory statistical activation maps for each group are shown in Figure 3. The older adult groups showed a trend toward greater overall activation that may be related to their slower behavioral response times. Of most relevance, all three groups showed repetition-related reductions for the left frontal regions.

For BA 45/47, overall activation was not significantly different across the three groups, $F(2, 88) = 2.14$, $MSE = 0.05$, $p = 0.12$, and there was a strong effect of repetition, $F(2, 88) = 63.80$, $MSE = 0.50$, $p < 0.0001$. The group X repetition interaction was not significant, $F(1, 88) = 1.11$, $MSE = 0.01$, $p = 0.33$. Post hoc tests revealed that each group independently demonstrated significant repetition-related reductions, all $p < 0.05$. For BA 44/6, there was a small but significant main effect of group, $F(2, 88) = 4.15$, $MSE = 0.12$, $p < 0.05$. The trend was for the overall magnitude of activation in BA 44/6 to increase across categories of age and dementia status, but this increase was only statistically significant when comparing DAT participants to the young adults, $F(1,56) = 9.10$, $MSE = 0.24$, $p < 0.005$. As was the case for BA 45/47, left BA 44/6 showed a strong effect of repetition, $F(1, 88) = 70.79$, $MSE = 0.27$, $p < 0.0001$, that did not interact with group, $F < 1$. Again, each of the three groups showed significant effects of repetition, all $p < 0.01$. For both BA 45/47 and BA 44/6, reanalyzing the data using standard transformations to reduce the potential influence of group differences in overall activation (log scores, [new − old] / new proportional scores [c.f. Faust et al., 1999; Zheng et al., 2000]) did not reveal any group differences in the size of the repetition effect, all $F < 1$.

In summary, all groups showed strong effects of repetition that were significant for both frontal regions. However, a possible drawback to the use of predefined, a priori regions is that group differences outside these regions may be missed. Figure 3 suggests the potential for group differences, although visual comparisons across these within-group threshholded maps may be misleading due to differences in sample size and variance (Buckner et al., 2000b; Huettel and McCarthy, 2001). A formal voxelwise analysis (data not shown) found minimal evidence for group differences in the size of the repetition effect throughout the brain. Two additional, post hoc regions taken from another study of controlled verbal processing were also analyzed (peak points −47, 17, 24 and −55, −1, 28 [from Gold and Buckner, 2002]) to test the possibility that different results might have been found for different regions of interest. Like the a priori regions and the voxelwise analysis, these post hoc regions showed significant effects

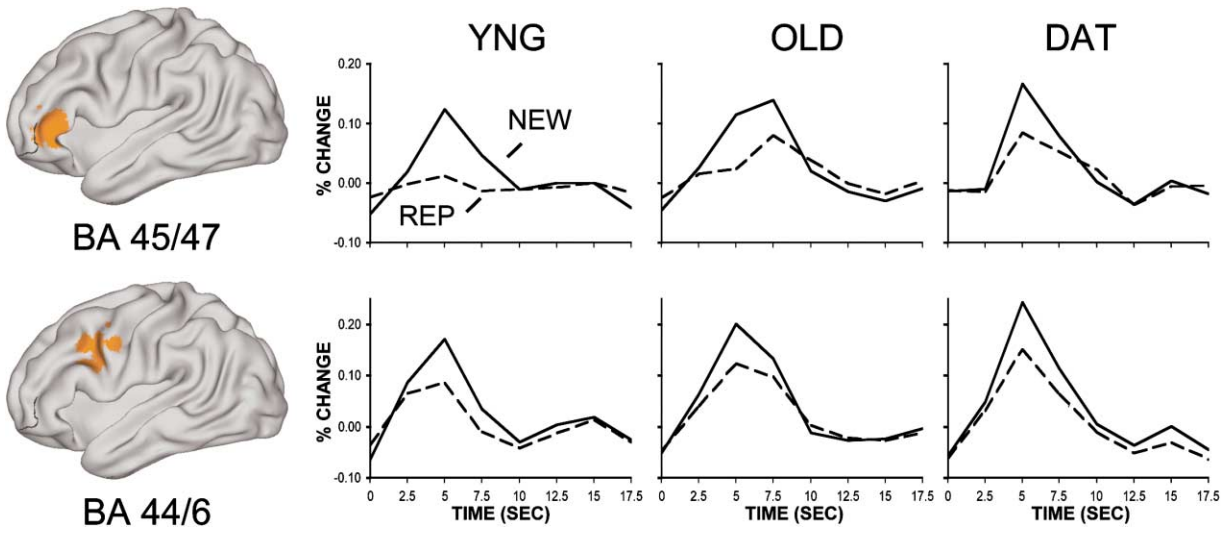

Figure 2. Left Frontal Regions Show Repetition-Related Activity Reductions in Old Age and Dementia

Regions of interest and time courses of activation for new and repeated items are displayed. Regions are projected onto a slightly inflated surface view of cortex (Van Essen and Drury, 1997). All groups show reduced activity, as indirectly measured by fMRI, for repeated compared to new items.

of repetition, both $p < 0.001$, and minimal evidence for group differences in the size of the repetition effect, both $p > 0.11$.

To further explore the possibility of group differences, we conducted additional post hoc analyses on the time course data. In particular, it should be noted that there were significant group differences in activation during the repeated condition for BA 45/47, $F(88) = 3.59$, $MSE = 0.05$, $p < 0.05$ (see Figure 2). For young adults, activation in this region was reduced such that it was no longer significantly above zero, $t(33) = 1.42$, $p = 0.17$, whereas for older adults without dementia it was marginally greater than zero, $t(32) = 1.88$, $p = 0.07$, and for the DAT group it was significantly so, $t(23) = 3.66$, $p < 0.005$. Thus, these data suggest that the effects of repetition on left prefrontal cortex are robust and present in aging and dementia but are not necessarily identical.

Older adults frequently show increased activation in

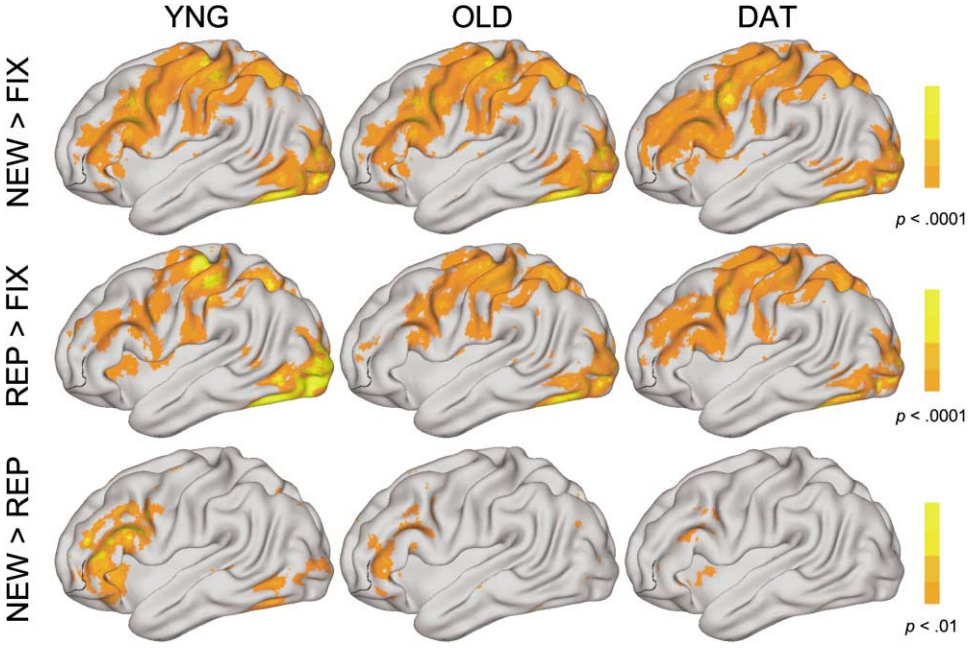

Figure 3. Exploratory Whole-Brain Statistical Activation Maps Are Displayed for the Three Possible Comparisons: New Words > Fixation, Repeated Words > Fixation, New Words > Repeated Words

Each column displays activation maps from one group. Activation and repetition-related reductions in activation in left prefrontal cortex are apparent for each group. Note that apparent differences between the groups should not be interpreted quantitatively (see text).

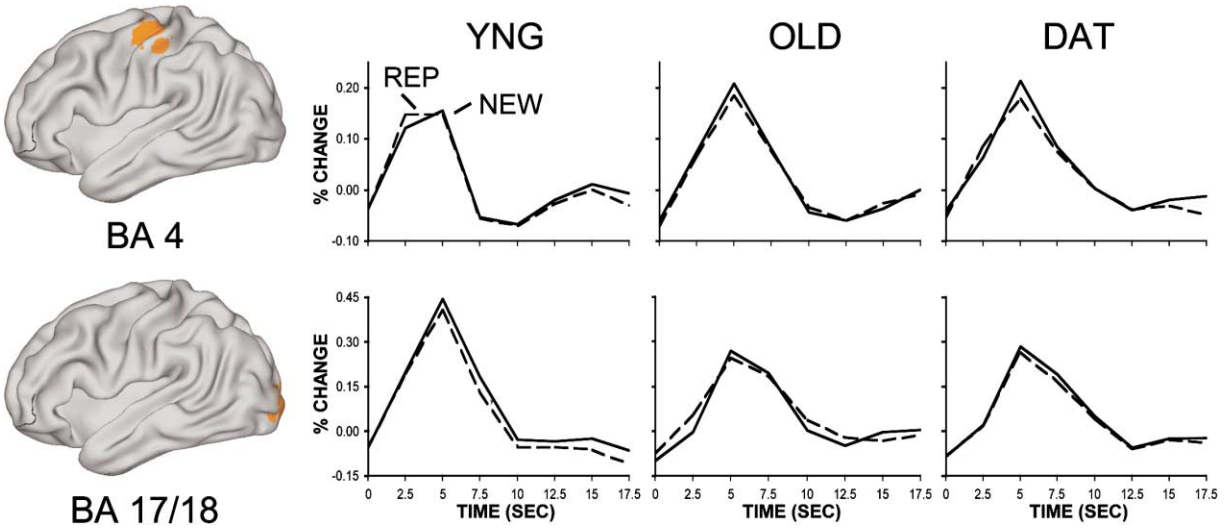

Figure 4. Control Visual and Motor Regions Show Little or No Effect of Repetition

Regions of interest and time courses of activation for new and repeated items are displayed. The older adult groups have lower absolute magnitudes in visual cortex compared to young adults (see also Buckner et al., 2000b).

right frontal regions on verbal tasks (see reviews by Cabeza, 2002; Park et al., 2001; Reuter-Lorenz et al., 2001). To investigate this possibility in the current data set, and also to explore the influence of repetition, we examined an additional, right BA 44/6 region (peak 43, 3, 32), homologous to the left BA 44/6 region used in the a priori analyses. There were group differences in overall activation for this right BA 44/6 region, $F(2, 88) = 3.92$, $MSE = 0.08$, $p < 0.05$. These differences followed a pattern similar to that shown by the a priori left BA 44/6 region: There was a trend for activation magnitudes to increase across categories of age and dementia status, but this increase was only statistically significant when comparing DAT participants to young adults, $F(1, 56) = 12.79$, $MSE = 0.17$, $p < 0.001$. Also similar to the a priori left hemisphere region, the magnitude of activation in right BA 44/6 showed a large effect of repetition, $F(1,88) = 22.29$, $MSE = 0.07$, $p < 0.0001$, that did not interact with group, $F < 1$. Both young adults, $t(33) = 3.12$, $p < 0.005$, and DAT participants, $t(23) = 3.37$, $p < 0.005$, showed a significant effect of repetition, with a marginal effect for the older adults without dementia, $t(32) = 1.80$, $p = 0.08$. In an analysis directly comparing left and right BA 44/6, hemisphere (left or right) did not significantly interact with group or group $\times$ repetition, both $p > 0.25$. Thus, these data provide evidence for increased and bilateral recruitment in the older adult groups. However, in a slight variation from previous findings (c.f. Logan et al., 2002), the increased recruitment of right hemisphere appears to be proportionate to the increased recruitment of left hemisphere regions by the older adults. Relevant to the current study's focus on the neural correlates of priming, the repetition-related reductions of activity in right hemisphere paralleled those in the left hemisphere.

Two sets of secondary analyses tested the possibility that our findings might be confounded by group differences in gender ratio or response time. First, the analyses on the predefined left hemisphere regions of interest were replicated on a gender-matched subset of participants, with 8 females and 12 males per group. The two older adult subsets were also matched for age (mean age 76.1 yrs for older adults without dementia, 76.8 yrs for DAT participants). Patterns were generally the same as in the full group analyses, with the exception that a marginal effect of group was now found for BA 45/47, $F(2, 57) = 2.70$, $MSE = 0.07$, $p = 0.07$, and the effect of group for left BA 44/6 was not significant, $F(2, 57) = 2.25$, $MSE = 0.07$, $p = 0.12$. Of primary importance, in the gender-matched subset, both left BA 45/47 and left BA 44/6 showed a significant effect of repetition, both $p < 0.0001$, and in neither region did repetition interact with group, $F < 1$ for left BA 45/47; $F(1, 57) = 1.27$, $MSE = 0.00$, $p = 0.29$ for left BA 44/6. Thus, gender does not appear to affect our main conclusion that both older adults without dementia and DAT participants show repetition-related reductions similar to young adults.

Second, we asked whether our results might be influenced by age-related slowing as indicated by group differences in baseline response time (see discussions by Faust et al., 1999; Zheng et al., 2000). To that end, the earlier analyses were replicated on a subset of participants whose mean response times for new items fell into a distribution covered by all three groups (between 928 and 1216 ms). This subset consisted of 16 young adults (mean response time 1043 ms), 24 older adults without dementia (1079 ms), and 15 DAT (1086 ms) participants. Within this subset, there was no effect of group on response time, $F(2, 52) = 1.44$, $MSE = 18{,}569.51$, $p = 0.25$. There was a significant effect of repetition on response time, $F(1, 52) = 256.62$, $MSE = 493{,}548.42$, $p < 0.0001$, indicating behavioral priming, that did not differ between the groups, $F < 1$. All fMRI analyses replicated in the response-time matched subset, with some changes in statistical significance likely due to reduced power. For left BA 45/47, there was no effect of group, $F < 1$, a strong effect of repetition, $F(1, 52) =$

31.35, MSE = 0.02, $p < 0.0001$, and no group X repetition interaction, $F(2, 52) = 2.10$, MSE = 0.02, $p = 0.13$. For left BA 44/6, the main effect of group was now marginal, $F(2, 52) = 2.79$, MSE = 0.08, $p = 0.07$. Left BA 44/6 showed a strong effect of repetition, $F(1, 52) = 40.90$, MSE = 0.18, $p < 0.0001$, that did not interact with the group, $F < 1$. Thus, our findings of similar repetition-related reductions across groups are not dependent on differences in baseline response time.

Early Visual and Motor Regions Show Group Differences in Overall Activation but Not Repetition-Related Reduction

To examine the specificity of the repetition effects, we analyzed data from control regions in early visual cortex (at or near BA17/18) and motor cortex (at or near BA 4) that do not typically show repetition-related reductions in event-related paradigms with young adults (e.g., Buckner et al., 1998). Regions in early visual and motor cortex have also been used to test the comparability of the hemodynamic response across young adults, older adults without dementia, and older adults with early-stage DAT (Buckner et al., 2000b; see also D'Esposito et al., 1999; Huettel and McCarthy, 2001). Figure 4 shows the results of these analyses.

For the visual region, there was a main effect of group, $F(2,88) = 10.02$, MSE = 0.68, $p < 0.0001$, but no effect of repetition or group X repetition interaction, both $F < 1$. Both older adults without dementia, $F(1, 65) = 19.65$, MSE = 1.20, $p < 0.0001$, and DAT participants, $F(1, 56) = 10.29$, MSE = 0.71, $p < 0.005$, had smaller activation magnitudes than did young adults, as has been found previously (Buckner et al., 2000b), and these differences were present for both new and repeated items. The two older adult groups did not differ from each other, $F < 1$. All patterns remained the same for the gender-matched and response-time-matched subsets.

For the motor region, there was no effect of group, $F(2, 88) = 1.91$, MSE = 0.07, $p = 0.15$, a nonsignificant trend toward a repetition effect, $F(1,88) = 3.13$, MSE = 0.01, $p = 0.08$, and no group X repetition interaction, $F(2, 88) = 1.17$, MSE = 0.01, $p = 0.31$. The gender-matched subset analysis showed a similar pattern, with no group effect, $F(2, 57) = 1.27$, MSE = 0.04, $p = 0.29$, a nonsignificant effect of repetition, $F(1, 57) = 3.00$, MSE = 0.01, $p = 0.09$, and no interaction with group, $F < 1$. The results for the response-time matched subset yielded no group differences in overall magnitude of activation, $F(2, 52) = 1.25$, MSE = 0.05, $p = 0.29$, no effect of repetition, $F < 1$, and no group X repetition interaction, $F < 1$. Thus, while differences in baseline response magnitudes were noted in visual cortex, as have been observed previously, effects of repetition were largely absent in control regions, barring a nonsignificant trend in motor cortex that may be related to response time.

Reductions in Left Prefrontal Cortex Activation Correlate with Reductions in Behavioral Response Time

Behavioral response time reductions and neural repetition effects did not correlate with explicit recognition scores either across or within any of the three groups, consistent with previous dissociations between explicit memory and priming (Donaldson et al., 2001; Jacoby and Dallas, 1981; Tulving and Schacter, 1990). For the older adult groups, the possibility of correlations with the standardized neuropsychological test scores was also explored, but should be considered post hoc and tentative. These scores are collected as part of a longitudinal study (Berg et al., 1982; Botwinick et al., 1986), and correlations were therefore adjusted for practice effects by partialling out the number of longitudinal sessions taken part in by each participant. For the older adults without dementia, recognition scores were correlated with tests tapping long-term semantic memory retrieval and executive function, such as the Boston Naming Test, $r = 0.48$, $p < 0.01$, the WAIS Information subtest, $r = 0.42$, $p < 0.05$, and the WAIS Block Design subtest, $r = 0.41$, $p < 0.05$. For the DAT participants, a similar trend was only found for the WAIS Block Design subtest, $r = 0.37$, $p = 0.08$. These measures did not show consistent correlations with either behavioral or neural repetition effects for either group.

Of greater interest, across all subjects the repetition-related reductions in activation magnitude for BA 45/57 correlated with the repetition-related reductions in behavioral response time, $r = 0.32$, $p < 0.005$, and correlations of a similar magnitude were found within each of the three groups ($r = 0.24$, $p = 0.17$ for young adults; $r = 0.35$, $p < 0.05$ for older adults without dementia; $r = 0.39$, $p = 0.07$ for DAT participants; see Figure 5; Maccotta and Buckner, 2004). The correlation magnitude for the young adults was numerically but not significantly less than that for the two older adult groups; the trend toward smaller correlations may be due to the young adults being somewhat less variable on both the behavioral and activation measures. These correlation

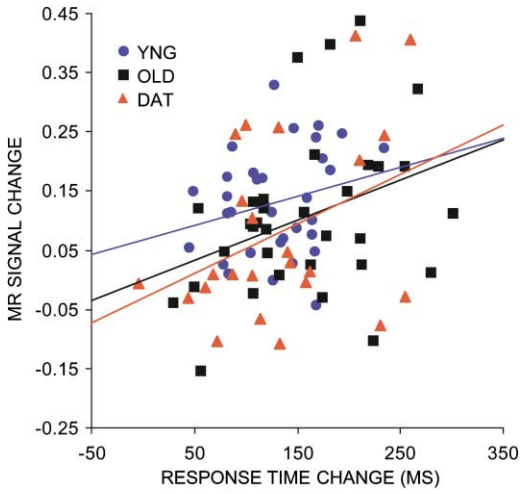

Figure 5. Correlations between Repetition-Related Reductions in Frontal Activity and Behavioral Priming Are Preserved in Old Age and Dementia

Repetition-related changes in frontal activation magnitude (new − old; BA 45/47) are plotted against repetition-related changes in behavioral response time (priming). Correlations are similar for young adults and older adults with and without dementia, suggesting a preserved coupling between the behavioral and neural effects of repetition across these three groups.

patterns suggest that repetition not only has similar effects on left anterior prefrontal cortex activation and behavioral response times across these groups, but that the relation between neural and behavioral repetition effects is also preserved.

Discussion

The current study provides evidence that at least one form of implicit memory is present in old age and early-stage DAT. Similar to young adults, older adults with and without DAT showed decreases in response time (priming) for judgments made on repeated versus new words, and these response time decreases were associated with decreases in left frontal cortex activity as indirectly measured using fMRI. There were trends toward smaller repetition effects on response time and prefrontal activity for the two older adult groups and, in particular, older adults may continue to show significant frontal activation for repeated items where young adults do not. However, within each group the response time and neural repetition effects were robust, suggesting that high-level, controlled processes can benefit from learning in old age and early-stage DAT. Of additional interest, the repetition-related changes in left frontal activity correlated with repetition-related changes in response time (see also Maccotta and Buckner, 2004). This relation was at least as strong for both older adult groups as for the young adults. Thus, individual differences in the behavioral benefits of repetition were linked to individual differences in brain activity modulation.

The present data extend previous findings of preserved repetition-related behavioral response time benefits and event-related potential (ERP) modulations in old age and dementia (e.g., Gabrieli et al., 1999; Karayanadis et al., 1993; Lazzara et al., 2002; Light et al., 2000a; Pfutze et al., 2002; Swick and Knight, 1997; Trott et al., 1999). First, in addition to the preserved repetition-related effects found at the group level, the individual-differences level analyses allow a direct comparison of the quantitative link between behavior and frontal activity changes in young adults, older adults without dementia, and older adults in the early stages of DAT. Second, the present analyses tie the preserved behavioral effects of repetition commonly found in old age and dementia to repetition-related changes in specific frontal brain regions that are associated with high-level, controlled processing. As described earlier, repetition-related reductions for these left frontal regions occur regardless of whether stimuli are read or heard (Buckner et al., 2000a), making it unlikely that they represent modulation of perceptual processes. Furthermore, these reductions show a high degree of task specificity, being sensitive to the degree to which the study and test tasks overlap in their processing and response requirements (Demb et al., 1995; Dobbins et al., 2004; Wagner et al., 2000).

Both the focus on high-level, frontally mediated processes and the recapitulation of processing requirements from study to test may be important for the preservation of behavioral and neural repetition effects. Behaviorally, older adults, especially those with dementia, frequently show priming deficits when the processing task changes from study to test, particularly if the test task introduces changes in the demands for controlled, strategic processing (Fleischman and Gabrieli, 1998; Gabrieli et al., 1999; Light et al., 2000b). The only previous exploration of these three groups' hemodynamic responses in an implicit memory paradigm focused on potentially more perceptually related processes and brain regions, and used a procedure that changed the processing requirements from study to test. These studies found similar patterns when comparing young and older adults without dementia (Backman et al., 1997), but opposing patterns for DAT participants (Backman et al., 2000).

Specifically, these earlier positron emission tomography studies (Backman et al., 1997, 2000) used a word-stem completion paradigm (e.g., study the word WINDOW, later complete the stem WIN- with the first word that comes to mind) that often leads to age- and DAT-related differences in behavioral priming (see reviews by Fleischman and Gabrieli, 1998; Light et al., 2000b; Rybash, 1996). Both young adults and older adults without dementia showed repetition-related decreases in a region of right occipitotemporal cortex near BA 19 (Backman et al., 1997). In contrast, repetition led to increased activity in this region for DAT participants (Backman et al., 2000). Repetition-related reductions in this occipitotemporal region likely represent the reprocessing of perceptual or surface features (Badgaiyan et al., 1999; Buckner et al., 1995; Schacter et al., 1999; Squire et al., 1992; for discussion, see Buckner et al., 2000a). Further suggesting the influence of perceptual processing, behavioral priming on this variation of the word-stem completion task is sensitive to manipulations of perceptual variables including modality (visual or auditory) (e.g., Rajaram and Roediger, 1993; see review by Roediger and McDermott, 1993). Finally, this variation of the word-stem completion task is thought to introduce novel demands for strategic processing at test that are not present at study, and previous investigations of older adults have linked the ability to meet those demands to performance on neuropsychological tests of frontal lobe status (Nyberg et al., 1996; Winocur et al., 1996). Thus, the apparent differences between the DAT participants' results in the current study as compared with Backman et al. (2000) may be due to the different tasks used to measure implicit memory, and more importantly, to the resulting differences in the processes and brain regions that were the locus of repetition-related change.

The present results demonstrate clear preservation of repetition-related activity reductions in frontal cortex regions associated with controlled verbal processing and repetition-related reductions in young adults—a finding that may seem counterintuitive, given that frontal brain regions and associated controlled processes show age-related decline (Hasher and Zacks, 1979; Head et al., 2004; Hedden and Gabrieli, 2004; Jennings and Jacoby, 1993; Moscovitch and Winocur, 1995; Raz et al., 1997, 2000; Salat et al., 2004; West, 1996). The focus here was on prefrontal brain regions strongly associated with controlled verbal processing and repetition-related reductions in young adults (e.g., Buckner et al., 1995, 2000a; Demb et al., 1995; Dobbins et al., 2004; Gabrieli et al., 1996; Raichle et al., 1994; Wagner et al., 1997, 2000), and used a task that often leads to relatively preserved priming effects in old age and DAT (see re-

views by Fleischman and Gabrieli, 1998; LaVoie and Light, 1994; Light et al., 2000b; Rybash, 1996). As noted above, studies focusing on different processes and brain regions may yield different results. Of relevance, patients with frontal lobe damage often show performance patterns similar to those of older adults: somewhat slower and more error-prone initial performance, but relatively preserved priming (e.g., Gershberg, 1997; Swick, 1998; but see Swick and Knight, 1996).

Preserved priming in patients with frontal lobe damage and older adults may be related to compensatory recruitment. Older adults in the present study tended toward greater overall activation of frontal cortex in comparison to young adults (see reviews of similar findings by Cabeza, 2002; Park et al., 2001; Reuter-Lorenz et al., 2001). The frontal regions showing greater recruitment by the older adults included right frontal cortex, which is not strongly associated with controlled verbal processing in young adults, but which can show increased activation in patients with damage to left frontal regions due to stroke (e.g., Buckner et al., 1996; Rosen et al., 2000). Priming effects for this region were similar to those found for the left frontal regions. We therefore speculatively propose that at least some of the repetition-related effects associated with priming are fundamentally preserved even in populations with frontal cortex damage due to age, dementia, or lesion. To the degree that initial performance can be maintained by relying either on relatively intact brain regions or via compensation, repetition-related reductions may also be maintained. Thus, although the initial recruitment of frontally mediated controlled processes may be more difficult for older adults, the effects of repetition may still parallel those observed in young adults: a reduced need for controlled, strategic processing, resulting in reduced frontal activity and response times.

Taken together, these findings may have implications for designing environmental modifications and training programs to maintain and improve the performance of older adults and possibly other clinical populations. For the groups observed here, the neuroimaging findings help to localize the benefits of repetition to a reduced need for frontally mediated, controlled processing, rather than a nonspecific facilitation of early perceptual or motor processes. In combination with previous behavioral and neuropsychological findings, this suggests that manipulations that reduce the need for such controlled processing by recapitulating task structure, rather than only items, may have the best chance of improving the performance of older adults both with and without dementia. This suggestion may also apply to patients with frontal lesions, who often show patterns of spared and impaired performance similar to those shown by older adults. In addition, the similar changes in frontal activation across the three groups observed here imply that despite age- and dementia-related physiologic changes in frontal brain regions, these regions retain some plasticity and are amenable to, or benefit from, experience-based change. Such preserved plasticity raises the intriguing possibility that appropriately designed cognitive training regimens with older adults could also lead to change and facilitation of frontally mediated controlled processing per se (c.f. Jennings and Jacoby, 2003).

In summary, the present study found that preserved priming in old age and early stages of dementia is associated with preserved modulation of brain regions that are involved with relatively high-level, controlled stages of information processing. Furthermore, the quantitative relation between modulations of brain activation in these regions and changes in behavior was of a similar strength across all three groups. Frontally mediated controlled processes, and the neural activity patterns underlying them, thus appear amenable to experience-based change in old age and early-stage dementia, making them attractive targets for cognitive training and rehabilitation.

Table 1. Demographic and Performance Variables

	Young (n = 34)	Old (n = 33)	DAT (n = 24)
Female/Male	16/18	21/12	8/16
Age[a]	22.3 (3.5)	78.3 (9.1)	76.3 (6.6)
Education (yr)		14.3 (0.6)	13.7 (2.9)
MMSE[b]		28.9 (1.2)	25.7 (3.3)
WAIS information[b]		20.7 (4.8)	17.0 (5.6)
WAIS block design[b]		31.0 (9.1)	24.7 (12.2)
WAIS digit symbol[b]		47.2 (10.4)	35.3 (13.4)
Boston naming[b]		54.7 (5.0)	49.8 (7.9)
Word fluency (S + P)[b]		33.4 (12.6)	25.0 (9.5)
WMS mental control[b]		7.7 (1.4)	6.4 (2.1)
WMS digit span (backwards)[b]		5.2 (1.3)	4.1 (1.0)
WMS logical memory[b]		9.4 (4.2)	6.4 (3.2)

Note: means and standard deviations (in parentheses) for demographic and performance variables. MMSE, Mini Mental State Examination; WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale. Variables with values for all three groups were analyzed using one-way ANOVA followed by post hoc t tests. Variables with values only for the older adult groups were analyzed using independent sample t tests

[a] Significant difference between young and old, $p < 0.05$. [b] Significant difference between old and DAT, $p < 0.05$.

Experimental Procedures

Participants

Ninety-one people participated. Clinical, demographic, and behavioral data are presented in Table 1. Young adults (age 18–34 yr) were Washington University students or staff. Older adults (age 61–93 yr) were recruited from the Washington University Alzheimer Disease Research Center (ADRC) and classified using the Clinical Dementia Rating (CDR) scale (Morris, 1993) as being without dementia (CDR = 0) or in the early stages of DAT (20 participants with CDR = 0.5, 4 participants with CDR = 1). One older adult without dementia did not complete the full battery of standardized tests, and of those scores only contributed data to WAIS Digit Symbol. Although a number of our DAT participants had cognitive test scores that might qualify for classification as mild cognitive impairment (MCI), a CDR score of 0.5 or greater in this sample is highly predictive of Alzheimer disease, both in clinical progression and neuropathologic diagnosis at autopsy (Morris et al., 2001). All testing was conducted within guidelines established by the Washington University Human Studies Committee.

Behavioral Procedure

After structural imaging, but prior to the study reported here, participants completed a separate experiment consisting of two block-design runs of a semantic classification task on novel words (Lustig et al., 2003). This was followed by an unscanned recognition test, during which participants were presented with words from that previous experiment, intermixed with new words, and asked to indicate which were old and which were new. Recognition data were lost from one young adult. The recognition test was followed by a short

(12 items) unscanned version of the semantic classification task to reorient participants to this procedure.

The data forming the basis of the current paper were collected in two rapid event-related runs following this reorientation. For each run, participants first completed a prescan study phase during which they made semantic classification judgments on visually presented words. An event-related fMRI run followed, during which semantic judgments of new words and words repeated from study were randomly intermixed with baseline fixation trials (design similar to Buckner et al., 1998; Koutstaal et al., 2001).

During the semantic classification task, participants indicated whether words represented living or nonliving entities. Each word was presented for 2000 ms, followed by a 500 ms intertrial interval consisting of a fixation crosshair. A fiber-optic button press was used to collect responses (right button for living and the left button for nonliving). In the prescan study phase, 12 words (6 living, 6 nonliving) were each repeated 3 times, for a total of 36 trials. Words were randomly intermixed, with the restriction that no word could be repeated until all words had been presented.

Each functional run began with 10 s of passive fixation to allow MR signal stabilization, and ended with 10 s of passive fixation to allow capture of the full hemodynamic response. In between, participants were presented with 36 semantic classification trials using 36 new words (New condition, N), 36 classification trials using the 12 words repeated from the prescan study phase and each repeated three times during the run (Repeated condition, R), and 36 passive fixation (Fixation, F) trials. Repeated, new, and fixation trials were randomly intermixed with first-order counterbalancing such that each trial type followed all trial types an equally often. Trial orders were further counterbalanced across participants within each group (i.e., if participant 1 had order R-N-F, participant 2 had order N-F-R, and participant 3 had order F-R-N) to allow subtraction to cancel out the effects of hemodynamic overlap across adjacent trials (see Dale and Buckner, 1997; Buckner et al., 1998). Words were counterbalanced across participants within a group such that repeated items for one participant were new items for another participant.

Imaging Methods

Images were collected using a 1.5T Siemens Vision scanner (Erlangen, Germany). Cushions, a plastic face mask, and headphones were used to reduce movement, dampen scanner noise, and communicate with the participant. Stimuli were projected (AmPro model LCD-150) onto a screen at the head of the bore and viewed via a mirror attached to the head coil. Participants were fitted for MR-compatible lenses based on autorefractor readings (Marko Technologies model 760A) and subjective report of improved acuity. Participants not in need of vision correction wore plain lenses without refraction.

Each scanning session began with a scout image to center the field of view on the brain, followed by a high-resolution ($1 \times 1 \times 1.25$mm) structural T1-weighted MPRAGE sequence (TR = 9.7 ms, TE = 4 s, flip angle = 10°, TI = 20 ms, TD = 200 ms). Functional acquisitions were obtained using an asymmetric spin-echo sequence sensitive to blood oxygenation level dependent (BOLD) contrast (TR = 2.5 s, T2* evolution time = 50 ms, 180 offset = −25 ms). Each functional run acquired 116 sequential whole-brain image acquisitions (168 mm thick contiguous slices, 3.75×3.75 mm in-plane resolution, aligned to the anterior-posterior commissure plane). To increase hemodynamic sampling, for each participant, one run was synced to begin at the onset of the TR, while the other was synced to begin after a 1250 ms delay (Miezin et al., 2000). The order of delayed versus nondelayed runs was counterbalanced across participants.

Imaging Analysis

Functional data were first preprocessed to correct for slice timing, odd/even slice intensity differences, head movement, and differences in whole-brain intensity using procedures similar to Logan et al. (2002). Individual subject data were transformed into stereotaxic atlas space (Maccotta et al., 2001; Talaraich and Tournoux, 1998) and resampled to 2 mm^3 isotropic voxels. To help compensate for structural differences associated with aging, the atlas-representative target image was composed of a merged young-adult/older-adult reference (Snyder et al., 2002). The atlas-transformed image for each subject was checked against a reference average to ensure appropriate registration. As a final preprocessing step, linear slope was removed on a voxel-by-voxel basis to counteract effects of drift, and data were spatially filtered using a one-voxel radius Hanning filter. After preprocessing, selective averaging techniques described previously were used to extract the deconvolved hemodynamic response (Dale and Buckner, 1997; Buckner et al., 1998). Eight mean images and their variance were retained for each trial type (one image for each 2.5 s TR, for a total response window of 17.5 s). Three trial types were included: New words, Repeated words, and Fixation. Estimates of the hemodynamic response for the New and Repeated word trials were obtained by subtraction of the Fixation response.

Hypothesis-directed analyses were initially conducted at a regional level to explore effects of repetition between- and within groups. The a priori regions of interest were defined on a separate large sample of young adults pooled across several studies of intentional memory encoding (Konishi et al., 2001) (see Logan et al. [2002] for prior use of these regions). Regions are labeled by their approximate Brodmann area (BA) based on the Talairach and Tournoux (1988) atlas. Locations of peak activation served as region seed points, and regions were defined to include all significantly activated voxels within 12 mm. The left frontal regions (left BA 45/47, *x*, *y*, *z* peak location −45, 29, 6 and left BA 44/6, −43, 3, 32) are often activated during controlled processing tasks using verbal materials. Control regions in visual (BA 17/18, left and right 17, −96, 3) and motor (BA 4, left and right 37, −25, 50) cortex were also defined for both the left and right hemisphere and averaged to obtain bilateral regions. These left frontal and control regions were chosen because they correspond to those targeted for analysis in previous neuroimaging studies of priming in young adults (e.g., Buckner et al., 1995; 2000a; Maccotta and Buckner, 2004; Raichle et al., 1994; Wagner et al., 1997; 2000). An additional, right frontal region (right BA 44/6, corresponding to the homologous left BA 44/6, with peak location 43, 3, 32) was also included because of interest in possible group differences in bilateral recruitment (e.g., Logan et al., 2002; see reviews by Cabeza, 2002; Park et al., 2001; Reuter-Lorenz et al., 2001).

Regional magnitude estimates were computed separately for each participant by averaging the time courses for each voxel included in the region. Magnitude estimates for statistical analyses were computed by subtracting the average of the first and last two points in the time course (0, 15, and 17.5 s after trial onset, respectively) from a time point approximating the peak of the hemodynamic response (5 s after trial onset). Magnitude estimates for each individual were then entered into group comparisons based on a mixed-effect model, treating participants as a random variable (Figures 2 and 5).

In addition to the hypothesis-directed regional analyses, exploratory map-wise analyses were performed using a fixed-effect analysis. Exploratory activation maps were computed by averaging together the selectively averaged maps of trial-related activity for each participant within a group, and then extracting the z statistic maps comparing timecourses for New versus Fixation, Repeated versus Fixation, and New versus Repeated (similar to Buckner et al., 1998; Wagner et al., 1998). Trial-related activity was modeled using a set of predicted hemodynamic curves with variable onset delays (γ functions, delay range 1–8 s relative to trial onset). These activation maps illustrate each group's activation patterns across the experimental conditions. However, apparent differences between the groups should not be quantitatively interpreted; differences in sample size and variance will influence the appearance of activity in threshold-based maps between groups (Buckner et al., 2000b; Huettel and McCarthy, 2001). For this reason, quantitative values and contrasts between groups should only be interpreted for the unbiased, a priori regions described earlier.

Acknowledgments

We thank Katherine O'Brien for assistance in data collection and Luigi Maccotta and Abraham Snyder for discussion. The Washington University ADRC including John Morris, Martha Storandt, Elizabeth

Grant, and Amy Buckley provided valuable assistance with participant recruitment, clinical evaluation, and psychometric data. This work was supported by NIH grants AG05886, AG05681, AG03991, AG00030, and P50 AG05681, the Howard Hughes Medical Institute, the Alzheimer Association, and the James S. McDonnell Foundation. C.L. also received support from a Richard and Mildred Poletsky Education Award. Reprints should be requested from Cindy Lustig (clustig@artsci.wustl.edu).

Received: November 25, 2003
Revised: April 8, 2004
Accepted: April 22, 2004
Published: June 9, 2004

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