Isolating the neural mechanisms of age-related changes in human working memory

Bart Rypma and Mark D'Esposito

Helen Wills Neuroscience Institute and Department of Psychology, University of California, Berkeley, 3210 Tolman Hall, Berkeley, California 94720-1650, USA
Correspondence should be addressed to B.R. (rypma@socrates.berkeley.edu)

Working memory (WM), the process by which information is coded into memory, actively maintained and subsequently retrieved, declines with age. To test the hypothesis that age-related changes in prefrontal cortex (PFC) may mediate this WM decline, we used functional MRI to investigate age differences in PFC activity during separate WM task components (encoding, maintenance, retrieval). We found greater PFC activity in younger than older adults only in dorsolateral PFC during memory retrieval. Fast younger subjects showed less dorsolateral PFC activation during retrieval than slow younger subjects, whereas older adults showed the opposite pattern. Thus age-related changes in dorsolateral PFC and not ventrolateral PFC account for WM decline with normal aging.

Age-associated PFC decline is documented in anatomical and physiological studies of human and nonhuman primate brains[1–4]. Age-associated differences in WM performance may be related to the PFC changes that occur with age. Neuroimaging studies suggest that PFC is functionally divided such that maintenance of subcapacity information (for two to three items[5,6], not generally affected by aging[7]) is supported by ventrolateral regions of PFC[8,9]. Dorsolateral regions of PFC are engaged selectively in WM tasks that require supracapacity information maintenance[10,11] or manipulation of the maintained information[12], tasks for which age differences in performance are often observed[7].

Behavioral studies demonstrating age differences in WM maintenance when memory loads exceed capacity[13,14] and neurophysiological and neuroimaging studies demonstrating functional subdivisions of PFC[15–18] led us to hypothesize that the neural basis of age-related declines in WM performance may be related specifically to age-related changes in dorsolateral, but not ventrolateral, PFC. We tested this hypothesis in a principal experiment and two replication experiments (with different groups of subjects) using functional MRI (fMRI). All three experiments involved delayed-response WM tasks in which, on each trial, subjects first encoded either high or low memory loads (letters in experiments 1 and 2, objects and locations in experiment 3). Second, they retained the information over an unfilled retention interval, and third, they determined whether or not a single item was part of the memory set (**Fig. 1a**). We used event-related fMRI designs to examine age-related changes in neural activation patterns in dorsolateral and ventrolateral PFC uniquely associated with stimulus encoding, memory maintenance and memory retrieval during these three WM tasks (**Fig. 1b**).

Results

Behavioral data

Subjects performed the principal WM task with high accuracy (**Table 1**). There were minimal accuracy differences between the two memory-load conditions ($F_{1,10}$ = 1.46, p < 0.25, m.s.e. = 25.7). Reaction times (RTs) were slower in the 6-letter than in the 2-letter condition ($F_{1,10}$ = 29.0, p < 0.001). Performance accuracy did not differ significantly between younger and older subjects ($F_{1,10}$ = 1.24, p < 0.29), but younger subjects were faster than older subjects ($F_{1,10}$ = 7.44, p < 0.02). Similar behavioral results were observed in the two replication experiments (**Table 1**).

Imaging data

Across all subjects (young and old) in the three experiments, suprathreshold voxels (mapwise) for each task period revealed activity in a number of brain regions (**Table 2**). Age-related hypotheses were tested within dorsal and ventral PFC ROIs (**Fig. 2**). As predicted, analyses of imaging data in the principal WM experiment (**Fig. 3**) revealed no signficant age-related differences in ventrolateral PFC activation, collapsed across hemispheres, in either of the memory-load conditions during any of the task periods (stimulus encoding, retention interval and response). In dorsolateral PFC, there were no significant age differences in regional activation during the encoding period or the retention period. Younger subjects, however, showed significantly greater activation than older subjects in the 6-letter condition during the response period (younger M = 0.21, older M = 0.06, Mann-Whitney U, p = 0.01). Similar effects were observed in dorsalateral PFC in the two replication experiments, in the high-memory- load response periods (replication experiment 1 younger M = 0.15, older M = 0.08, p = 0.04; replication experiment 2, younger M = 0.83, older M = 0.59, p = 0.04). No other effects reached significance (p > 0.10). Analyses in separate hemispheric ROIs indicated similar effects in both hemispheres.

In the principal WM experiment, we observed considerable intersubject variability in fMRI signal in PFC. We therefore sought to explore the age-group differences we found in dorsolateral PFC activity in terms of individual performance differences between subjects in the younger and older groups. Individual analyses of subjects' activation patterns suggested a relationship between dorsolateral PFC activity in the response

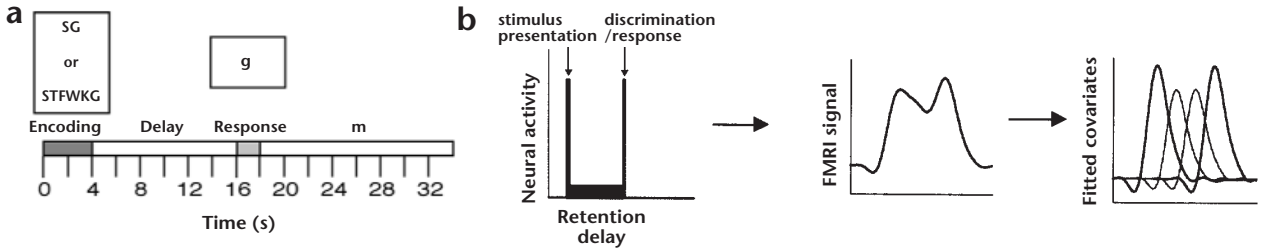

Fig. 1. Experimental design and analysis (**a**) Trial sequence of the behavioral task. On each trial, subjects first encoded either 2 or 6 letters (experiments 1 and 2), presented for 4 seconds. Second they retained the letters across an unfilled 12-second interval. Third, a single letter appeared on the screen and subjects determined, within 2 seconds, whether or not that letter was part of the memory set. A 16-second intertrial interval followed each trial. (**b**) Analysis logic. Left, brief periods of neural activity associated with the encoding and the response task components, and sustained neural activity increase relative to baseline during the delay. Middle, how such neural activity change may lead to a profile of fMRI signal change. Right, the resulting model covariates (shifted HRFs) scaled by their resulting least-squares parameter estimates (βs; gray lines, delay covariates; black lines, encoding and response covariates).

period and RT. Within PFC, cortical regions activated during the response period are shown for subjects with the lowest and highest RT in each age group (**Fig. 4**). For younger subjects, dorsolateral PFC activity increased with increasing RT[11], whereas the reverse pattern was observed for older subjects.

To formally test relationships between cortical activity and performance, we performed regression analyses of subjects' overall RT and PFC activity (indexed by mean parameter estimates in dorsolateral and ventrolateral PFC in each task period). Tests of the regression coefficients that characterize the relationship between mean RT and ventrolateral PFC activity were nonsignificant in all task periods. In dorsolateral PFC in younger subjects, response period regression coefficients showed a significant positive correlation between mean RT and cortical activity (slope = 0.84, $p < 0.03$) that accounted for 71% of the variance. In contrast, in dorsolateral PFC in older subjects, response-period regression coefficients showed a significant negative correlation between mean RT and cortical activity (slope = –0.85, $p < 0.03$) that accounted for 72% of the variance (**Fig. 5a**).

We similarly analyzed data from replication experiment 1 (with a second group of younger and older subjects performing the same WM task as in the principal experiment) to determine the replicability of these findings. We also carried out similar analyses on replication experiment 2 (with a third group of younger and older subjects and a different WM task) to determine the generalizability of these findings. In both replication experiments, we observed similar activation patterns in dorsolateral PFC and ventrolateral PFC. In replication experiment 1, response-period regression coefficients in dorsolateral PFC showed a significant positive correlation (slope, 0.87; $p < 0.01$, $r^2 = 0.76$) between mean RT and cortical activity in younger subjects but a significant negative correlation (slope, –0.82; $p < 0.04$, $r^2 = 0.68$) between mean RT and cortical activity in older subjects (**Fig. 5b**). No such correlations were observed in ventrolateral PFC. In replication experiment 2, we also observed significant patterns of RT–fMRI signal correlations that were positive for the younger age group only in dorsolateral PFC (slope = 0.88, $p < 0.05$, $r^2 = 0.78$) but negative for the older age group (slope, –0.87; $p < 0.02$, $r^2 = 0.76$). No such correlations were observed in ventrolateral PFC (**Fig. 5c**). To test the possibility that speed-related decreases in activation resulted from greater age-related cortical changes in dorsalateral PFC in slower compared with faster older subjects, we also tested correlations between dor-

Table 1. Demographic and performance data.

	Principal exp.		Replication exp. 1		Replication exp. 2	
	Young	Old	Young	Old	Young	Old
Demographics						
n	6	6	7	6	6	6
Age range	21–30	61–82	19–26	55–83	20–29	66–71
Male/female	3/3	3/3	4/3	2/4	4/2	3/3
Mean years of education	15.4	17.6	16	14.5	15.5	16.8
Mean brief WAIS vocabulary	22.5	24.2	27.0	23.0	24.0	24.0
Reaction times (mean ± se)						
Low memory load (2 letters in exps. 1 & 2; 1 feature in exp. 3)	837.2 ± 90.7	1094.0 ± 63.2	812.0 ± 28.0	1233.0 ± 56.7	978.9 ± 109.0	1266.0 ± 34.5
High memory load (for 6 letters in exps. 1, 2; 2 features in exp. 3)	1061.7 ± 156.4	1245.3 ± 41.9	1113.7 ± 47.7	1420.3 ± 91.6	1345.3 ± 84.4	1566.9 ± 142.6
Accuracy (% ± s.e.)						
Low memory load	90.2 ± 2.0	87.7 ± 1.9	97.1 ± 1.8	85.0 ± 4.3	96.8 ± 1.4	92.0 ± 2.2
High memory load	89.0 ± 4.2	80.3 ± 5.2	85.7 ± 2.0	80.0 ± 3.7	86.1± 1.2	78.0 ± 4.8

Table 2. Regions of significant activation in each task period for principal and replication experiment 1.

Lobe	Activation region	Hemisphere/ Brodmann area	Talairach coordinates x	y	z	t-score	voxel number
Encoding							
Frontal	Inferior, premotor	R6, 4, 44	41	–19	55	7.98	113
		L6, 4	–56	–15	45	9.64	58
	Inferior	L44, 45, 47	–30	26	–10	6.84	17
	Medial	B6, 24	4	4	55	11.04	111
	Middle	R9, 46*	26	38	35	7.43	17
Cingulate	Anterior, middle	B32, 24	11	0	45	9.72	120
Parietal	Superior	R7, 40	26	–60	55	9.09	74
		L7	–30	–60	50	9.02	72
		L40	–49	–45	45	6.03	3
Fusiform		R19, 37	45	–68	–10	7.30	14
Precuneus		L19	–34	–83	40	8.57	32
		R19	26	–75	40	7.44	33
Occipital	Middle	R18	30	–90	5	8.21	20
	Middle, inferior	L18, 19	–41	–83	–5	7.42	35
Insula		R*	34	15	5	6.30	9
Subcortex	Hippocampus, parahippocampal gyrus	B30	–4	–34	–5	7.91	164
	Putamen	L	–26	15	–10	7.55	7
	Caudate head	R*	15	15	5	6.20	4
Maintenance							
Frontal	Inferior, premotor	L4, 6, 44	–53	–15	45	10.30	105
		R6*	26	–15	55	6.06	1
	Medial	B6*	–8	–4	55	13.10	99
	Middle	R9*	26	34	35	6.27	3
Cingulate	Anterior, middle	B32, 24*	–8	0	45	10.11	53
Temporal	Superior	L22*	–56	4	55	7.22	6
Parietal	Inferior, superior	L40*	–49	–45	55	6.46	12
		L7*	–34	–71	45	6.26	5
Precuneus		L19*	–30	–70	40	6.28	6
Retrieval							
Frontal	Middle	R9, 46	34	34	25	6.44	23
	Inferior	R44, 45, 47	26	26	–10	9.04	131
		L47	–30	23	–10	7.09	9
	Inferior, premotor	R6, 44	49	4	25	8.96	58
		R6, 4	41	–11	40	7.49	168
		L6	–56	–8	35	7.42	80
	Medial	B6	4	0	55	9.90	208
Cingulate	Anterior, middle	B24, 32	4	–4	45	8.95	168
Parietal	Superior, inferior	R7, 40	34	–60	55	9.92	299
		L7, 40	–41	60	55	11.13	324
	Inferior	R40	56	–41	25	7.95	105
		L40	–50	–41	40	9.98	63
Precuneus		L7, 19	–38	–68	40	7.41	13
Temporal	Superior	R22	56	–41	20	7.97	75
		L22	–45	–4	5	6.99	7
Insula		R	41	11	0	8.45	64
Subcortex	Hippocampus, parahippocampal gyrus	B	19	–33	–5	5.64	114
	Thalamus, putamen caudate head, GP	R	15	0	5	7.48	254
	GP	L	–15	–8	0	5.97	8

Data from the principal experiment and replication experiment 1 were combined into a single data set. Regions are listed where period-specific parameter estimates were significantly different from baseline (ITI) in a random-effects *t*-test that included all subjects (younger and older) in these two experiments (with the same behavioral task). Regions of activation in replication experiment 2 (with a different behavioral task) were similar to those in the first two experiments, though fewer activations were observed during maintenance. Asterisks indicate where activations were not observed in replication experiment 2. Talairach coordinates and *t*-values are for the centroid of activation in each region listed.

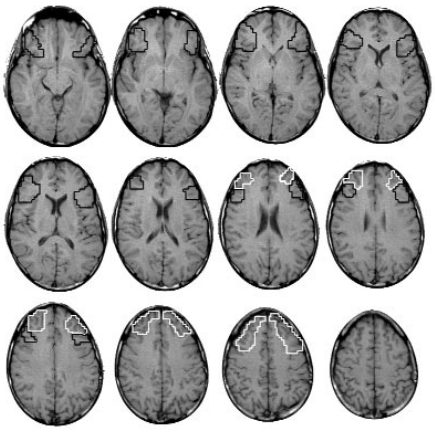

Fig. 2. Regions of interest. Dorsolateral (white) and ventrolateral (black) regions of interest (ROIs) superimposed on T1-weighted images from one subject's brain.

salateral ROI size and activation. These tests were not significant (slope, 0.06; $p < 0.91$, $r^2 = 0.003$; similar tests in the younger subject group were also nonsignificant). Similar effects were observed in the replication experiments. Finally, influence diagnostics[19] performed on all three datasets gave no indication that the observed effects were driven by outliers.

Discussion

In the principal experiment, we observed significant age-associated differences in fMRI signal in dorsolateral PFC but minimal age-associated differences in ventrolateral PFC only during retrieval of high memory loads. Regression analyses of subjects' overall RT and fMRI signal indicated significant correlations between performance and PFC activity only in dorsolateral PFC and only during the response period. In those analyses, slower younger adults showed increased cortical activity relative to their faster counterparts, whereas slower older adults showed decreased cortical activity relative to their faster counterparts. Although analyses of load-dependent activation indicated increases at encoding in PFC within younger subjects[11], our results emphasize that age-related differences are limited to retrieval processes.

The persistence of the effects found in the principal experiment in a second group of subjects performing the same WM task and in a third group of subjects performing a different WM task permits some speculation about the mechanisms underlying age differences in WM. These results suggest that decreased speed of information retrieval at response (possibly reflecting less efficient memory-scanning processes[20]) 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 decreases in the overall efficiency of cognitive processing for younger and older adults[21]. 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[22]. 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 behavioral level[23,24]. Response selection may be characterized 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[25]. 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 harder to discriminate (**Fig. 6**).

The age-related differences we observed in the relationship between neural activation and performance suggest that, with aging, higher neural activation levels may be required to achieve optimal response discriminability. That is to say, for older adults, the sigmoid activation function may be shifted to the right (**Fig. 6**). In this model, low activation levels allow optimum response discriminability for younger adults but suboptimum response discriminability for older adults. As neural-activation levels increase and move to the right of the sigmoid functions, response discriminability becomes optimum for older adults but supra-optimum for younger adults. Such a model is speculative at this stage, and other explanations are possible. One implication of our model, however, is that increases in neural activation would produce improvements in performance for older adults but decrements in performance for younger adults. We observed just such relationships between neural activation and performance in the principal experiment, and we replicated them in two subsequent experiments.

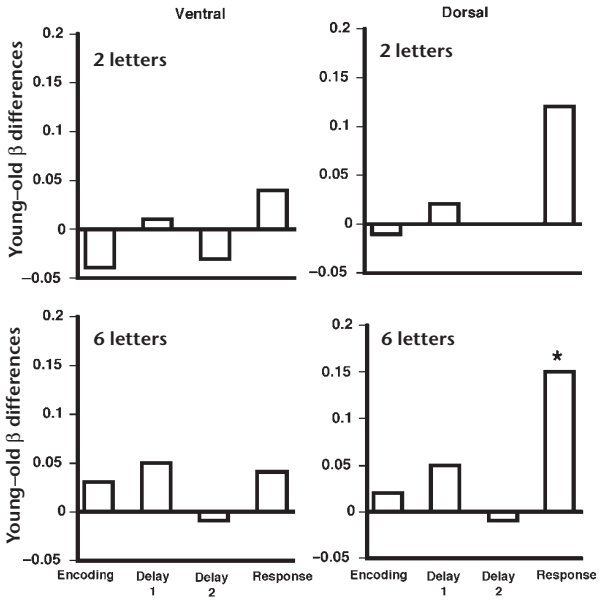

Fig. 3. Age-group differences in activation by PFC region, memory-load condition and task period. Age-group differences in regional mean parameter estimates (β) for dorsal and ventral PFC ROIs at each task period (encoding, delay and retrieval) in the 2- and 6-letter memory-load conditions. Asterisk denotes statistically significant age-group difference.

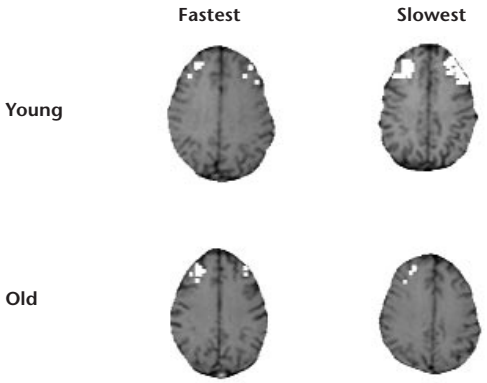

Fig. 4. Neural activity in the fastest and slowest subjects in each age group. Examples of activation in dorsolateral PFC ROIs for the fastest and slowest subjects in the young and old subject groups indicated age-related differences in performance–activation relationships.

It is possible that two separate mechanisms (rather than a single mechanism) account for the age-related differences in brain–behavior relationships. For instance, RT-related decreases in activation may be the result of increased cortical atrophy in slow older adults. The absence of any relationship between activation and regional ROI size provides some evidence against such a hypothesis. Definitive tests of such hypotheses, however, must await the development of adequate white–gray matter segmentation methods. Increases in RT-related activation in younger adults may have resulted from increased time spent on response processes by slower younger adults. The absence of RT-fMRI signal correlations in ventrolateral PFC despite its increased involvement in retrieval processes (similar to dorsolateral PFC; **Table 2**) ameliorates this concern. Future research may help clarify the mechanisms underlying the brain–behavior relationships we observed here.

Our results suggest three main conclusions. First, they suggest that distinct neural systems in dorsolateral and ventrolateral PFC selectively mediate different WM operations, consistent with evidence that functional segregation of PFC may be based on the types of operations performed on information held in WM[12,17,18]. Second, age-related WM decline may be tied more to age-related physiological changes in dorsolateral than in ventrolateral PFC. Third, age-related differences in function of dorsolateral PFC may exert their effects mainly during the retrieval of temporarily stored information but not necessarily during the encoding and maintenance of such information. Age-related declines in WM performance may be mediated by reductions in retrieval-related neural activity in dorsolateral PFC.

Methods

Subjects. Younger subjects (age $M = 25.0$ across experiments) were recruited from the medical and undergraduate campuses of the University of Pennsylvania. Older community-dwelling subjects (age $M = 68.8$ across experiments) were recruited from the greater metropolitan Philadelphia area by newspaper ads (**Table 1**). Subjects were excluded if they had any medical, neurological or psychiatric illness or if they were taking any type of prescription medication. All subjects gave informed consent. Olderer subjects showed no evidence of dementia (all scores for mini-mental status exams were greater than 26) or depression (all Beck depression-inventory scores less than 10).

Cognitive tasks: principal experiment and replication experiment 1. Subjects underwent fMRI while performing a delayed-response task. On each trial, they first encoded either 2 or 6 letters presented for 4 s (experiments 1 and 2); second, retained them across an unfilled 12-s interval and third, determined within 2 s whether or not a single letter was part of the memory set. A 16-s intertrial interval followed each trial to allow the fMRI signal to return to baseline. This event-related fMRI design allowed us to examine neural activity associated with stimulus encoding, memory maintenance and memory retrieval separately. Subjects responded with a right-thumb button press if the probe letter was contained in the memory set or a left-thumb button press if the probe letter was not contained in the memory set. Subjects viewed a backlit screen from within the magnet bore through a mirror mounted on the head coil. Stimulus presentation and RT recording were handled by a Macintosh computer. Each experimental run in the scanner consisted of a block of eight trials. Each subject performed 10 runs, yielding a total of 80 trials.

Replication experiment 2. On each trial, subjects first viewed a cue instructing them to attend to objects, locations or objects and locations[26]. Next, 3 different objects were presented for 1 s each sequentially in a 3 × 3 grid (each grid contained a different object drawing in a different location) followed by an 8-s retention interval. A test probe then appeared for 2 s, followed by a 12-s intertrial interval (ITI). Thus each trial including the ITI was 26 s long. On object trials, the test probe was a black and white object in the center of a grid; subjects responded 'yes' (right-thumb button press) if the probe corre-

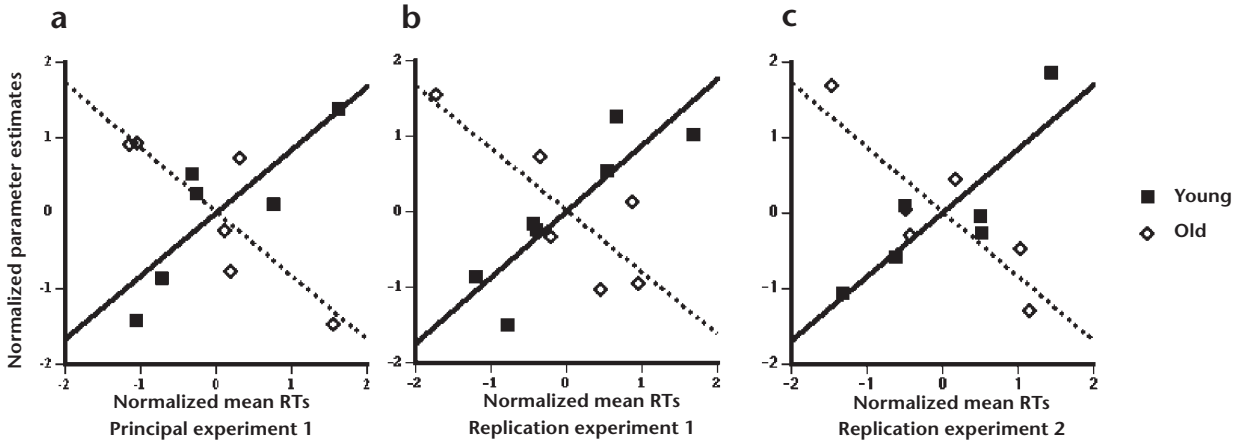

Fig. 5. Scatterplots of activation–performance relationships. Scatterplots of the normalized regional mean parameter estimates during the response period in dorsolateral PFC plotted against normalized RTs in young subjects (filled squares; exp. 1 slope = 0.84, $r^2 = 0.71$, $p < 0.03$; exp. 2 slope = 0.87, $r^2 = 0.76$, $p < 0.01$; exp. 3 slope = 0.88, $r^2 = 0.78$, $p < 0.05$) and older subjects (open diamonds; exp. 1 slope = –0.85, $r^2 = 0.72$, $p < 0.03$; exp. 2 slope = –0.82, $r^2 = 0.68$, $p < 0.04$; exp. 3 slope –0.87, $r^2 = 0.76$, $p < 0.03$).

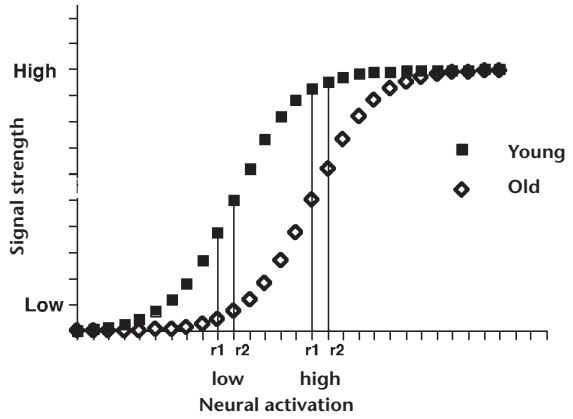

Fig. 6. A sigmoid activation model of age-related differences in brain–behavior relationships. The age-related differences we observed in the relationship between neural activity and performance suggest that a sigmoid function may characterize the relationship between neural activation levels and WM 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 old 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 behavioral level, the implication is that low levels of activation lead to optimum response discriminability for young adults but to suboptimum response discriminability for older adults. As neural-activation levels increase and shift to the right of the sigmoid functions, they become optimal for response discriminability in older adults but supra-optimal for young adults.

sponded to a studied item on that trial or 'no' (left-thumb button press) if it did not. On location trials, the test probe was a black dot in one of the grid cells (other than the center), and participants responded 'yes' if it appeared in a location that an object had occupied on that trial or '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 or 'no' if it did not. Distractor items in this condition were always re-pairings of objects and locations from the current trial. The objects on each trial were drawn randomly from a set of eight to equate the number of different objects with the number of different locations, with the restriction that each item appear equally often in each condition.

Image acquisition. Imaging was carried out on a 1.5 T SIGNA scanner (GE Medical Systems, Milwaukee, Wisconsin) equipped with a fast gradient echo-planar imaging system. A standard radiofrequency head coil was used with foam padding to restrict head motion. High-resolution sagittal and axial T1-weighted images were obtained for every subject. A gradient echo, echoplanar sequence (TR = 2000 ms, TE = 50 ms) was used to acquire data sensitive to BOLD signal. Resolution was 3.75 mm^2 in plane and 5 mm between planes (21 axial slices). Twenty seconds of gradient and RF pulses preceded data acquisition to allow steady-state tissue magnetization.

Data analysis. Data preparation proceeded as follows: image reconstruction; sinc interpolation in time (to correct for fMRI slice acquisition sequence); motion correction (six-parameter, rigid-body, least-squares realignment); slice-wise motion compensation (to remove spatially coherent signal changes via application of a partial correlation method to each slice in time[27]). Because fMRI data are temporally autocorrelated under the null hypothesis, data analysis was conducted within the framework of the modified general linear model for serially correlated error terms[28]. Low-frequency sinusoids and trial means were included as nuisance covariates. In the convolution matrix, we placed a time-domain representation of the expected $1/f$ power structure and a filter that removes frequencies above 0.244 Hz (at and around the Nyquist frequency) and below 0.01 Hz (the portions of highest power in the noise spectrum). The data were not smoothed temporally with a low-pass filter because including a $1/f$ model adequately controls the false-positive rate under relatively high-frequency protocols. The event-related fMRI analysis used in this study consisted of modeling fMRI signal changes occurring during each task period with covariates composed of shifted BOLD hemodynamic response functions (HRF; **Fig. 1**). An HRF estimate was obtained from each subject immediately before fMRI scanning[29] (see below). Relationships with each task period and the ITI were assessed by contrasts (yielding *t*-statistics with ~1195 df) involving the parameter estimates that corresponded to the independent variable that modeled each task period. (We analyzed two delay-period covariates, designated as delays 1 and 2.) To determine mapwise activation across subjects and conditions in each task period, parameter-estimate maps for each subject were first normalized to an average brain in a normalized coordinate system[30]. We then applied a Gaussian spatial filter (15 mm FWHM) to the maps and analyzed differences between mean parameter estimates and baseline at each task period with random-effects tests. We used random-effects tests of age differences in mean parameter estimates and baseline at each task period to assess hypotheses of age differences in activation of dorsolateral and ventrolateral PFC regions in WM[31]. Because we observed reliable age differences in the noise component[32], which could lead to the spurious inference of age differences in intensity of neural activity, we used this method to avoid use of the noise component of the fMRI signal. As analyses indicated similar effects in both hemispheres, data are presented as averages across left and right PFC ROIs.

Our rationale for deriving an HRF for each subject was based on observations of significant variability between individuals but not within individuals across scanning sessions[29]. An HRF was derived from primary sensorimotor cortex in each subject in the following manner. Before performing the WM task described above, each subject performed a simple RT task in which a central white fixation cross changed briefly (500 ms) to a circle every 16 s, cueing subjects to make a bilateral button press. During the 320-s scan (160 images), 20 such events occurred. All scanning parameters were identical to those used for the WM experiment.

To examine activity in specific regions of PFC, we created separate dorsolateral and ventrolateral PFC regions of interest (ROIs) for each subject. ROIs were created for each subject by first creating a standard set of ROIs on a representation of a brain corresponding to a standardized coordinate frame[30]. The dorsolateral ROIs corresponded to Brodmann's areas 9 and 46. The ventrolateral ROIs corresponded to Brodmann's areas 44, 45 and 47. (These ROIs were superimposed on a normalized average of subjects' brains from our study; **Fig. 2**.) These standardized ROIs were then transformed into coordinates corresponding to each subject's fMRI scan (effectively, a reverse normalization). Thus the fMRI data for this experiment were analyzed in the coordinates in which they were acquired. By defining our anatomical ROIs objectively, on a normalized brain, we intended to restrict our hypothesis testing to volumes defined in a standard anatomical space, thereby reducing bias for an anatomical dissociation. Because some individual anatomical variability is preserved in the reverse-normalization process, we adjusted the ROIs after transformation to better correspond to the anatomical images of some subjects and thus more accurately demarcate the intended brain regions.

Acknowledgements

This research was supported by American Federation for Aging Research and NIH grants NS01762, AG15793 and AG13483. We thank Jeffrey S. Berger, Ron Collis, David Dorfman, Eric Zarahn and Geoff Aguirre for their support on this project. We thank Marcia K. Johnson, Karen Mitchell and Carol Raye for the design of replication experiment 2.

RECEIVED 26 OCTOBER 1999; ACCEPTED 13 MARCH 2000

1. Raz, N. *et al*. Selective aging of the human cerebral cortex observed *in vivo*: Differential vulnerability of the prefrontal gray matter. *Cereb. Cortex*, **7**, 268–282 (1997).
2. Heilbroner, P. L. & Kemper T. L. The cytoarchitectonic distribution of senile plaques in three aged monkeys. *Acta Neuropathol*. **81**, 60–65 (1990).
3. Haug, H. & Eggers, R. Morphometry of the human cortex cerebri and corpus striatum during aging. *Neurobiol. Aging* **12**, 336–338 (1991).
4. Goldman-Rakic, P. M. & Brown, R. M. Regional changes of monoamines in cerebral cortex and subcortical structures of aging rhesus monkeys. *J. Neurosci*, **6**, 177–178 (1981).
5. Waugh, N. C. & Norman, D. A. Primary memory. *Psychol. Rev*. **72**, 89–104 (1965).
6. Glanzer, M. & Razel, M. The size of the unit in short term storage. *J. Verb. Learn. Verb. Behav*. **13**, 114–131 (1974).
7. Craik, F. I. M. & Jennings, J. M. in *The Handbook of Aging and Cognition* (eds. Craik, F. I. M. & Salthouse, T. A.) 51–110 (Erlbaum, Hillsdale, New Jersey, 1992).
8. Awh, E. *et al.* Dissociation of storage and rehearsal in verbal working memory: evidence from PET. *Psychol. Sci*. **7**, 25–31 (1996).
9. Paulesu, E., Frith., C. & Frackowiak, R. The neural correlates of the verbal component of working memory. *Nature* **362**, 342–345 (1991).
10. Rypma, B., Prabhakaran, V., Desmond, J. E., Glover, G. H. & Gabrieli, J. D .E. Load-dependent roles of prefrontal brain regions in the maintenance of working memory. *Neuroimage* **9**, 216–225 (1999).
11. Rypma B. & D'Esposito, M. The roles of prefrontal brain regions in components of working memory: Effects of memory load and individual differences. *Proc. Natl. Acad. Sci.USA* 96, 6558–6563 (1999).
12. D'Esposito, M., Postle, B. R., Ballard, D. & Lease, J, Maintenance versus manipulation of information held in working memory: An event-related fMRI study. *Brain Cognit*. **41**, 66–86 (1999).
13. Anders, T. R., Fozard, J. L. & Lillyquist, T. D. Effects of age upon retrieval from short-term memory. *Dev. Psychol*. **6**, 214–217 (1972).
14. Van der Linden, M., Bredart, S. & Beerten, A. Age-related differences in updating working memory. *Br. J. Psychol.* **85**, 145–151 (1994).
15. Fuster, J. M. *The Prefrontal Cortex: Anatomy, Physiology, and Neuropsychology of the Frontal Lobes* (Raven, New York, 1989).
16. Smith, E. E. & Jonides, J. Storage and executive processes in the frontal lobes. *Science* **283**, 1657–1661 (1999).
17. Petrides, M. in *Handbook of Neuropsychology* (eds. Boller, F. & Grafman, J.) 75–90 (Elsevier, Amsterdam, 1989).
18. Owen, A. M., Evans, A. C. & Petrides, M. Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: a positron emission tomography study. *Cereb. Cortex* **6**, 31–39 (1996).
19. Belsley, D. A., Kuh, E. & Welsch, R. E. *Regression Diagnostics: Identifying Influential Data and Sources of Collinearity* (Wiley, New York, 1980).
20. Sternberg, S. High speed scanning in human memory. *Science* **153**, 652–654 (1966).
21. Salthouse, T. A. The processing speed theory of adult age differences in cognition. *Psychol. Rev.* **103,** 403–428 (1996).
22. Myerson, J., Hale, S., Wagstaff, D., Poon, L. W. & Smith, G. A. The information-loss model: a mathematical theory of age-related cognitive slowing. *Psychol. Rev.* **97**, 475–487 (1990).
23. Servan-Schreiber, D., Printz, H. & Cohen, J. D. A network model of catecholamine effects: gain, signal to noise ratio, and behavior. *Science* **249**, 892–895 (1990).
24. Cohen, J. D. & Servan-Schreiber, D. Context, cortex, and dopamine: A connectionist approach to behavior and biology in schizophrenia. *Psychol. Rev*. **99**, 45–77 (1992).
25. Kimberg, D. Y., D'Esposito, M. & Farah, M. T. Effects of bromocriptine on human subjects depend on working memory capacity. *Neuroreport* **8**, 3581–3585 (1997).
26. Mitchell, K. J. *et al*. Aging and reflective processes of working memory: Binding and test load deficits. *Psychol. Aging* (in press).
27. Zarahn, E., Aguirre, G. K. & D'Esposito, M. A trial based experimental design for functional MRI. *Neuroimage* **6,** 122–138 (1997).
28. Worsley, K. J. & Friston, K. J. Analysis of fMRI time-series revisited-again. *Neuroimage* **2**, 173–182 (1995).
29. Aguirre, G. K., Zarahn, E. & D'Esposito, M. The variability of human BOLD hemodynamic responses. *Neuroimage* **8**, 360–369 (1998).
30. Talairach, J. & Tournoux, P. *Co-Planar Stereotaxic Atlas of the Human Brain* (Thieme, New York, 1988).
31. Kleinbaum, D. G., Kupper, L. L. & Muller, K. E. Applied regression analysis (Duxbury, Belmont, California, 1988).
32. D'Esposito, M., Zarahn, E., Aguirre, G. K. & Rypma, B. The effect of normal aging on the coupling of neural activity to the BOLD hemodynamic response. *Neuroimage* **10,** 6–14 (1999).