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# Neurocognitive ageing of storage and executive processes

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Converging behavioural and neuropsychological evidence indicates that age-related changes in working memory contribute substantially to cognitive decline in older adults. Important questions remain about the relationship between working memory storage and executive components and how they are affected by the normal ageing process. In several studies using positron emission tomography (PET), we find age differences in the patterns of frontal activation during working memory tasks. We find that separable age differences can be linked to different cognitive operations underlying short-term information storage, and interference resolution. Some operations are associated with age-related increases in activation, with older adults displaying bilateral activations and recruiting prefrontal areas more than younger adults. Other operations are associated with age-related decreases in activation. We consider the implications of these results for understanding the working memory system and potential compensatory processes in the ageing brain.

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Baddeley's model of working memory postulates separable storage and executive components (Baddeley, 1986, 1992). The storage buffers are generally viewed as relatively passive, "slave" systems operating in the service of the executive processing components that mediate coding, manipulation, and selection of stored contents. A major focus of neurocognitive research on working memory is to define the neural and cognitive operations that underlie storage and executive processes and to specify the functional relationship between these components of the working memory system. This agenda has important implications for advances in cognitive ageing research because alterations in working memory play a central role in age-related cognitive decline (Engle, Kane, & Tuholski, 1999; Park et al., 1996; Salthouse, 1992; Salthouse & Babcock, 1991; Zacks, Hasher, & Li, 2000). There is broad agreement in the cognitive ageing literature that basic measures of short-term storage ability, as indexed by digit span and item recognition tasks, are less affected by ageing than working memory tasks that draw heavily on executive processing components, such as the reading span and operation span tasks (Babcock & Salthouse, 1990; Craik & Jennings, 1992; Dobbs & Rule, 1989; Salthouse, 2000; Salthouse & Babcock, 1991). Thus, on the face of it, ageing appears to honour the distinction between storage and processing components of the working memory system by affecting the latter disproportionately.

This apparent behavioural dissociation could result from any of several different neurobiological substrates. Most obviously, it could be that ageing selectively affects the neural operations associated with executive processing while sparing storage operations. If so, ageing would provide evidence for the structural and functional independence of these components of the working memory system. Furthermore, evidence that ageing affects only the processing components of the working memory system would challenge the idea that cognitive ageing effects stem from a unitary, globally acting mechanism (e.g., Salthouse, 1992).

An alternative account for the disproportional effects of age on tasks requiring executive processing turns on the notion of selective compensation (cf. Cabeza et al., 1997; Grady et al., 1992). It may be that both storage and executive processes decline with age. However, during simple retention tasks executive operations can be recruited to compensate for storage decline, thereby ameliorating storage deficiencies.[1] Once enlisted

[1]According to some models, storage capabilities are inherent to the executive processes that are mediated by dorsolateral prefrontal cortex (DLPFC) (e.g., Cohen, Botvinick, & Carter, 2000; Goldman-Rakic, 1987). For example, Cohen and his colleagues propose that executive control entails the modulation of attentional and response processes by stored information about task demands (Cohen et al., 2000).



in the service of storage, however, executive operations are less available for other more demanding cognitive operations thereby accentuating impairments on executive processing tasks. According to this hypothesis, ageing affects multiple components of the working memory system at the level of neural substrate, but at the level of behaviour the effects appear selective. Note that these two hypotheses need not be mutually exclusive. Ageing could indeed have a disproportional effect on executive processes but to the extent that such operations remain functional they may be recruited to compensate for declining storage operations.

Evaluating these hypotheses will require defining the cognitive operations that mediate storage and executive processing demands, identifying the neural mechanisms and loci that implement these operations, and determining the structural and functional integrity of these mechanisms in the ageing brain. Towards these goals we have conducted a series of experiments on working memory in older adults (Jonides et al., 2000; Reuter-Lorenz et al., 2000). One of the key results to emerge from this work is that older and younger adults differ markedly in their patterns of frontal activation, while displaying similar patterns of activation in posterior cortical areas. We find that separable age differences can be linked to different cognitive operations underlying short-term information storage, and interference resolution. Some operations are associated with age-related increases in activation, with older adults displaying bilateral activations and recruiting prefrontal areas more than younger adults. Other operations are associated with age-related decreases in activation. Here we consider the implications of these results for understanding the working memory system and potential compensatory processes in the ageing brain. Before describing our work in detail, we highlight some of the evidence from primates and human patients with prefrontal lesions. These lines of work provide additional constraints on the localization and functional organisation of the working memory system that can inform our interpretation of the age-related changes we have observed.

## FRONTAL CONTRIBUTIONS TO DELAYED RESPONSE PERFORMANCE: LESION EVIDENCE

Impaired delayed response performance has been traditionally associated with prefrontal damage. Variants of this task have become part of the canon of working memory research. It appears however that prefrontal lesions have different effects on delayed response performances in monkeys and in humans. Here we briefly review these differences and suggest several ways they may be instructive about the mechanisms of working memory.

Jacobsen's classic experiments (1931) on the delayed-response performance in monkeys were among the first to reveal the importance of prefrontal cortex to mnemonic processes. Basically, the delayed response task requires the monkey to view one of two identical stimuli (e.g., food wells) being baited with a reward, to retain this information while the stimuli are briefly hidden from view, and then to retrieve the reward. Thus, as in the item recognition task to be discussed later, a limited amount of information must be retained over a delay of only several seconds. The spatial delayed response task and certain of its variants are exquisitely and selectively sensitive to damage to the lateral regions of prefrontal cortex in monkeys, namely the caudal territory of the principal sulcus which corresponds to Brodmann's area (BA) 46/9 in humans (Goldman-Rakic, 1987; Petrides, 1994). This task would therefore seem to hold great promise in revealing the secrets of frontal lobe functions. Yet, despite its simplicity, the precise role of dorsolateral prefrontal cortex in the delayed response task in monkeys is still debated (see, e.g., Goldman-Rakic, 1998; Petrides, 1998).

In the human lesion literature, the link between prefrontal cortex and delayed response performance is less remarkable. In a recent review D'Esposito and Postle (1999) found significant delayed response deficits from prefrontal lesions in only three out of eight conditions[2] (across six different studies). Prefrontal deficits were more robust when the delay period was filled with distraction, in which case five out of seven conditions across five different studies yielded reliable differences between frontal patients and intact controls. As D'Esposito and Postle point out, the discrepancies among the human studies could be due to differences in task parameters, such as memory set size, delay period, material type, and response demands. In addition, the extent, loci, and aetiology of frontal lesions differ greatly among the patients in these samples, and thus lack the precision and uniformity of the primate studies.

But the species difference in delayed response deficits may stem from other factors as well. One important possibility is the laterality of prefrontal damage. The experimentally produced prefrontal cortex (PFC) lesions in monkeys typically are bilateral whereas the human lesion patients usually have damage confined to one hemisphere or the other. To the extent that both hemispheres can mediate working memory processes, human patients with unilateral prefrontal damage could

[2]A condition here refers to whether the delayed response test used spatial or non-spatial materials. D'Esposito and Postle (1999) categorise their meta-analytic observations with respect to test type and lesion subgroup (e.g., invading or sparing 46/9).



perform the tasks using the intact hemisphere. Two additional pieces of information are consistent with this suggestion. First, a comparison of patients with unilateral and bilateral frontal lobe excisions revealed more pronounced deficits in the two bilateral patients (Owen, Sahakian, Semple, Polkey, & Robbins, 1995). In the face of excellent simultaneous matching performance, the bilateral patients showed dramatic deficits when matching consecutively presented visual-spatial displays at a delay of 0 ms (Owen et al., 1995). The unilateral groups showed delayed matching deficits but only at delays of 4 s or more. Lesion size could have contributed to this difference assuming that the bilateral lesions were larger than the unilateral lesions. Nevertheless, the effects are consistent with the possibility that the differences between monkey and human studies may stem from compensation by the intact hemisphere in human patients.

The second relevant fact is that three of the four studies (Chao & Knight, 1998; Ptito, Crane, Leonard, Amsel, & Caramanos, 1995; Verin et al., 1993) for which D'Esposito and Postle find significant delay response deficits report that lesion side has no impact on the magnitude of the deficit. This is also true of lateralised groups studied by Owen et al. (1995). This lack of asymmetry suggests functional overlap of the left and right prefrontal regions, and potential compensation by the intact hemisphere in cases with unilateral damage. Here again is a caveat to bear in mind. These tasks may have made minimal demands on putative "material-specific" processors. For example, the spatial delayed response tasks used by Verin et al. and by Ptito et al. were modelled closely on those used with monkeys and required the retention of a single location. Likewise, Chao and Knight used a single sound, and Owen used a single pattern. Had the memory load (or other task demands) been greater, lesion side may have played a greater role thereby reflecting the limits of compensation from intact brain regions (for a review see Jonides et al., 1996).

Human lesion studies, particularly the older ones, do not provide precise information about the contributions of different frontal subregions in the delayed response task. One notable exception is the report by Ptito et al. (1995), in which patients were subgrouped according to whether or not their excision included Brodmann's area 46. Indeed, only those patients with involvement of 46 showed deficits relative to normal controls in the unfilled delay condition. Although this result is consistent with the monkey work, the excisions involving area 46 appear to be larger than those that do not (see Ptito et al., 1995, Figure 1). The possibility remains, then, that involvement of some other PFC subregions underlie impaired performance in this group. Fortunately, the roles of frontal subregions in the human brain can be addressed by functional

neuroimaging studies of delayed-response type tasks using PET and fMRI. We turn now to consider this body of work.

## FRONTAL CONTRIBUTIONS TO WORKING MEMORY

### Neuroimaging evidence

Neuroimaging studies have left no doubt that prefrontal regions are engaged when humans perform delayed-response type tasks. Several recent reviews, based largely on positron emission tomography (PET) studies of healthy young adults, reach the same conclusion: tasks that require the simple retention of up to four items, and test memory with a yes/no recognition test, activate one or more sites within Brodmann's area 6 as well as ventral prefrontal areas including Brodmann's 44, 45, and/or 47 (for reviews see Cabeza & Nyberg, 2000; D'Esposito et al., 1998; Smith & Jonides, 1999). The pattern of laterality is orderly, with a predominance of left-sided activation in these areas, particularly areas 6 and 44 (Broca's area), for verbal tasks, and right-sided activation, particularly areas 6 and 47 for spatial location memory. Several groups have proposed that these regions mediate the maintenance or storage components of working memory in conjunction with parietal sites in Brodmann's areas 40 and 7 (e.g., D'Esposito, Postle, Ballard, & Lease, 1999; Owen et al., 1999; Smith & Jonides, 1997).

Of interest is the fact that significant activation of dorsolateral prefrontal sites, 46 and 9, is relatively rare in studies requiring simple retention. It is now widely believed, however, that when executive demands are increased, by requiring that the stored items be manipulated in some way, by recoding them or monitoring and tracking contextual codes, then dorsolateral prefrontal (DLPFC) sites are engaged (e.g., Cabeza & Nyberg, 2000; Owen et al., 1999; D'Esposito, Postle, Ballard, & Lease, 1999; Petrides, 1998; Smith & Jonides, 1999; see also D'Esposito et al., 1995). There are also indications that DLPFC involvement is increased by lengthening the retention interval (Barch et al., 1997) or by increasing the memory load to supraspan levels (i.e., greater than five for verbal items; Rypma & D'Esposito, 1999; Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999). There is some contention however about the laterality of DLPFC activation in relation to the type of material being employed in the working memory task. Studies that have directly compared well-matched verbal and spatial analogues of the same working memory task have found the expected left-right differences, although activations tend to be more broadly bilateral (e.g., Smith, Jonides, & Koeppe, 1996). This asymmetry is not always found however (e.g., D'Esposito et al., 1998), making the functional lateralisation of DLPFC operations a topic of ongoing investigation, and one that may be particularly relevant to ageing, as we shall see.



### A summary

To summarise, the precise role of prefrontal cortex in delayed response and item recognition tasks is a matter of some debate. Bilateral damage to DLPFC in primates leads to frank and robust disruption, whether or not the retention interval is filled. Unilateral prefrontal lesions in humans (which may or may not include DLPFC) have more detrimental effects when interference occurs during the retention intervals. Some functional overlap between left and right prefrontal subregions is suggested by the inconsistent effects of unilateral damage, and by the absence of a clear laterality effect when deficits do emerge. For basic storage tasks, neuroimaging studies reveal fairly reliable patterns of hemispheric dominance for verbal and nonverbal materials in ventrolateral prefrontal and premotor areas. There is little evidence for DLPFC activation for loads less than five, with several indications that this area is recruited for higher loads and/or longer delays. The evidence for DLPFC activation is highly consistent for tasks that include additional processing and manipulation of stored items (i.e., executive demands), with a tendency toward bilateral activations under these conditions. Thus, the picture in young adults is that DLPFC does not have an obligatory role in short-term retention as measured by delayed response and item recognition tasks. With these considerations in mind, we turn to our own neuroimaging evidence addressing the neural substrate of working memory in the ageing brain.

## AGEING AND THE NEURAL SUBSTRATE OF WORKING MEMORY

In one of the first neuroimaging studies to examine the effects of age on verbal working memory, we found striking differences between older and younger adults. The participants were 16 older adults between the ages of 65 75, and 8 younger adults aged 21 30. All were females. After a session of practice, PET images were obtained for each subject in a memory task in which subjects viewed four uppercase letters, retained them for 3 s, and then responded manually to indicate whether a lowercase probe letter matched or did not match one held in memory (Sternberg, 1966). Subjects were also scanned while performing a minimal memory control task that was matched for perceptual and response requirements (see Figure 1; see Reuter-Lorenz et al., 2000 for a detailed

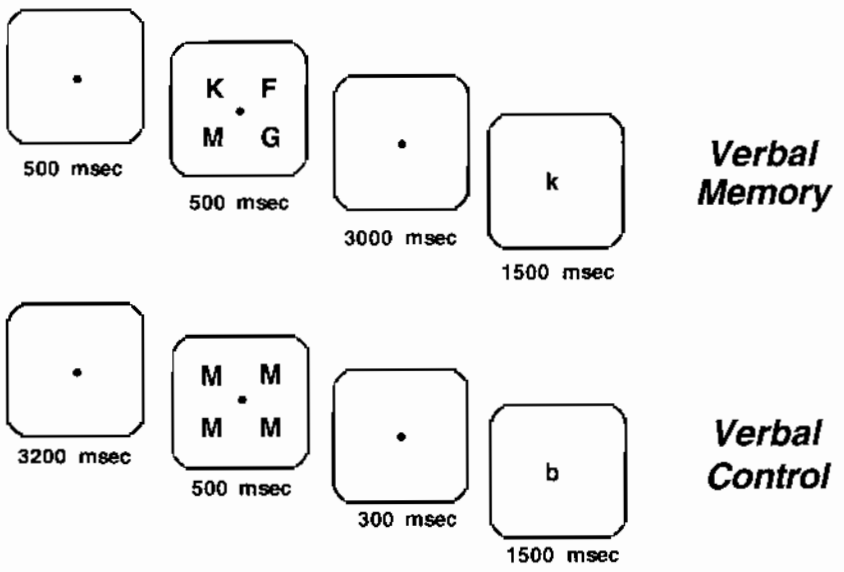


**Figure 1.** Cognitive tasks. Sequence of events and timing parameters for the verbal memory task and the minimal memory control. See Reuter-Lorenz et al. (2000) for more details.

description of methods). As expected, older adults had longer response latencies than younger adults on both tasks. For both groups control accuracy was at ceiling. The older adults were, however, less accurate than the younger adults on the memory task (92% vs 97%: $p < .02$).

Several different analyses were performed on the imaging data. First, we used a region of interest analysis to determine that the memory-related activations in the younger group were characteristic of previous results from our lab obtained with a similar task in young adults. Indeed, the regions of significant activation in our earlier study (see Smith et al., 1996), left 44 (Broca's area), left 6 (supplementary motor area), and left parietal sites in Brodmann's areas 7 and 40, were again active in our new sample of young adults. Moreover, the older adults showed reliable activation in each of these regions as well. Thus, there was an excellent correspondence between the left hemisphere areas activated in a verbal short-term retention task in younger and older adults.

However, visual inspection of the PET activation images and several additional analyses revealed a pronounced age difference (see Reuter-Lorenz, 2000, Figure 6.3): Older adults showed greater activity in the



right hemisphere than the younger group, particularly in frontal regions. Even the most conservative analysis[3] revealed right 46/9 as one of the most active sites in older adults (see Reuter-Lorenz, et al., 2000, Table 2). We also devised additional analyses specifically to examine age differences in laterality of activations using documented evidence of the working memory circuitry. We compiled a corpus of active sites from published reports of verbal working memory tasks. Spherical volumes 1.5 cm in diameter were created around each reported peak pixel, and then a sister volume was created with the homologous coordinates in the opposite hemisphere. This allowed us to identify activation asymmetry (or its absence) throughout the working memory circuitry in both hemispheres for each age group.[4]

This circuitry analysis revealed significant activation in posterior regions including parietal areas 40 and 7 that was highly left lateralised in both younger and older adults. However, the differences in anterior asymmetry were striking. Overall, the older group activated the left and right anterior components of the working memory circuitry whereas younger adults showed only left hemisphere activation. A regional analysis indicated that the two RH areas that were uniquely activated in the older group were 44 ($p = .02$) and 46/9 ($p < .0004$; see Reuter-Lorenz et al., 2000, Table 3). These data were the first to indicate age differences in the lateral organisation of the verbal working memory circuitry.

We have since had the opportunity to replicate these results with a new group of older adults and here we report the results from this replication. Once again we used a four-item letter recognition task. One aim of this experiment, which we discuss later, was to examine age differences in resolving interference from prepotent responses (Jonides et al., 2000).

[3] $Z$-tests were performed on each pixel of the difference image resulting from the subtraction of the control image from the memory image. This analysis is conservative because it is entirely post hoc and requires corrections for numerous multiple comparisons.

[4] A set of 85 regions of interest (ROIs) was derived from published reports of peak pixels active during PET studies of verbal working memory tasks, including our own (see Reuter-Lorenz et al., 2000, Figure 2). The majority of these regions were in the left hemisphere and include frontal sites in Brodmann's 45, 46, 10 and 9, 44 (Broca's area), 6 (premotor and supplementary motor sites), parietal sites in areas 40 and 7, and temporal sites in 42 and 22. Spherical volumes were constructed around reported peak pixels, replicated in the symmetrical location in the opposite hemisphere, and then applied to each subject's memory-minus-control subtraction images, thereby permitting a comparison of the average activation changes across homologous regions. To assess differences in asymmetry in the front and back of the cortex, an anterior subset ($n = 34$) was defined in Talairach space as those ROIs with a $y > 0$ and a posterior subset ($n = 33$) with $y < -10$ and $z > -10$. The same approach was used to define spatial ROIs (see later) using a set of 98 regions from the published literature (see Reuter-Lorenz et al., 2000, Figure 2).

This required that in some conditions the probe item was familiar and thus highly associated with a "yes" response, while requiring a "no" response on that trial. Except for this manipulation and the fact that the memory set appeared on the screen for 750 rather than 500 ms, the task was the same as that used in the original ageing study reported by Reuter-Lorenz et al. (2000). There were 12 male participants in each age group (younger 19–30 years; older 61–72 years). Again, the older adults were significantly slower (e.g., 815 ms versus 683 ms for "yes" responses, $p < .001$) and slightly less accurate than the younger group (95% and 99% respectively, $p < .03$).[5] Our original ageing study armed us with a set of predicted sites of activation (ROIs) that could now be tested in a new sample of older adults, and we could test for age differences by applying them to the new group of young adults as well. Both age groups showed significant activation in the left hemisphere sites typically associated with verbal storage including supplementary motor area and parietal areas 40/7. However, only the older group showed activation in right 46/9 ($p < .008$). The younger group did not have reliable activation at this site.

The circuitry analysis based on working memory ROIs from the published literature again confirmed that younger adults activated prefrontal sites only in the left hemisphere, whereas older adults showed significant activation in prefrontal sites bilaterally. In this data set, the older group actually activated left 44 less than the younger group, while showing greater activation of right 44 (see Figure 2). The younger adults did not activate DLPFC in either hemisphere, whereas the older group showed marked right-sided activation in this site (see Figure 3). Unique to this replication experiment is the finding that older adults tended to activate left and right parietal sites in 40 and 7, whereas for younger adults activation in these regions was highly left lateralised.[6]

This pair of experiments demonstrates that in addition to activating the

[5]See Jonides et al., 2000 for detailed performance analyses. As we discuss subsequently, older adults performed more poorly than young adults in the high interference condition. However, only young adults showed a significant difference in activation between the high and low interference conditions which was exclusive to Brodmann's area 45 in the left hemisphere (Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998, Jonides et al., 2000). Therefore, the activation analyses we present here are from the average of the high and low interference conditions. For all of the analyses we report, the same patterns are also evident in each interference condition (versus the minimal memory control condition) alone.

[6]The subset of published ROIs that fell within Brodmann's areas 40 and 7 (see Reuter-Lorenz et al., 2000) was associated with 1.5% activation change in the left hemisphere ($p < .02$) and 0.3% change in the right hemisphere for younger adults. This left/right difference was significant ($p < .03$). For older adults there was 0.9% change in the left hemisphere and 0.8% in the right, both of which differed from zero ($p < .025$) and did not differ from each other.



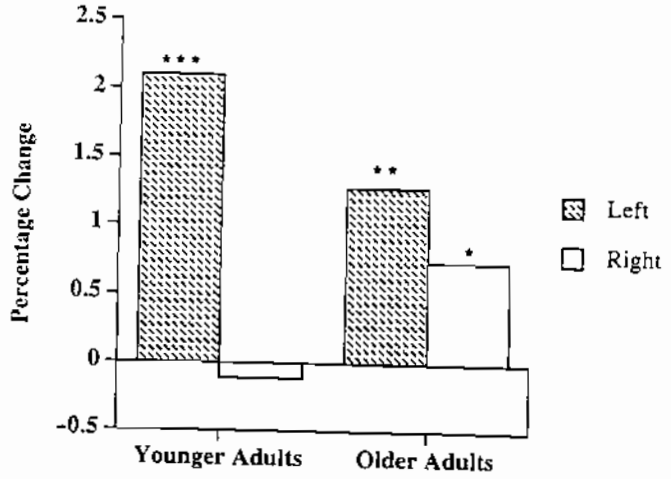


**Figure 2.** Working memory induced activation changes in Brodmann's area 44. Graph depicts percentage change in activation for the memory minus control subtractions in regions of interest falling within Brodmann's area 44. Asterisks denote significance levels when comparing activation changes to zero using one-tailed tests: * = $p < .06$; ** = $p < .001$; *** = $p < .0001$. The graph illustrates lateralised activation in 44 for younger adults but bilateral activation for older adults— left vs. right $t$-tests for younger and older respectively: $t(11) = 5.46$, $p = .0002$; $t(11) = 0.85$, $p > .20$. Younger adults activated left 44 more so than the older group, $t(22) = 1.63$, $p = .05$, whereas the opposite was true for right 44, $t(22) = 1.69$, $p = .05$.

canonical LH areas involved in short-term verbal storage, older adults activate several RH regions as well. One of these areas, DLPFC, is largely associated in young adults with working memory tasks that explicitly require executive processing operations in addition to storage. As noted earlier, two other manipulations have been shown to influence the magnitude of DLPFC activation in young adults in the context of working memory tasks. First, Barch et al. (1997) reported that lengthening the delay interval increased the magnitude of DLPFC activation, whereas visually degrading the memory items increased task difficulty but did not affect DLPFC. Second, Rypma and D'Esposito (1999) report an increase in the magnitude of right DLPFC activation as memory load increased from two to six items. Using an event-related fMRI design, they were able to isolate this load-dependent effect to the encoding phase of the trial. Thus, DLPFC involvement in younger adults appears to be modulated by load and storage duration manipulations. By specifically increasing the working memory demands, these manipulations could conceivably recruit executive operations such as attentional selection, contextual coding, or both.

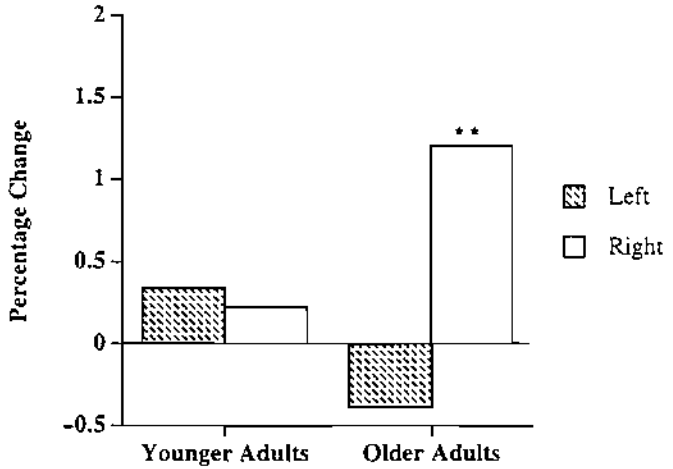


**Figure 3.** Working memory induced activation changes in dorsolateral prefrontal region. Graph depicts percentage change in activation for the memory minus control subtractions in regions of interest falling within Brodmann's areas 46/9. Asterisks denote significance levels when comparing activation changes to zero using one-tailed tests: ** = $p < .007$. Older adults show highly lateralised right-sided activity, whereas younger adults do not reliably activate this area in either hemisphere. The difference in the magnitude of right dorsolateral prefrontal cortex activation for older versus younger adults is reliable, $t(22) = 1.94$, $p = .03$.

These possibilities are important for our interpretation of right DLPFC activation in older adults. Their slower response times and reduced accuracies imply that older adults find these tasks more demanding than do younger adults. This difference in effective task difficulty could be driving the recruitment of DLPFC in older adults. In other words, in the ageing brain a memory load of four items retained for 3 s may be functionally equivalent to the same load at a longer delay or a greater load (six or more) at the same delay in the younger brain. Normally, DLPFC is recruited to meet these greater demands, and that is what we observe in older adults.

Our hypothesis, then, is that older adults recruit executive processes at lower levels of task demand than do young adults. By this account the additional sites of activation that we observe in older adults constitute a compensatory response to the age-related increase in task difficulty. Consistent with this proposal is the fact that combining the samples of older adults from both studies we find a significant inverse correlation between the magnitude of right DLPFC activation and response time ($r^2 = 0.143$; $p = .05$; see Figure 4). There was a non-significant trend toward a positive correlation between right DLPFC and right 44 activation ($p = .08$), although only the former was statistically related to performance.[7]



Several age-related changes could effectively increase task demands for older adults, such as decreased efficiency of rehearsal processes and increased vulnerability to interference. Indeed we have reason to think that both factors could be at work when older adults are performing

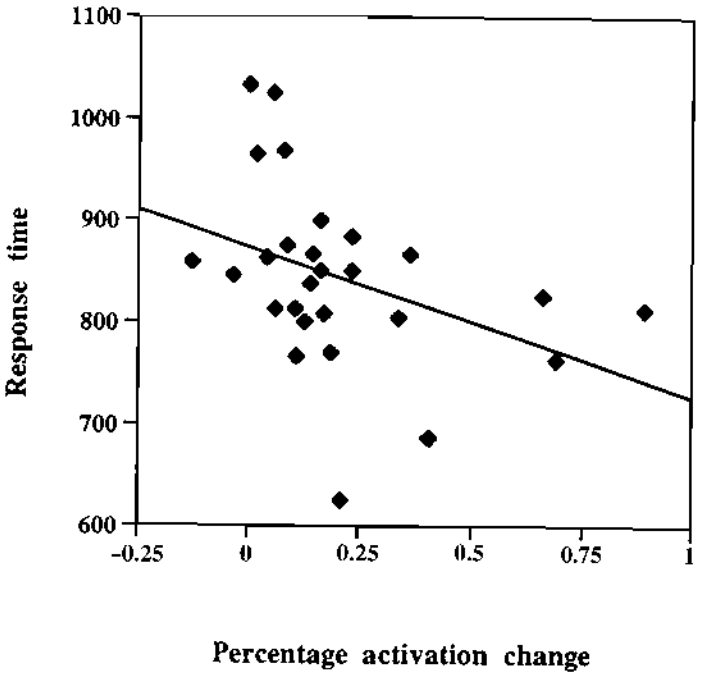


**Figure 4.** Scatter plot with regression line relating response times to the percentage activation change (verbal working memory vs minimal memory control) in right dorsolateral prefrontal cortex in older adults. The data include the set reported by Reuter-Lorenz et al. (2000) and those reported in the present paper.

[7]Using fMRI, Rypma and D'Esposito (2000, this issue) have found less DLPFC activity in older than younger adults at high memory loads (six items). This difference may stem from age differences in hemodynamic coupling (D'Esposito, Zarahn, Aguirre, & Rypma, 1999), although Rypma and D'Esposito (this issue) have developed new analysis methods to reduce this possibility. Nevertheless, Rypma and D'Esposito find that higher DLPFC activation in older adults is associated with better performance, a result that converges nicely with the pattern reported here.

these working memory tasks. Activation of right 44 could result if this right hemisphere homologue of Broca's area is recruited in the service of rehearsal in the older brain. This suggestion is motivated by several observations. Evidence indicates that left 44 contributes to overt and covert articulatory processes (e.g., rehearsal; Awh et al., 1996). There are also numerous indications that RH regions are capable of assuming some language functions of their LH counterparts (e.g., Baynes, Wessinger, Fendrich, & Gazzaniga, 1995; Kinsbourne, 1971). This compensatory potential is evident after early brain damage (e.g., Muller et al., 1999), and after LH injury occurring later in life (e.g., Buckner, Corbetta, Schatz, Raichle, & Petersen, 1996). Likewise, ageing may reveal the latent potential for RH compensation of certain language functions. Moreover, animal models of plasticity and recovery of function indicate that homologous regions in the opposite hemisphere provide a crucial substrate for functional compensation (see Nudo, 1999).[8]

On the other hand, DLPFC may be critical for modulating at least some forms of interference. Recall from our earlier review of the lesion literature that prefrontal damage including DLPFC is particularly detrimental when interference is high. Conceivably then, the DLPFC activation that we see in older adults may represent increased attention to rehearsal processes or contextual coding operations that can mitigate adverse effects of interference to which older adults are more prone (e.g., May, Hasher, & Kane, 1999). Although these suggestions are speculative they are clearly amenable to experimental analysis and our future studies will aim to test these hypotheses.

## AGEING AND RESPONSE INTERFERENCE IN VERBAL WORKING MEMORY

Interference can arise from such varied sources as environmental input, irrelevant or no-longer relevant memory traces, or competing response tendencies. Prefrontal subregions may contribute differentially to resolving interference from these various sources. We have recently linked one particular site in ventrolateral prefrontal cortex (left 45) to the resolution of interference from prepotent responses (Jonides et al., 1998). Moreover, we have found that older adults are especially vulnerable to this form of interference and they are deficient in their activation of left 45 (Jonides et al., 2000).

This experiment used the basic letter recognition task with an important variation. Negative trials, requiring a "no" response, could be of two types. For "recent-negative" trials, the probe was a member of the memory set on the previous trial. Therefore it was highly familiar and had recently been associated with a "yes" response. As an example, the memory set on trial $n-1$ could consist of M, R, K, D and the set on trial $n$ would consist of F, B, S, C. As a recent-negative probe for trial $n$, "k" would be familiar because of its membership in set $n-1$, but requires a "no" response. Recent-negatives were the predominant negative trial type in the high-recency condition (high interference). "Non-recent-negative" probes, on the other hand, had not been members of a memory set for at least the two prior trials. This type of negative trial defined the low-recency condition (low interference). Both younger and older adults required more time to reject recent-negative probes than non-recent negatives, but for older adults the difference between these conditions was disproportionately greater suggesting that it posed a particular challenge to them.

To identify the neural substrate associated with the processing of nonrecent compared to recent negative probes, blocks of trials with a preponderance of one trial type or the other were compared using PET. This analysis revealed a single site of activation in area 45 in prefrontal cortex that was present in younger adults but absent in their older counterparts (Jonides et al., 1998, 2000). We have proposed that this site is involved in processes that reduce response-related interference in younger adults, and that the inability to recruit this region by older adults contributes to their poorer performance.

The precise contribution of left 45 and its role in interference resolution is not yet known. However, event-related fMRI results from this task in younger adults (D'Esposito, Postle, Jonides, & Smith, 1999) indicate that area 45 activation emerges in the retrieval epoch of the task associated with the presentation of the probe. This temporal localisation implicates left 45 in mediating competing response tendencies and suggests that older adults have difficulty with this form of interference resolution. A related possibility is that area 45 is involved in resolving conflict between a familiarity code and a temporal code that, in the case of recent-negative probes, would lead to opposite responses.

[8] In both of these observations plasticity and compensation are associated with the frankly compromised functioning of specialised regions. Our original study (Reuter-Lorenz et al., 2000) showed equivalent activation of Broca's area in younger and older adults. However, in the follow-up study reported here weaker left 44 activation was coupled with stronger right 44 activation in older compared to younger adults. It is conceivable that the global physiological, metabolic, and structural alterations that are part of the normal ageing process (e.g., Haug, 1997; Woodruff-Pak, 1997) compromise the efficiency of rehearsal mechanisms to an extent that can promote the recruitment of additional neural units in right 44. Accordingly, other lines of work have documented age-related reductions in left hemisphere dominance (i.e., greater bilaterality) for language with behavioural and electrical measures (see Bellis, Nicol, & Kraus, 2000).

It is interesting to note that, under the conditions where we observe an age-related absence of activation in area 45, we find that older adults are activating right DLPFC and right 44 to a greater extent than the younger group. This was established by our earlier comparisons of the high and low recency conditions to the minimal memory control condition (see earlier). The activations associated with these two levels of interference did not differ from each other in older adults, and, as described in the previous section, both were associated with significant activation of the right hemisphere homologues of the verbal working memory circuitry. These results suggest that rather than mediating verbal response inhibition *per se*, these right hemisphere regions may be contributing to contextual coding, attentional selection, or other processes that may be associated with working memory storage.

## AGEING AND THE LATERAL ORGANISATION OF WORKING MEMORY

Our results indicate that ageing is accompanied by an alteration in the left lateralisation of neural activity associated with verbal working memory. As we noted previously, activation tends to be more bilateral in younger adults for high levels of working memory demand. The increased right anterior activation in our older group could reflect the same type of recruitment seen in the younger brain but at lower levels of task demand. Alternatively, the age differences in laterality could reflect adverse or compensatory changes that are unique to the ageing process. Whatever their functional significance, reports of age-related changes in the pattern of lateralised activity are becoming increasingly common.

For example, with a location recognition task (a variant of the spatial-delayed response task) we have shown an age difference in laterality that parallels that found in our work on verbal memory (Reuter-Lorenz et al., 2000). Designed as the spatial analogue of the verbal memory tasks, each trial consisted of a display of three dots at semi-random locations around a fixation cross. Subjects held these locations in mind for 3 s and, when the probe circle appeared, subjects indicated whether or not the probe encircled one of the remembered target locations. Region-of-interest analyses established that, as in previous work from our laboratory (Smith et al., 1996), the younger group showed a predominance of activation in parietal areas 7 and 40, and in right supplementary motor area (Brodmann's area 6) and ventral PFC (Brodmann's area 47). The older group also displayed significant activation in these areas; however as in the verbal study, their activation was more bilateral. Specifically, older adults significantly activated left supplementary motor area, and left



DLPFC (see footnote 4). It is noteworthy that the left DLPFC activation is nearly homologous to the right hemisphere activation in the verbal task. We cannot yet explain this paradoxical pattern of DLPFC asymmetry in the older group. The net result, however, is that tasks that produce asymmetrical activation in younger adults activate a bilateral network of prefrontal areas in older adults.

Other laboratories have also reported age differences in patterns of lateralised activity. Grady and her colleagues have found greater left DLPFC activation in older than younger adults in a short-term retention task using faces as the to-be-remembered items (Grady et al., 1998). This left-sided activation was coupled with less right ventrolateral prefrontal activity in the older than the younger group. In a series of studies on episodic memory, Cabeza and his colleagues (Cabeza, Anderson, Mangels, Nyberg, & Houle, 2000; Cabeza et al., 1997) found greater frontal bilaterality in older adults than younger adults have during the retrieval phase. Madden et al. (1999) have found a similar pattern in a semantic memory task. Outside the domain of memory, greater bilaterality in older adults has been found in a go/no-go task (Nielson, Garavan, Langenecker, Stein, & Rao, 2000) using fMRI, and in a phoneme processing task using ERPs (Bellis et al., 2000).

Do these age-related alterations in laterality have a common basis despite their emergence in seemingly diverse tasks? Do they stem from compensatory recruitment of additional brain regions or from a breakdown in inhibitory interactions between the two hemispheres? Definitive answers to these questions await future research. There are several reasons, however, to interpret these changes as compensatory. First, in our verbal working memory studies we find that activation of right DLPFC is positively correlated with performance speed among older adults. Similarly, in the spatial working memory task, the older adults were selected so that their level of accuracy was at least as good as the young adults in our sample. None the less, the older adults showed more bilateral anterior activation than the younger group. Second, the review of the human lesion literature presented in the introduction to this paper suggests functional overlap in the contribution of left and right prefrontal cortex to working memory, which could provide a substrate for compensation.

Another indication that bilateral activation is beneficial to older adults comes from our investigation of age-differences in a visual-matching task (Reuter-Lorenz, Stanczak, & Miller, 1999). This task was first developed by Banich and her colleagues (Banich, 1998; Belger & Banich, 1992) to examine the cognitive functions of interhemispheric interactions and the corpus callosum. Banich has shown that for easy matching tasks (e.g., smaller set size, physical identity match), young adults perform better

when the matching letters are presented to the same visual field (i.e., hemisphere) than when they are presented to different hemispheres. However, as the match gets more complex (by including more letters or making the match more abstract) performance is better when the letters are presented to different hemispheres. We reasoned that if older adults benefit from engaging both hemispheres at lower levels of difficulty than do young adults, the bilateral presentation condition should be more advantageous for them. Indeed, this is what we have found. Older adults showed a performance advantage in the bihemispheric condition relative to the unilateral condition at lower levels of task difficulty than did the younger adults (Reuter-Lorenz et al., 1999; Reuter-Lorenz & Stanczak, 2000). The integrity of interhemispheric interactions in these matching tasks argues against the idea that changes in laterality result from a general decline in callosal function or impaired inhibition between the hemispheres with age (see Reuter-Lorenz & Stanczak, 2000). Instead, the ageing brain seems to benefit from engaging bilateral circuitry, as does the younger brain for higher levels of task demand.

## CONCLUDING REMARKS

Our neuroimaging evidence suggests that for both verbal and spatial tasks that require simple storage, older adults recruit different brain areas with a greater bilateral distribution than do their younger counterparts. These differences occur even in the face of comparable accuracy levels suggesting that older adults achieve optimal performance by way of an altered neurocognitive route. We have proposed that older adults recruit executive processing operations controlled in part by DLPFC to mediate attentional or contextual coding operations, thereby bolstering their ability to meet the storage demands of the task. Yet, there are good reasons to believe that these executive operations are themselves vulnerable to ageing and will therefore be limited in the compensation they can offer. First, DLPFC is particularly vulnerable to age-related atrophy (Raz, 2000). Moreover, the greatest age-differences have been documented on tasks that draw heavily on executive operations (Fabiani & Wee, in press; Moscovitch & Winocur, 1995). It follows from our hypothesis that the disproportional decline in working memory tasks with explicit executive processing demands has at least two sources. Structural decline of DLPFC coupled with a compensatory role in storage tasks could severely limit the capacity of DLPFC to meet such demands. The compensatory application of executive mechanisms may exact a price on other tasks.

In conclusion, we have offered several hypotheses about the relationship between executive processing and storage components of the working memory system and the effects of ageing on this system. Although admittedly speculative, these hypotheses are testable. Clearly, the next decade of cognitive neuroscience promises to yield valuable new insights into the mechanisms of normal ageing. Likewise, studies of ageing should continue to raise important questions about the structure of the cognitive system and the life-long potential for plasticity, compensation, and neurocognitive reorganisation.



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