Age-related changes in brain–behaviour relationships: Evidence from event-related functional MRI studies

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A fundamental aim of studies in neurocognitive ageing is to understand age-related changes in brain–behaviour relationships. Neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) can be used for observation of these age-related changes only if the assumption of age-equivalent relations between neural activity and haemodynamic activity is valid. In one study, we characterised age-related differences in the coupling of the haemodynamic response to neural activity and found greater voxel-wise noise in older than in younger adults, but age-equivalent signal magnitude. These results suggested that alternative techniques may be necessary for analysing age-related differences in neuroimaging data. In a second study, we utilised one alternative method for comparing fMRI activation between younger and older adults performing a working memory (WM) task. Across three experiments, the results suggested that age-related functional changes in fMRI activation can be isolated to dorsolateral prefrontal cortex (PFC) during memory retrieval. These results suggest a plausible model for WM decline with normal ageing. In a third study we propose and test a model of age-related PFC dysfunction that may account for these and other age-related differences in cognitive performance.

A fundamental aim of studies in neurocognitive ageing is to understand how the ageing brain mediates age-related changes in the performance of cognitive tasks. The advent of neuroimaging techniques such as PET and fMRI permits more direct observation of these age-associated changes in the brain than has been possible in the past. Thus, hypotheses developed through behavioural comparisons of younger and older adults, and older
normal adults with older neurological patients (such as those with Alzheimer’s or Parkinson’s disease and focal brain injury; e.g., Gabrieli, 1991, 1996), may now be further tested and extended (Gabrieli & Rypma, 1997; Prull, Bunge, & Gabrieli, 2000; Raz, 2000; Rypma & Gabrieli, in press). The proposal that insights regarding age-related changes in cognitive performance may be gained from data acquired through functional neuroimaging techniques implies that the relationship between changes in neural activity with advancing age and changes in performance with advancing age must be examined directly.

Most neurocognitive ageing studies have tended to focus on age-group differences in mean or median neural activity and performance (a relatively distal level of analysis). Less emphasis has been placed on individual-subject variability in these measures or the relationships between them (a relatively proximal level of analysis; cf. Salthouse, 1991). Thus, age-related differences in activation have not been consistently linked to increases or decreases in cognitive performance. Regions of increased activity in older adults, relative to younger adults, have been observed in a number of studies using PET and fMRI (e.g., Cabeza et al., 1997; Grady et al., 1995; Reuter-Lorenz et al., 2000; Rypma, Prabhakaran, Desmond, & Gabrieli, 2000). Reuter-Lorenz, Marshuetz, Jonides, Smith, Hartley, and Koepppe (this issue) review studies that show age-related increases in activity that have been accompanied by age-equivalent performance in some cases (Cabeza et al., 1997), and age-differential performance in others (Reuter-Lorenz et al., 2000, this issue). Reuter-Lorenz and her colleagues (Jonides et al., 2000, and Reuter-Lorenz et al., this issue) have observed a third relationship between performance and neural activity, age-related reductions in PET activation associated with reduced cognitive performance in elderly relative to young. Such divergent patterns of results suggest that the relationship between neural activity and performance is quite complex. We propose that such complex relationships may be better understood by examining the relationship between neural activity and performance at the level of individual subjects; understanding the neural factors that underlie age-related changes in performance may best be approached by the study of individual differences in brain–behaviour relationships. There are at least two methodological requirements of this relatively proximal analysis level.

One requirement is that fMRI analytic methods must afford valid comparisons of neural activity between younger and older adults. Although it may seem trivially obvious, this requirement has proven extremely difficult to satisfy. For instance, many current methods of analysis assume that physiological consistencies exist between the individuals or groups under analysis. There are reasons to doubt the viability
of this assumption however. The ageing brain undergoes dramatic changes involving global volume, synaptic density, oxygen uptake, and microvascular organisation. These assumptions are critical for valid observation of age-related changes in neural activity because many extant analysis methods use a common estimate (e.g., a gamma function or a Poisson function) of the haemodynamic response to model neural activity in both groups. In this paper, we will review evidence from our own laboratory, and from the laboratories of others, that suggests that the assumption of common haemodynamic response properties may be untenable. In the context of our own studies of age-related differences in neural activity, we will illustrate one method we have used (Rypma & D'Esposito, 2000) that permits circumvention of the assumption of common haemodynamic response properties.

The second methodological requirement of this proximal analysis level is the use of fMRI data collection methods that permit isolation of neural activity to particular task components (and thus, cognitive processes). Cognitive tasks used in neuroimaging experiments generally require a number of component cognitive processes. For instance, delayed-response tasks are comprised of at least three cognitive operations: encoding, maintenance, and retrieval of to-be-remembered information. There is behavioural evidence to suggest the importance of analysing neural activity in each of these task components. Burke and Light (1981), for instance, reviewed a broad literature on age differences in each of these component memory processes. Their analyses implicated retrieval deficits as a principal source of the age-related performance differences observed in memory tasks. Indeed, data from our laboratory suggests that some brain regions appear exquisitely sensitive to changes in performance specifically during memory retrieval and not other task components (Rypma & D'Esposito, 1999, 2000).

In this paper, we will first review data that address the assumption, implicit in many studies of age differences in cortical activity, that relationships between neural activity and haemodynamic activity are age-equivalent. These data have suggested to us one alternative analytic method that increases our confidence in the validity of our comparisons between younger and older adults. Second, we will review studies from our laboratory in which we have applied these alternative analytic methods in conjunction with event-related fMRI to more precisely interpret age-related differences in our fMRI data. From these data we have proposed a model of age-related changes in brain–behaviour relationships that we will test further using parallel distributed processing (PDP) modelling techniques.
TESTING HAEMODYNAMIC EQUIVALENCE ASSUMPTIONS IN YOUNGER AND OLDER ADULTS

Observation of neural activity during cognitive performance using fMRI and some forms of PET depend critically on the reliability of haemodynamic responsiveness to neural activity. The haemodynamic response is the basis for blood-oxygen level dependent (BOLD) contrast fMRI. It is the change in fMRI signal that results from a brief (i.e., <1 s) period of neural activity (e.g., Aguirre, Zarahn, & D’Esposito, 1998). Accordingly, the haemodynamic response has been carefully studied and characterised as a function that is delayed in onset and evolves over a 10–12 s period following neural activity (e.g., Aguirre et al., 1998; Blamire et al., 1992). Studies of age-related differences in the neural substrates of cognitive processes (those studies that quantitatively compare changes in fMRI signal intensity across age groups), in turn, rely upon the assumption of age-equivalent coupling of neural activity to fMRI signal in time and space. As was stated previously, there are reasons to question this general assumption. First, histological studies of cerebral microvasculature have demonstrated considerable age-related variability in the organisation of intercerebral arterioles, capillaries, and venules. Fang (1976), for instance, observed age-related increases in the winding, coiling, and number of “blind-ends” in the cerebral vascular microlattice, most notably in the arteriole-venous-capillary bed. Because the BOLD fMRI signal has been shown to have a significant contribution from the capillary bed (Menon et al., 1995), these age-related differences in vasculature could conceivably produce age-related differences in BOLD fMRI signal responsiveness. Differences in experimentally induced fMRI signal change between younger and older subjects are indicative in general of differences in neural activity only if the coupling between neural activity and fMRI signal does not change with age.

In one study, we tested this assumption by measuring the temporal and spatial characteristics of the fMRI haemodynamic response in younger and older subjects to equivalent neural input (D’Esposito, Zarahn, Aguirre, & Rypma, 1999). Differences in the haemodynamic response between age groups in either time or space would indicate a failure of the assumption that the coupling of neural activity and haemodynamic activity are age-equivalent. In this study, random samples drawn from a young population (ages 18–32) and an older population (ages 65–82) were subjected to identical behavioural paradigms while being scanned with BOLD fMRI. The behavioural paradigm was a simple reaction time task that involved a visually cued, bilateral button press every 16 s. Therefore, the spatial characteristics (i.e., where the stimulus was to appear and what kind of movement would be required) and the temporal characteris-
tics (i.e., when the visual cues for movement appeared) were predictable. These task characteristics make tenable the assumption that neural activity was not different between younger and older subjects. We believe that this is a reasonable assumption for two reasons. First, movement-related electrical potentials in younger and older adults, recorded at a central scalp electrode, appear to be similar under conditions such as those present in our paradigm (Cunningham, Iansek, Bradshaw, & Phillips, 1995). Second, there is neuropathological evidence that primary motor cortex does not exhibit significant neuronal loss in normal ageing (Haug, 1997).

Analyses of the behavioural data from this experiment indicated that accuracy rates for younger (100%) and older subjects (98.9%) were similar. Older subjects’ mean reaction time (414.8 ms), however, was significantly slower than that of younger subjects (368.1 ms). Three observations were made from the neuroimaging data. First, 32/32 (100%) of the young subjects exhibited suprathreshold activity in an anatomically defined region of interest (ROI) comprising primary sensorimotor cortex (along the central sulcus), whereas only 15/20 (75%) of the older subjects exhibited suprathreshold activation in the analogous region. Moreover, there was a significantly greater number of suprathreshold voxels in the central sulcus ROI of the younger compared to that of the older subjects (median of the young = 30.5 voxels; median of the older = 6.0 voxels; U = 60.5; p < .0001). This difference in spatial extent of activation could not be explained by age-related differences in the search-region volume. These search regions were slightly larger in the older (M = 385 voxels) group than in the younger group (M = 364 voxels).

For each subject, estimates of noise variance (i.e., the denominator of the F statistic), signal variance (i.e., the numerator minus the denominator of the F-statistic), and their ratio (i.e., signal : noise) were made from the time series of suprathreshold voxels. From this analysis, the second major observation was that the voxel-averaged noise magnitude was significantly greater in the older subjects than in the young (U = 125; p = .009), but signal magnitude was not (u = 194; p = .29). As expected from these results, the signal : noise ratio was significantly greater in the young than in the older group (median of the young = 7.6; median of the older = 5.9; U = 107; p = .002; Figure 1). Examination of the averaged power spectra from the suprathreshold voxels showed that the increased noise in the older over the younger subjects was greater in the lower than higher frequencies (Figure 1).

The third major observation was that of apparent age-related differences in the shape of the haemodynamic response function. Specifically, we tested the trial-averaged time series (from single, randomly chosen voxels) for age differences in shape and magnitude. This test was imple-
mented using a multivariate analysis of variance, which, for a basis-set of Fourier coefficients, compared the variability within each age group to the variability between age groups (with variability pooled across Fourier coefficients). A comparison of the within-group variability in the haemodynamic responses between the younger and older groups revealed no significant difference, $F(84, 186) = 1.18, p = .17$. The between-groups test yielded a trend towards a difference between young and older groups in the shape and scaling of the haemodynamic response, $F(6, 270) = 2.06, p = .06$. The individual and across-subject average haemodynamic responses (with each subject contributing the time series of one randomly selected voxel) for the older and the younger groups are presented in Plate 1. (The colour plate section is situated between pages 240 and 241. Online readers click here.)

One way to interpret the results of this study is to assume that the spatio-temporal pattern and intensity of neural activity in the vicinity of the central sulcus is the same between the populations from which the young and older groups were sampled (Cunnington et al., 1995; Haug, 1997). Given this assumption, any difference between groups in the

![Figure 1](image-url)

**Figure 1.** The average power spectra for the younger ($N = 32$) and older ($N = 20$) subject groups. For each group, frequency in Hertz is plotted on the x-axis and power (squared fMRI signal amplitude) is plotted on the y-axis. For both groups the spectrum is an average across subjects of the within-subject average spectra (across all suprathreshold voxels). It can be seen that the power at the fundamental frequency of the behavioural task (marked by the arrow) is nearly identical in the two groups. The greatest disparity between noise in the younger and the older groups is at the lowest frequencies, although the noise tends to be greater in the older group throughout the spectrum.
spatial and temporal fMRI results would be attributable to differences in haemodynamic coupling between neural activity and BOLD fMRI signal change and/or other factors that can affect the BOLD fMRI signal (such as motion). There are a few possible explanations for changes in coupling between neural activity and BOLD signal in normal ageing. One hypothesis would be that age differences in the spatial properties of the vascular bed (Fang, 1976) cause changes in the spatial properties of this coupling. Another hypothesis would link vascular pathology (known to increase with normal ageing; Bohl & Hori, 1997) with spatial extent of this coupling.

The reduced spatial extent of fMRI activation we observed in the older subjects suggests that age-related comparisons of task-related fMRI activation using traditional statistical parametric mapping (SPM; Friston, 1994/1995) methods cannot be expected to yield age-equivalent fMRI activation in the presence of age-related neural activity. This is because, following the application of a Gaussian smoothing kernel, the intensity value of a given voxel will be a function of the intensity value of adjacent voxels, in addition to the intensity value of the given voxel. Thus, differences in the spatial extent of activation translate into differences in intensity after spatial smoothing of the imaging data. To illustrate this point, we performed a group analysis on our data and observed greater “activation” in primary sensorimotor cortex in the younger subjects as compared to the older subjects (Figure 2). If the results of Cunnington et al. (1995) are reliable, and evoked potentials are a reliable measure of spatially averaged neural activity, then this is an example of a positive fMRI result in the presence of a null neural result.

In addition to the differences in spatial extent between groups (in those subjects who had a detectable fMRI response), the observation that there was a substantial proportion of subjects in the older group who did not evince detectable responses bolsters the conclusion of the previous paragraph. That is, it is not likely that these subjects had no neural activity near the central sulcus associated with the button presses. Rather (based on Cunnington et al.’s 1995 results), it seems more likely that there was a greatly weakened, or perhaps non-existent, coupling between neural activity and fMRI signal in these subjects.

The implication of our finding that greater levels of noise per voxel may be observed in older compared to younger adults is that inferences based on statistical maps that rely on scaling of signal components by noise will yield potentially erroneous results in quantitative comparisons of younger and older adults. Several scenarios are possible (see Plate 2—colour plate section situated between pages 240 and 241; online readers click here). For instance, one is in an inferentially ambiguous situation if comparison of brain activity in younger and older adults yielded less
activation in the older, compared to the younger subjects across the entire statistical map, but no greater activation in the older compared to the younger (see Plate 2, scenario 1). In this scenario, it is possible that the observed age-related differences are not due to differences in signal intensity per se, but rather to other non-neuronal contributions, i.e., age-related differences in haemodynamic coupling. One may be on more solid inferential ground under circumstances where greater activation is observed in the older compared to the younger group (see, e.g., Grady, 1996; Rypma et al., 2000), at least in some regions (see Plate 2, scenario 2). In this scenario, it is unlikely that regional variation in haemodynamic coupling would account for such age-related differences in activation patterns. In a third possible scenario (see Plate 2, scenario 3), a different pattern of activation between groups (that is, new brain regions are activated in older individuals that are not active in younger individuals during performance of the same cognitive task) can be seen. This pattern
could indicate some fundamental change in functional organisation with advanced age. It may also indicate compensatory mechanisms if it is accompanied by an improvement in performance over conditions where the activation is not present. Of course, any combination of these scenarios is also possible.

Our study of the haemodynamic response in normal ageing indicated that the magnitude of voxel-wise task-related signal *per se* was not detectably different between the age groups, nor was the shape of the average haemodynamic response. The implication of this finding is that more accurate inferences about age differences in cortical activity may come from analyses of the signal component of fMRI data, separate from the noise component.

**STUDIES OF AGE-RELATED DIFFERENCES IN NEURAL ACTIVITY WITHOUT THE ASSUMPTION OF AGE-EQUIVALENT HAEMODYNAMICS**

In a series of studies, we have implemented analyses that examined age-related differences in cortical activity that accompany age-related differences in cognitive performance. In one study, we (Rypma & D’Esposito, 2000) used an event-related fMRI design to explore the relative roles of dorsal and ventral PFC regions during specific components (Encoding, Delay, Response) of a WM task under different memory-load conditions. Our interest was in testing the hypothesis that age-related changes in the PFC may be the source of WM decline in normal ageing.

Evidence from behavioural and neuroimaging studies together suggests that the neural basis of age-related WM performance decline may be related specifically to age-related changes in one region of PFC, the dorsolateral region, whereas ventrolateral PFC regions may remain relatively unaffected by ageing. In behavioural research it has been observed that minimal age differences nearly always occur in memory-span tasks that do not involve delay components (e.g., Botwinick & Storandt, 1974; Bromley, 1958; Craik, 1968; Friedman, 1974; Gilbert & Levee, 1971; Taub, 1973). When memory demand is increased by (1) the imposition of delays between information encoding and retrieval, or (2) increases in the amount of information that must be maintained over a delay period, however, age-related declines in performance are often observed (Anders, Fozard, & Lillyquist, 1972; Craik, 1977; Marsh, 1975; Nielsen-Bohlman & Knight, 1995; Poon & Fozard, 1980; Smith, 1975). In neuroimaging research it has been observed that patterns of activity in PFC change with (1) increasing delay intervals (e.g. Awh et al., 1996) and (2) increases in the amount of information that must be maintained over
a delay interval (Rypma & D'Esposito, 1999, 2000; Rypma & Gabrieli, in press; Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999). Specifically, low memory-demand conditions (e.g., maintenance of two or three letters) involved mainly ventrolateral PFC, whereas high memory-demand conditions involved dorsolateral PFC, in addition to ventrolateral PFC.

Behavioural studies demonstrating age differences in WM maintenance when memory loads exceed capacity, and neuroimaging studies demonstrating functional subdivisions of PFC in conditions under which age-related behavioural differences are observed, led us to hypothesise that the neural basis of age-related WM performance declines may be related specifically to age-related changes in dorsolateral, but not ventrolateral, PFC. Results from three experiments, described next, provided evidence to support this hypothesis.

In the first study, six younger subjects (mean age = 25.0) and six older community-dwelling subjects (mean age = 68.8) underwent fMRI while performing a delayed response WM maintenance task (see Figure 3) in which, on each trial, they first encoded either two or six letters, presented for 4 s; second, retained them across an unfilled 12-s interval; and, third, determined, within 2 s, whether or not that letter was part of the memory set. A 16-s intertrial interval that allowed fMRI signal to return to baseline followed each trial. We used an event-related fMRI design that allowed us to examine separately age-related differences in neural activity associated with stimulus encoding, memory maintenance, and memory retrieval during the WM task.

In our event-related design, least-squares parameter estimates were

Figure 3. The trial sequence of the behavioural task. On each trial, subjects first encoded either two or six letters (in principal experiments and replication experiment 1), presented for 4 s. Second, they retained the letters across an unfilled 12-s interval. Third, a single letter appeared on the screen and subjects determined, within 2 s, whether or not that letter was part of the memory set. A 16-s intertrial interval followed each trial.
derived (for each subject) by modelling the hypothesised change in neural activity at each period of the task (Encoding, Delay, Response). Hypothesised neural activity in each task period was modelled with covariates comprised of blood-oxygen-level dependent (BOLD) haemodynamic response functions shifted in time to model activity at each task period. Details of this method can be found in, e.g., Zarahn, Aguirre, and D’Esposito (1997; see also Postle, Zarahn, & D’Esposito, 2000). The haemodynamic response function (HRF) used to construct the covariate was derived empirically for each subject from the (neuroanatomically defined) sensory-motor cortex (Aguirre et al., 1998). We assessed our hypotheses of age-related differences in PFC neural activity with random-effects tests of age-differences in the mean parameter estimates (i.e., the beta values derived from the least-squares solution of a linear model of the dependent data) that characterised fMRI signal during each task component. These parameter estimates were not scaled by the model error term (which would typically be used to obtain $t$-statistics for each voxel). This method avoided use of the noise component of fMRI signal since, in the study presented earlier, we observed reliable age-related differences in the noise component which could lead to the spurious inference of age-related differences in intensity of neural activity.

In the principal experiment, performance data indicated that subjects performed with high accuracy that did not differ between the two memory load conditions. Reaction times (RT) were faster in the two-letter than in the six-letter condition. Performance accuracy was not significantly different between younger and older subjects but younger subjects were faster than older subjects. Analyses of imaging data revealed no significant age-related differences in ventrolateral PFC regions, collapsed across hemispheres, in either of the memory load conditions during any of the task periods (i.e., stimulus encoding, retention interval, and response). In dorsolateral PFC, there were no significant age-related differences in regional activation during the encoding period and the retention period. Younger subjects, however, showed significantly greater activation than older subjects in the six-letter condition, during the response period (Mann-Whitney $U$, $p = .01$; Figure 4). No other effects reached significance (all $p$s > .10).

Similar to findings from our earlier study (Rypma & D’Esposito, 1999) with young adults, we observed considerable intersubject variability in fMRI signal in PFC in older adults. We therefore sought to further explore our findings of age group differences in dorsolateral PFC activity in terms of individual differences between subjects in the younger and older groups. To formally test relationships between cortical activity and performance, we performed regression analyses of subjects’ RT and PFC activity (indexed by mean parameter estimates in dorsolateral and
ventrolateral PFC in each task period). Tests of the regression coefficients that characterise the relationship between mean RT and ventrolateral PFC activity were nonsignificant. In dorsolateral PFC in younger subjects, response period regression coefficients showed a significant positive correlation (slope = .85, $p < .03$) between mean RT and cortical activity that accounted for 71% of the variance. In contrast, in dorsolateral PFC in older subjects, response period regression coefficients showed a significant negative correlation (slope = −.85, $p < .03$) between mean RT and cortical activity.
RT and cortical activity that accounted for 72% of the variance. These relationships are presented in Figure 5a.

It is important to note that our finding of significant age-related differences in fMRI signal in dorsolateral PFC cannot be attributed to differences in HRF coupling for at least two reasons. The first and most obvious is that our measurement of neural activity was based on parameter estimates (which index age-invariant fMRI signal components independent of age-variable noise components) derived from our regression analyses. This method permitted us to circumvent those aspects of fMRI signal that appear to vary with age. Second, the hypothesis that this result could be attributed to age differences in HRF coupling would seem to require that it was observed in all task periods, not just during the retrieval period (that is, haemodynamic coupling would not be expected to vary as a function of cognitive factors).

These results are intriguing because they suggest that the pervasive age-related slowing observed across many different kinds of widely divergent behavioural tasks may result from a fundamental change in brain–behaviour relationships with age. Our proposal is that changes in the relationship between neural activity and performance that we observed in these data reflect an age-related decrease in neural efficiency. This age-differential neural efficiency provides a plausible neural mechanism for age-related changes that are observed in performance. It may be that age-

Figure 5. Scatter plots of the normalised regional mean parameter estimates during the response period in dorsolateral PFC plotted against normalised RTs in younger subjects (squares, principal exp. (a): slope = .84, \( r^2 = .71 \), \( p < .03 \); replication. exp. 1 (b): slope = .87, \( r^2 = .76 \), \( p < .01 \); replication exp. 2 (c) = .88, \( r^2 = .78 \), \( p < .05 \)) and older subjects (diamonds, principal exp. (a): slope = –.85, \( r^2 = .72 \), \( p < .03 \); replication exp. 1 (b): slope = –.82, \( r^2 = .68 \), \( p < .04 \); replication exp. 2 (c) slope = –.87, \( r^2 = .76 \), \( p < .03 \)).
related changes in a specific region of the brain, dorsolateral PFC, may lead to a generalised age-related slowing of behaviour.

For such an argument to be plausible prima facie would seem to require that two minimal conditions be met. The first requirement is that this result would replicate with a different group of subjects performing a similar task. The second requirement is that this result would generalise to a different group of subjects performing a different kind of cognitive task. We therefore sought evidence for these two conditions in two subsequent experiments.

To test the replicability of our findings, we performed these analyses in a second experiment with a different group of six younger and six older subjects performing the same working memory task as was described previously. Analyses of the data from replication experiment 1 indicated that response period regression coefficients in dorsolateral PFC showed a significant positive correlation (slope = .87, \( p < .01, r^2 = .76 \)) between mean RT and cortical activity in younger subjects but a significant negative correlation (slope = – .82, \( p < .04, r^2 = .68 \)) between mean RT and cortical activity in older subjects (Figure 5b). No such correlations were observed in ventrolateral PFC.

To assess the generalisability of these findings, similar analyses were performed on data from a third group of younger and older subjects performing a different WM task (replication experiment 2). In this task, subjects initially viewed a series of three objects that sequentially appeared in three distinct locations in a 3 x 3 grid followed by an 8-s retention interval. Memory load was varied by requiring subjects to encode and maintain either two features (i.e., an object in a location) or only one feature (i.e., an object or a location). A test probe then appeared for 2 s, followed by a 12-s intertrial interval. On object trials, the test probe was a black and white object in the centre of a grid; subjects responded “yes” if the probe corresponded to a studied item on that trial and “no” if it did not. On location trials, the test probe was a black dot in one of the grid cells (other than the centre) and participants responded “yes” if it appeared in a location that an object had occupied on that trial and “no” if it appeared elsewhere. On combination trials, a black and white object appeared in one of the periphery cells and participants responded “yes” if the test probe corresponded exactly to a studied object/location pairing and “no” if it did not. Distractor items in this condition were always re-pairings of objects and locations from the current trial. The results indicated a replication of our main finding. Specifically, we observed (1) greater cortical activity in younger than in older in dorso- \( (U = 3.0, p = .05) \) but not ventrolateral PFC, and (2) significant patterns of RT–fMRI signal correlations that were positive for the younger age group (slope = .88, \( r^2 = .78, p < .05 \) but
negative for the older age group (slope = −.87, $r^2 = .76$, $p < .02$; Figure 5c).

These results suggest that decreased speed of information retrieval at response (possibly reflecting less efficient memory-scanning processes, Sternberg, 1969) is related to increases in dorsolateral PFC activation for younger subjects, but to decreases in dorsolateral PFC activation for older subjects. Much converging evidence now exists to suggest that reductions in processing speed are related to age-related decreases in the overall efficiency of cognitive processing (e.g., Myerson, Hale, Wagstaff, Poon, & Smith, 1990; Salthouse, 1996). The current results suggest that there may be age-related differences in the neural correlates of processing efficiency.

Reductions in neural efficiency may lead to slowing of cognitive processes, specifically, the speed with which information can be activated in WM. Slower activation at memory retrieval may lead to degradation in the quality of information available for later response-stage processing. One correlate of low quality information available at the response stage could be reductions in the neural activation levels that permit discrimination between potential responses.

Some models of response processes suggest that the sigmoid relationship between a neuron’s input activation and its firing probability may have consequences at the behavioural level (Kimberg, D’Esposito, & Farah, 1997; Servan-Schreiber, Printz, & Cohen, 1990). Response selection may be characterised as a signal detection mechanism in which the probability of a given response is determined by the relative strength of signal associated with each possible response. Thus, the sigmoid activation function relates neural activation levels to differences in signal strength between potential responses. Middle ranges of neural activation result in large differences in signal and easy discrimination between potential responses. As neural activation levels move above or below this range, potential responses become progressively less discriminable (Figure 6).

The age-related differences we observed in the relationship between neural activation and performance suggest that ageing may result in an overall reduction in neural activity in dorsolateral PFC. One consequence of this reduced neural activity may be that higher neural activation levels would be required to achieve optimal response discriminability. That is to say, for older adults, the sigmoid activation function may be shifted to the right (Figure 6). In this model, low levels of activation lead to optimum response discriminability for younger adults but to suboptimum response discriminability for older adults. As neural activation levels increase and move to the right of the sigmoid functions, response discriminability moves into the optimum range of older adults.
Figure 6. A sigmoid activation model of age-related differences in brain–behaviour relationships. The age-related differences we observed in the relationship between neural activity and performance suggest that a sigmoid function may characterise the relationship between neural activation levels and WM performance. In this model, potential responses (r1 and r2) are selected on the basis of signal strength. The sigmoid activation function is shifted to the right for older adults, suggesting that there may be age-related increases in the input activation required for cells to fire. This age-related change amounts to a bias-shift in the sigmoid equation. At the behavioural level, the implication is that low levels of activation lead to optimum response-discriminability for younger adults but to suboptimum response discriminability for older adults. As neural activation levels increase and shift to the right of the sigmoid functions, response discriminability moves into an optimal range for older adults but into a supraoptimal range for younger adults.
The model we have proposed suggests that reductions in a single parameter, the overall neural activity level, lead to the neural inefficiency that underlies the inefficiency associated with age-related performance reductions. Can this fairly complex mechanism result from the adjustment of a single parameter? We and our colleagues have attempted to answer this question (Bretscheider, Viviani, Rypma, & D’Esposito, 2000; Viviani & Rypma, 1999) using PDP modelling techniques. The model we tested was based on the equation that renders a sigmoid function:

\[ f_G(x) = \frac{1}{1 + e^{-(Gx + B)}} \]  

(1)

In equation 1, G refers to the level of gain in the function. Changes in the gain parameter alter the slope of the sigmoid function. B in the equation models the bias in the function. Changes in the bias parameter alter the X-offset, or left–right position, of the resulting function.

The prediction of the current model is that changes in the bias parameter, but not the gain parameter, result in the age differential patterns of brain–behaviour relationships that we have observed. Thus, age-related differences are modelled as different biases in the output. A positive bias is exactly equivalent to an activation function shifted to the left. A negative bias is exactly equivalent to an activation function shifted to the right. Thus, to test the model we gave older subjects lower biases in the output layer relative to younger subjects.

The input was set according to three parameters. The first is the input norm, i.e., the average total activation present in the input in each iteration. This parameter varied according to the differences in activation seen in the fMRI study presented earlier. The second is the average contrast between the highest and the lowest activation in the input. This parameter modelled the memory load in the two trial series. The third parameter regulated the variance of a noise term with a Gaussian distribution. The noise in the input translates into occasional incorrect responses, which are related to the accuracy level measured in the experiment.

To calculate the activation in the output, the sum of the input received from all connections was passed to the logistic function (equation 1). As is clear from equation 1, and as stated earlier, the output is regulated by two parameters. The first is the gain G (which regulates the slope of the logistic function). In the simulations, G was kept constant at a value of 2.5. The second is the bias B which regulates the shift of the logistic
function in the x-axis direction of the output nodes. As dictated by our hypothesis, we modelled the older condition with a lower bias (–1.8) than the younger (–1.0). These parameters yielded age-differential sigmoid functions similar to those in Figure 6.

The raw data of the simulation are presented in Table 1. In the left column the input parameters are listed. The right column lists the measurements averaged over 5000 trials of the gradient (inversely related to reaction times), the activation levels, and the accuracy. The activation level in the output has no correspondence in the experimental data, but is useful to assess in what region of the logistic function are situated the input data. An activation level of 0.50 means that the input values are optimal.

The data on the input activation norm and the gradient are plotted in Figure 7. As the figure shows, the reaction times are a linear transformation of the inverse of the activation gradients. Hence, the relationship between neural activity recovered from the simulation closely resembles those we observed in the studies presented previously. These results are consistent with the idea of a single mechanism of age-related changes in which WM performance declines are mediated by overall reductions in neural activity in dorsolateral PFC.

<table>
<thead>
<tr>
<th>Input</th>
<th>Output</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Younger adults, normal activation</strong></td>
<td></td>
</tr>
<tr>
<td>Norm</td>
<td>1.0</td>
</tr>
<tr>
<td>Contrast</td>
<td>0.145</td>
</tr>
<tr>
<td>Noise</td>
<td>0.1</td>
</tr>
</tbody>
</table>

| **Younger adults, higher activation** | |
| Norm  | 1.8    | Gradient | 0.031 (0.030) |
| Contrast | 0.145 | Activation | 0.88 |
| Noise | 0.1    | Accuracy | 0.84 |

| **Older adults, normal activation** | |
| Norm  | 1.0    | Gradient | 0.031 (0.030) |
| Contrast | 0.145 | Activation | 0.12 |
| Noise | 0.1    | Accuracy | 0.84 |

| **Older adults, higher activation** | |
| Norm  | 1.8    | Gradient | 0.072 (0.069) |
| Contrast | 0.145 | Activation | 0.49 |
| Noise | 0.1    | Accuracy | 0.85 |
These studies represent our initial efforts to understand the relationship between age-related changes in neural activity and performance. Our ability to make accurate observations rests not only on advanced technology but also on careful consideration of the potential pitfalls in this technology. The studies that we and others have conducted to understand the age-related differences in characteristics of fMRI signal have shown physiological changes in neural activity and fMRI signal with normal ageing and they have allowed us to develop techniques that take account of these differing signal characteristics. As a result, we have measurably greater confidence in our results than we might otherwise have.

The correlational methods we have employed to characterise brain–behaviour relationships allow us to tightly couple individual differences in performance to individual differences in neural activity. Thus, an understanding of age-related changes in the haemodynamic response to neural activity, the superior spatial resolution of fMRI, and the improved temporal resolution afforded by event-related fMRI methodology have permitted us to focus our analyses at a proximal analytic level. With these methodological improvements, we are able to advance more precise speculation about the nature of age differences in neural activity between younger and older adults.

The results of our studies suggest several empirically tractable hypotheses about the brain basis of age differences in performance that are consistent with emerging evidence that distinct neural systems in dorsolateral and ventrolateral PFC selectively mediate different WM opera-
tions. First, they suggest that age-related decline in WM performance may be tied more to age-related physiological changes in dorsolateral than ventrolateral PFC. Second, they suggest that age-related differences in dorsolateral PFC function may exert their effects mainly during the retrieval of temporarily stored information and not necessarily during the encoding and maintenance of such information. Finally, they suggest that age-related WM performance declines may be mediated by overall reductions in retrieval-related neural activity in dorsolateral PFC.

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