Aging and brain activation with working memory tasks: an fMRI study of connectivity

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SUMMARY

Background   White matter changes in aging and neuropsychiatric disorders may produce disconnection of neural circuits. Temporal correlations in regional blood oxygen level dependent (BOLD) signals may be used to assess effective functional connectivity in specific circuits, such as prefrontal cortex (PFC) circuits supporting working memory (WM) tasks. We hypothesized healthy older subjects would show lower connectivity than younger subjects.

Methods   Healthy younger ($n = 9$, 25.9 (SD 6.0) years) and older adults ($n = 11$, 68.3 (4.9) years) performed WM tasks during functional MRI. Subjects viewed images and were instructed to label them, either simultaneously or after a delay; BOLD responses with and without delay were contrasted to assess differential WM activation and connectivity. Two tasks were used: a semantic task, with line drawings categorized as 'alive' or 'not living', and an emotional task, with emotive faces as stimuli and subjects selecting the better emotional description.

Results   In both tasks, older subjects activated larger regions and had greater inter-individual variability in extent of activation. In the semantic task, connectivity was lower in the older subjects for the amygdala/orbital PFC circuit ($p = 0.04$). Contrary to our predictions, older subjects exhibited higher connectivity than younger subjects in the circuit linking orbital and dorsolateral PFC in both semantic ($p = 0.04$) and emotional ($p = 0.02$) tasks.

Conclusions   Healthy subjects exhibited age-dependent differences in connectivity in working memory circuits, but this may reflect effects of aging on white matter, compensatory mechanisms, and other factors. Volumetric determination of white matter hyperintensities in future studies may clarify the functional importance of structural damage. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS — fMRI; connectivity; aging; white matter; working memory

INTRODUCTION

It is well accepted that cognitive function depends upon intact gray matter tissue, both in the cortex and in subcortical nuclei. Neuroimaging studies using positron emission tomography (PET) or single photon emission computed tomography (SPECT) techniques have shown that individuals with cognitive deficits of dementia have metabolic or perfusion abnormalities in specific regions that are associated with those specific cognitive functions (e.g. reviewed by Marshall and Fink, 2003). Other neuropsychiatric disorders, such as depression and obsessive compulsive disorder, have been linked to abnormal metabolism and perfusion in specific brain regions such as elements of the limbic system (Baxter, 1992; Davidson *et al.*, 2002; Saxena *et al.*, 2002; Drevets, 2003; Mayberg, 2003; Saxena *et al.*, 2004). Function in these gray matter regions depends not only upon intact cortical elements but also on intact connections *between* these areas to accomplish their coordinated processing, and disruptions to white matter tracts, e.g. from cerebrovascular disease, can produce clinical syndromes via a 'disconnection' mechanism (Geschwind, 1962, 1965a, 1965b; Leuchter *et al.*, 1992, 1994; Dunkin *et al.*, 1995; O'Sullivan *et al.*, 2001; Cook *et al.*, 2002, O'Sullivan *et al.*, 2004). An examination of the integrity of circuit function represents a complementary approach to studying

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regional brain function, yet this has not been widely applied in studies of normal or healthy aging, or in depression (Kumar and Cook, 2002).

Numerous reports have indicated that white matter damage is common in the elderly (Longstreth *et al*., 1996; Fazekas *et al*., 1998; Ketonen, 1998; Smith *et al*., 2000). While widespread damage has been linked to impairments in cognition (de Groot *et al*., 2000; Initzari, 2000), in mood regulation (Lesser *et al*., 1996; Lenze *et al*., 1999; Kumar *et al*., 2000), and in mobility (Guttmann *et al*., 2000), the consequences of more subtle disease in normal, asymptomatic aging have not been as extensively examined. Recent work with healthy elders has indicated that subclinical structural brain disease (SSBD) is common and is associated with poor cognitive performance (Cook *et al*., 2002, 2004). Path analysis models (Cook *et al*., 2002) indicated that subclinical white matter damage may give rise to poor cognition by disconnection, even in subjects performing within the normal range on cognitive tests. Other investigations (e.g. Boone *et al*., 1992, 1993; Lesser *et al*., 1996; Gunning-Dixon and Raz, 2000; Ferro and Madureira, 2002; Gunning-Dixon and Raz, 2003; O'Sullivan *et al*., 2004) have reported that performance on frontal-executive tasks is especially vulnerable to the burden of white matter hyperintensities, though potentially with a variable effect size (Soderlund *et al*., 2003). Of note, both frontal task deficits and white matter hyperintensities have also been linked to the development of major depression in late life (Krishnan and McDonald, 1995; Alexopoulos *et al*., 1997; Krishnan *et al*., 1997; Kumar *et al*., 1997; Hickie and Scott, 1998; Kumar *et al*., 1998; O'Brien *et al*., 1998; Steffens and Krishnan, 1998; Lavretsky *et al*., 1999, 2000; Baldwin, 2005; Vataja *et al*., 2005) and to poorer response to antidepressant response in both younger (Dunkin *et al*., 2000) and older adults (Taylor *et al*., 2003; Baldwin *et al*., 2004). Biochemical abnormalities in 'normal appearing' white matter have been revealed in late life depression using magnetization transfer imaging and MR spectroscopy (Kumar *et al*., 2002; Wyckoff *et al*., 2003), along with disturbances in structural determinants of connectivity assessed with diffusion tensor imaging (Taylor *et al*., 2001). It appears that there are relationships between white matter disturbances, abnormalities in executive cognitive function, and treatment outcomes in depression. These findings motivated us to examine circuits supporting frontal-executive tasks, in order to understand more about disconnection phenomena in aging. Additional data suggest that patients with depression may exhibit impairments in identification of emotional stimuli (David and Cutting, 1990; Gur *et al*., 1992; Rubinow and Post, 1992; Sheline *et al*., 2001; Phillips *et al*., 2003), suggesting that an evaluation of executive functions using emotional charged and emotionally neutral stimuli would be of particular interest.

Within the broad category of executive functions, specific circuits in the PFC are important for the cognitive capabilities of working memory. Cooling experiments with primates demonstrate that reversible lesions of circuits in orbital and dorsolateral PFC disrupt working memory function (Bauer and Fuster, 1976, 1978; Quintana and Fuster, 1993; Shindy *et al*., 1994). It has been proposed that measures of functional connectivity can be derived from temporal correlations in the BOLD signal using contrasts between activated and resting states (Biswal *et al*., 1995; Casey *et al*., 1995; Cabeza *et al*., 1997; Lowe *et al*., 1998; Bullmore *et al*., 2000; Grady *et al*., 2003; Lee *et al*., 2003; Ramnani *et al*., 2004; Koshino *et al*., 2005). We hypothesized for this investigation that aging would be associated with alterations in connectivity in the PFC and that these changes could be assessed via working memory task challenge (Fuster, 2001). Specifically, we hypothesized that connectivity would be lower in our older subjects. We elected to employ two cognitive challenges: (a) an emotionally-neutral 'semantic working memory' task, involving labeling of images as 'alive' or 'not living,' and (b) an 'emotional working memory' task, involving selection of the better word to describe the emotion being conveyed by a facial expression. By using these two tasks, we sought to delineate first the effect of age on functional connectivity in WM circuits and second the impact of emotionally-charged content on measures of connectivity.

METHODS

Subjects

Subjects were all right-handed individuals who had neither a past history nor present symptoms of any neurological or psychiatric disorder (clinical assessment by board-certified research physicians). All were recruited from the community by flyers for subjects and referring physicians. In accordance with principles of the Helsinki Declaration, this protocol had been approved by the UCLA Institutional Review Board, and informed consent to participate in this research was obtained from all subjects. Twenty subjects participated in this project, and were enrolled

into two groups on the basis of age, using age 60 as a cutoff: 11 elder subjects (mean age 68.3 (SD 4.9) years, range 61–74) and 9 younger adults (mean age 25.9 (SD 6.0) years, range 19–34).

Imaging parameters

Each subject was imaged using a GE Signa 3T scanner (GE Medical Imaging, Waukesha WI) with an echo-planar imaging upgrade (Advanced NMR Systems, Wilmington, MA, USA), using methods similar to those previously described (Bookheimer *et al.*, 2000). First, an automated shim procedure was used to minimize magnetic field inhomogeneity. Second, a T2-weighted sagittal scout was used to determine locations for both structural and functional image planes. Third, co-planar high-resolution echo planar imaging (EPI) structural data were acquired, consisting of 26 slices (4 mm thick, 1 mm gap) covering the entire volume of the brain (TR/TE 4000/54 ms, 128×128). Finally, we acquired functional images from 16 of these slice planes, beginning near the base of the temporal lobes and moving upward (TR/TE 2500/45 ms, 64×64, Field of View 20×40 cm). The high-resolution EPI structural data were used to determine masks delineating regions of interest (below) to overlay on the functional scans.

Experimental paradigm

The working memory tasks employed in our experiment were delayed-match-to-sample tasks, based in part on designs described by McIntosh *et al.* (1996), Grady *et al.* (1998), and Hariri *et al.* (2000). Our experiment specifically introduced a requirement to transfer information both across modalities and with a delay, in order to probe circuitry involving dorsolateral and orbital prefrontal cortex regions and the amygdala. In both tasks, stimuli were visual images but the response targets were printed words. In the semantic WM task, line drawings from a standardized set of images (Boston Naming Test, Kaplan *et al.*, 1983) were presented as stimuli; in what we termed Condition A, subjects were presented simultaneously with the picture and a choice of 'alive' or 'not living' categories as response options, while in the contrast Condition B, a delay was introduced between viewing a stimulus and the response (Figures 1 and 2). In the emotional WM task, stimuli were photographic images of emotionally-expressive faces drawn from a standardized set of images (Ekman and Friesen, 1976) and the subjects selected which word (of two choices) was the better label of that emotion. Stimuli were presented
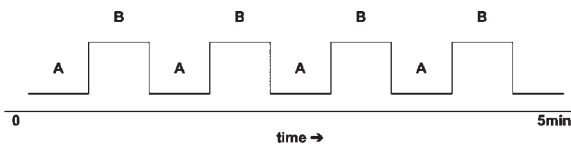

Figure 1. Block condition design. During blocks 'A,' response choices are presented simultaneously with stimuli. During blocks 'B,' there is a delay between stimulus presentation and response. By varying only the presence of the delay between conditions, the difference in activation can be attributed to the action of working memory circuits
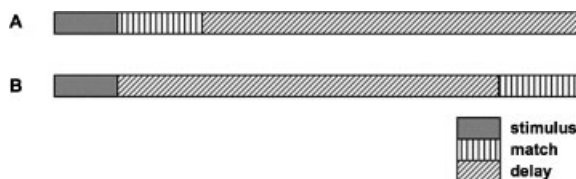

Figure 2. Experimental paradigm. Stimuli were presented for 1.5 sec and subjects were instructed to respond by selecting the correct category during the 2 second 'match' periods; these response periods occurred either directly after the stimulus presentation (row A, control condition) or after a 9 sec delay (row B, working memory condition)

and responses monitored with the MacStim software package (available from http://www.brainmapping.org/WhiteAnt/). The cross-modal feature (i.e. visual stimulus and text response) was included to increase the network load with a more challenging task (Rypma *et al.*, 1999; D'Esposito *et al.*, 2000); this was balanced with a concern about overburdening elderly subjects with an unduly frustrating test. Each block of condition A or B lasted for 37.5 sec and included three stimuli; four A blocks and four B blocks yield a total fMRI experiment duration of 5 min (for each of the emotional WM and semantic WM experiments). Subjects signaled their selection of response by pressing one of two buttons with their right hand; these performance data were unavailable for use in analysis due to an operator error. For each subject, 60 scans covered the 24 trials for the emotional WM experiment and another 60 scans covered the 24 trials for the semantic WM experiment.

Image preprocessing

Functional MRI image data were preprocessed prior to analysis, first by performing a linear drift correction and calculating the baseline variance. Images were spatially filtered using a 3 mm Hanning filter. Our high resolution EPI scans were coplanar with the functional runs and also matched for bandwidth, so that any distortion would be equivalent between the two.
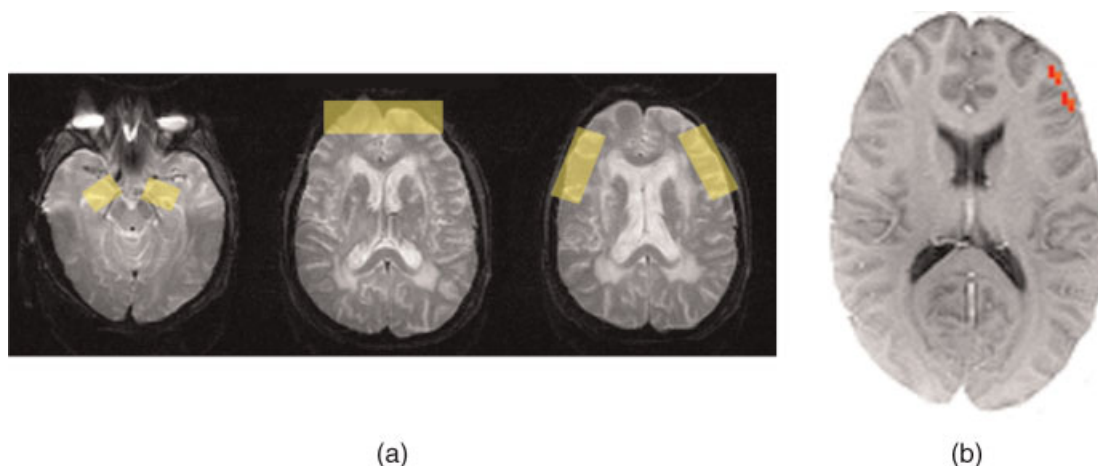
Figure 3. Regions of interest and an example activation. (a) Masks delineating the regions of interest are shown in yellow for amygdala, OFPFC, and DLPFC ROIs. Masks for each individual subject could span adjacent slides to encompass a region if anatomically needed. (b) Example activation during the emotional WM task is shown for a single subject; dorsolateral activation above threshold is visualized (red) within our DLPFC region

Modeling the hemodynamic response function was accomplished by performing a simple convolution of the blocked experimental paradigms of all conditions *vs* control with a delayed boxcar model of the hemodynamic response (Cohen, 1997). All images were placed into a multi-slice display format and put into cine-mode to permit a determination of any frames that warranted exclusion for significant head motion or image artifacts. Next, head motion correction was performed using the Automated Image Registration (AIR) program (Woods *et al.*, 1992, 1998a, 1998b). Images were aligned to the middle image in each set using a rigid body algorithm (Woods *et al.*, 1992, 1998a, 1998b).

Image analysis—extent of activation

The regions of interest (ROIs) for testing our hypotheses were identified manually on the high resolution EPI scans for each subject for three areas: (a) amygdala, (b) orbital prefrontal cortex (OPFC), and (c) dorsolateral prefrontal cortex (DLPFC). These regions were selected because they constitute gray-matter components of the circuits that are activated by our working memory tasks. Landmarks to guide placement of ROIs were chosen using neuroanatomic atlases (Talairach and Tournoux, 1988; Fischer and Ketonen, 1991). These ROIs were marked in their native coordinate space on the structural EPI scans, and were used as masks for the functional EPI scans. Within each region, voxels were compared for differences between delay and no-delay conditions;

extent of activation was assessed by summing the volume of all voxels within a region that showed an *apriori* threshold of $p < 0.02$ for differences between activation conditions (e.g. with *vs* without a delay). Figure 3 depicts an example of significant differential activation seen in dorsolateral prefrontal cortex during the emotional WM task for one subject.

Image analysis—functional connectivity

We assessed connectivity by examining the correlation between the values of the BOLD signal over time between regions. For each ROI, the average signal value in the activated voxels (determined above) was determined for each 2.5 s frame, and the (pearson) correlation in simultaneous signal value in pairs of ROIs was determined (using the CC_gr program, available from http://www.brainmapping.org/). For example, the BOLD signal for the OPFC ROI was compared with the signal for the DLPFC ROI for each 2.5 s frame over time, and the temporal correlation between these two signals served as a measure of functional connectivity between these two areas. Higher correlation coefficients can be interpreted as reflecting greater degrees of coordinated activity, demanding greater functional integrity of connecting tracts.

Statistical analysis

The SPSS program (version 11, SPSS, Inc., Chicago IL, USA) was used to perform analyses. Levene's

Table 1.   Semantic working memory task—extent of activation results

Group	Amyg	OPFC*	DLPFC*
Elder	10.2 (9.1)	28.2 (36.2)	36.3 (45.7)
Younger	6.8 (5.0)	4.6 (3.3)	2.4 (2.2)
One-tail *t*-test of means (*p*)	0.164	0.028	0.017
Levene's Test—*F* [*p*]	0.97 [*p* = 0.34]	14.74 [*p* = 0.001]	17.89 [*p* = 0.001]
Effect size [d]	0.37	0.65	0.74

For each group, the number of voxels showing significant differential activation is tabulated [mean (SD)] in each region of interest. Levene's test was used to assess the equivalence of variances, and *t*-tests were used to test equality of means. Cohen's d is shown as a measure of effect size.

test of homoscedasticity was used to assess whether the variance between groups differed significantly. Student's *t*-tests were used to compare mean values for continuous variables, with an assumption of equal or unequal variance determined from the Levene's test. Mann–Whitney *U*-tests were used for nonparametric comparisons. Effect size calculations were performed with the G•Power program (Buchner *et al.*, 1997). By virtue of our hypothesis-driven regions of interest, we confined our examination to these particular brain regions and the comparisons stated in the tables and text, rather than employing an approach that considers all voxels and demands careful correction for multiple comparisons.

RESULTS

Extent of activation—semantic WM task

The number of voxels within each ROI that demonstrated supra-threshold differences between conditions A and B were tabulated for each region (Table 1). The average number of voxels was significantly larger for elderly subjects in both orbital (4.6 (3.3) *vs* 28.2 (36.2) voxels, *p* = 0.028) and dorsolateral (2.4 (2.2) *vs* 36.3 (45.7) voxels, *p* = 0.017) prefrontal cortex ROIs, but not in the amygdala. Additionally, the variability of extent of activation was

significantly greater for elder subjects for orbital and dorsolateral ROIs (*p* = 0.001 for both regions) but not for the amygdala (*p* = 0.34).

Functional connectivity—semantic WM task

The correlation between signals in our ROIs was compared for subjects who activated at least one voxel in both ends of a circuit. Connectivity was significantly lower in older subjects in the circuit linking amygdala and orbital prefrontal cortex (*t* = −1.87, *p* = 0.04; Mann–Whitney *U* = 7.0, *p* = 0.03). Correlated activity shared between orbital and dorsolateral PFC was significantly higher in the older subjects (*t* = 1.87, *p* = 0.04; *U* = 8.0 *p* = 0.04). In contrast, there was no age-related difference in connectivity between amygdala and dorsolateral PFC (Table 2). Variability of the connectivity measure was not significantly different between groups for any of these circuits.

Extent of activation—emotional WM task

Significant differences in the extent of the activated region between subject groups were found for dorsolateral PFC (*p* = 0.02), again with the elder subjects activating a greater number of voxels

Table 2.   Semantic working memory task—connectivity results

Group	Amyg-OPFC*	Amyg-DLPFC	OPFC-DLPFC*
Elder	0.101 (0.164) (*n* = 7)	0.173 (0.166) (*n* = 8)	0.639 (0.300) (*n* = 7)
Younger	0.328 (0.268) (*n* = 6)	0.208 (0.104) (*n* = 6)	0.366 (0.208) (*n* = 6)
One-tail *t*-test of means (*p*)	*t* = −1.87, *p* = 0.04	*t* = −0.45, *p* = 0.33	*t* = 1.87, *p* = 0.04
Levene's Test—*F* [*p*]	0.69 [*p* = 0.43]	0.94 [*p* = 0.35]	0.14 [*p* = 0.71]
Mann Whitney-U [*p*]	7.0 [*p* = 0.03]	18.0 [*p* = 0.25]	8.0 [*p* = 0.04]
Effect size [d]	0.85	0.21	0.91

For each group, the mean (SD) strengths of the BOLD signal correlation between amygdala, dorsolateral and orbital prefrontal cortex regions of interest are shown. The number of subjects who activated voxels that entered into the analysis are noted for each pathway.

Table 3. Emotional working memory task – extent of activation results

Group	Amyg	OPFC	DLPFC*
Elder	12.9 (13.1)	21.9 (25.7)	24.8 (25.4)
Younger	8.9 (9.7)	14.3 (36.3)	5.4 (6.0)
One-tail *t*-test of means (*p*)	0.23	0.30	0.02
Levene's Test—F [p]	$F = 1.83, p = 0.19$	$F = 0.01, p = 0.95$	$F = 19.46, p < 0.001$
Effect size [d]	0.31	0.21	0.76

For each group, the number of voxels showing significant differential activation is tabulated [mean (SD)] in each region of interest. Levene's test was used to assess the equivalence of variances, and *t*-tests were used to test equality of means.

(Table 3). Variability between groups was significant for DLPFC but not for amygdala or OPFC regions.

Functional connectivity—emotional WM task

As in the semantic WM task, the older subjects showed significantly higher correlations between OPFC and DLPFC than younger subjects ($p = 0.02$) (Table 4). Older and younger subjects did not show significant differences in BOLD signal correlations between amygdala and OPFC or amygdala and DLPFC.

DISCUSSION

In this fMRI activation study of working memory circuits in healthy adult and elderly subjects, three important findings emerged. First, the older subjects showed significantly greater regional extent of activation to accomplish the tasks than did the younger adults, with both the semantic and emotional working memory tasks. Second, the older subjects exhibited significantly greater variability in the extent of activation for both tasks. Third, our measure of functional connectivity exhibited mixed age-related differences: in the semantic WM task, connectivity was lower in the older subjects for amygdala/OPFC circuit, as we had hypothesized, while in both semantic and emotional WM tasks, the older subjects

exhibited greater correlated activity in the OPFC/DLPFC circuit, contrary to our initial expectations.

Our first finding of greater extent of activation is consistent with some other studies in healthy aging. Using PET methods, Reuter-Lorenz *et al.* (2000) and Cabeza *et al.* (2002) have observed that elderly subjects who performed well on a working memory task recruited greater areas than younger subjects. In another PET experiment, Madden *et al.* (1999) observed activation in greater areas of the PFC in elderly subjects during an episodic memory task than was seen in younger adults. Rypma and D'Esposito (2000) used an event-related fMRI design with a working memory task, and reported age differences in activations primarily in the retrieval phase of the task, with older adults showing more activation of the dorsolateral prefrontal cortex than younger adults when load was higher. Bookheimer *et al.* (2000) examined patterns of fMRI brain activation during memory tasks in healthy adults with or without genetic risk for developing Alzheimer's disease; subjects at risk showed significantly greater extent and magnitude of activation. Lamar *et al.* (2004) examined OFPFC with fMRI, using delayed match-to-sample and nonmatch-to-sample tasks, and reported that younger adults activated well delineated portions of OFPFC, while elders activated a more diffuse set of structures, including posterior structures as well as anterior ones. Cabeza (1997) noted similar patterns of findings for

Table 4. Emotional working memory task—connectivity results

Group	Amyg-OPFC	Amyg-DLPFC	OPFC-DLPFC*
Elder	0.166 (0.183) (n = 7)	0.237 (0.136) (n = 7)	0.654 (0.330) (n = 7)
Younger	0.093 (0.105) (n = 4)	0.132 (0.116) (n = 4)	0.270 (0.208) (n = 5)
One-tail *t*-test of means (*p*)	$t = 0.73, p = 0.24$	$t = 1.31, p = 0.11$	$t = 2.28, p = 0.02$
Levene's Test—F [p]	$F = 0.42, p = 0.54$	$F = 0.11, p = 0.92$	$F = 0.78, p = 0.40$
Mann–Whitney-U [p]	11.0 [p = 0.33]	11.0 [p = 0.23]	6.0 [p = 0.04]
Effect size [d]	0.40	0.77	1.16

For each group, the mean (SD) strengths of the BOLD signal correlation between amygdala, dorsolateral and orbital prefrontal cortex regions of interest are shown. The number of subjects who activated voxels that entered into the analysis are noted for each pathway.

episodic retrieval, and raised the possibility that greater neural activation in the frontal cortex might be viewed as a compensatory response to decreased neural efficiency with age. Velanova (2006) has reported that older subjects recruited additional frontal regions for memory retrieval when the task load was high.

Our second finding, of greater inter-individual variation in our elders, is also consistent with some prior reports. Our group has previously reported an increased variability with increased age in the volume of subclinical structural brain disease (SSBD) in healthy aging; this was particularly true of white matter hyperintensities, with an inflection point around age 70 (Cook *et al.*, 2002). Vandenbroucke *et al.* (2004) recently reported considerable inter-individual variation in elders between 60 and 70 years of age in regional fMRI activation, and cautioned that anatomical differences may make it preferable to analyze data in each subject's native space (as we did in our analysis) rather than to make comparisons using data transformed into a standardized space (e.g. Talairach and Tournoux, 1988). More broadly, D'Esposito *et al.* (2003) have asserted that any interpretation involving comparisons in BOLD signal between healthy younger and older subjects must be tempered by considering numerous confounding factors that may alter the underlying neurovascular coupling processes, including mechanical capacity of cerebral arterioles to dilate, cerebrovascular dynamic factors, ultrastructural damage to blood vessel walls, tortuosity of vessels in the elderly, different availability of nitric oxide, disruptions to the neuronal-astrocytic-vascular interactions, and the potential development of collateral circulation. The increased variability in extent of activation and correlation of activation in our data may reflect some inter-individual differences in these and other spheres, and future studies may examine the relative importance of these factors explicitly.

Our third finding, of age-related differences in our measures of functional connectivity, extends prior observations and raises additional questions. Prior investigations of functional connectivity across the age spectrum (e.g. Duffy *et al.*, 1996; Kikuchi *et al.*, 2000; Cook *et al.*, 2002) found that older subjects had lower measures of connectivity at rest, so that our finding of lower connectivity measures in the older subjects in the amygdala/OPFC circuit with the semantic WM task activation is consistent with these earlier reports. Several factors have been suggested as potential causes for decreases in connectivity, including macroscopic and microscopic damage to structural

elements (e.g. Taylor *et al.*, 2001; Cook *et al.*, 2002, 2004) and biochemical abnormalities (Kumar *et al.*, 2002; Wyckoff *et al.*, 2003). Further work that combines observations across functional and structural neuroimaging and biochemical measures may clarify the nature of these possible relationships.

The finding of evidence of *higher* connectivity in the older subjects for one circuit (OPFC/DLPFC) was contrary to our initial expectations, and suggests that measures of connectivity may be influenced by a number of factors, with damage to connecting white matter fibers being only one of them. This is also consistent with other findings in the literature. Others have observed that older adults recruit a broader set of brain regions to accomplish a given cognitive task than do younger adults, in efforts to compensate for age-related cognitive changes. This has been reported in other types of working memory and other executive tasks (Reuter-Lorenz *et al.*, 2000; Rypma and D'Esposito, 2000; Rypma *et al.*, 2001; Park *et al.*, 2003; Langenecker *et al.*, 2004; Noppeney *et al.*, 2004; Colcombe *et al.*, 2005; Rajah and D'Esposito, 2005) and in emotional recognition tasks (Gunning-Dixon *et al.*, 2003) in which older subjects activated not only the same regions as younger adults but additional regions as well. Bokde *et al.* (2006) also found increases in connectivity in some circuits for older patients with Minimal Cognitive Impairment (MCI), which they interpreted as indicative of compensatory mechanisms. It is possible that our observation of increased correlated activity between orbital and dorsolateral regions of the frontal lobe in the older subjects might reflect a similar phenomenon, and is consistent with our own prior findings (Bookheimer *et al.*, 2000). Additionally, the wider variance we observed in extent of activation by the elder subjects may also reflect greater heterogeneity in how elder subjects deploy neurological resources to accomplish a cognitive task. We favor an explanation of compensatory differences in how subjects engage brain regions to perform the task, and note that this could be examined in future studies by having subjects perform a task at variable levels of difficulty, to determine whether extent of activation was related to difficulty and effort, similar to what Rympa *et al.* (2005) have reported. Alternatively, there may be relevant underlying neurobiological differences between a cortical-subcortical circuit (amygdala/OPFC) and a cortico-cortical circuit (OPFC/DLPFC), such as variable passage of the connecting white matter fibers through the 'watershed' areas at risk for ischemic damage (e.g. Mantyla *et al.*, 1999). This possibility may better be tested using animal models,

where controlled placement of lesions of known size could be performed.

Yet another factor influencing this measure of connectivity may be the nature of the activation task. The task-related differences in our findings suggest that, in addition to structural factors (e.g. white matter hyperintensities) that were presumably stable over the time frame of our experiments, other factors about the nature of the task may also be important, i.e. emotionally-valenced vs emotionally-neutral tasks. Aftanas and Golochiekine (2001) investigated alterations in connectivity, assessed with EEG coherence during meditation, and found that positive emotional states were associated with increased measures of connectivity. Given that endogenous levels of dopamine may serve a modulatory role in emotional experiences, it is noteworthy that Honey et al. (2003) reported that fMRI connectivity measures in cortico-striato-thalamic circuits were modulated by pharmacological manipulation of dopaminergic neurotransmission with methylphenidate (dopamine reuptake inhibitor) or sulpiride (D2 receptor antagonist). In other work, Williams et al. (2002) reported a relationship between levodopa administration and cortico-subcortical connectivity assessed with depth electrodes in patients with Parkinson's Disease. It is possible that the emotionally-expressive qualities of the facial images in our experiment exerted some modulatory influences on the activity assessed via the BOLD signal analysis, and that this might account for different patterns in our emotionally-neutral and emotionally-charged tasks. More recent reports suggest that attentional factors, intention, and cognitive load may modulate connectivity, whether assessed with EEG (Gootjes et al., 2006) or by fMRI (Fu et al., 2006; de Marco et al., 2006). Future studies may be able directly to test the possibility that the emotional qualities of stimuli influence measures of connectivity assessed with a cognitive activation task. In addition, future studies that seek to study the influence of white matter damage on connectivity measures should include features to control for these potential modulatory factors.

There are several limitations of this study, including the modest sample size, the large difference in mean age between the two subject groups, and the heterogeneity that accompanies samples of healthy, community dwelling subjects. Future studies of the influence of aging on fMRI might examine age as a continuous rather than categorical parameter, and employ more stringent entrance criteria to ensure greater homogeneity of subject groups. Additionally, scanner characteristics did not permit us to acquire structural MRI data in a way that would allow volumetric analysis of subtle amounts of white matter hyperintensities (as we had done in Cook et al., 2002, 2004), and so we cannot examine directly the potential relationship between volume of hyperintensities with connectivity with the present dataset; future extensions of this work could test explicit hypotheses if precise morphometric data were also acquired. Finally, other methods have been suggested for assessing the degree of connectivity that exists between brain regions, including some precautions (Arfanakis et al., 2000; Della-Maggiore et al., 2000, 2002; Horwitz, 2003; Glabus et al., 2003; Greicius et al., 2003; Kondo et al., 2004).

Despite these limitations, our investigation supports the use of working memory tasks as stimuli in fMRI experiments to examine differences in connectivity between elderly and younger adults. As interest in the function of prefrontal circuitry in normal aging and late-life depression expands, fMRI experiments using working memory and other executive tasks may allow an even greater delineation of the role these circuits may play in contributing to symptoms and disability.

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REFERENCES

Aftanas LI, Golocheikine SA. 2001. Human anterior and frontal midline theta and lower alpha reflect emotionally positive state and internalized attention: high-resolution EEG investigation of meditation. *Neurosci Lett* **310**(1): 57–60.

Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 1997. Vascular depression' hypothesis. *Arch Gen Psychiatry* **54**(10): 915–922.

Arfanakis K, Cordes D, Haughton VM, et al. 2000. Combining independent component analysis and correlation analysis to probe interregional connectivity in fMRI task activation datasets. *Magn Reson Imaging* **18**(8): 921–930.

Baldwin RC. 2005. Is vascular depression a distinct sub-type of depressive disorder? A review of causal evidence. *Int J Geriatr Psychiatry* **20**(1): 1–11.

Baldwin R, Jeffries S, Jackson A, et al. 2004. Treatment response in late-onset depression: relationship to neuropsychological, neuroradiological and vascular risk factors. *Psychol Med* **34**(1): 125–136.

Bauer RH, Fuster JM. 1976. Delayed-matching and delayed-response deficit from cooling dorsolateral prefrontal cortex in monkeys. *J Comp Physiol Psychol* **90**(3): 293–302.

Bauer RH, Fuster JM. 1978. Effects of d-amphetamine and prefrontal cortical cooling on delayed matching-to-sample behavior. *Pharmacol Biochem Behav* **8**(3): 243–249.

Baxter LR Jr. 1992. Neuroimaging studies of obsessive compulsive disorder. *Psychiatr Clin North Am* **15**(4): 871–884.

Biswal B, Yetkin FZ, Haughton VM, Hyde JS. 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med* **34**(4): 537–541.

Bokde AL, Lopez-Bayo P, Meindl T, et al. 2006. Functional connectivity of the fusiform gyrus during a face-matching task in subjects with mild cognitive impairment. *Brain* **129**(5): 1113–1124.

Bookheimer SY, Strojwas MH, Cohen MS, et al. 2000. Patterns of brain activation in people at risk for Alzheimer's disease. *N Engl J Med* **343**(7): 450–456.

Boone KB, Miller BL, Lesser IM, et al. 1992. Neuropsychological correlates of white-matter lesions in healthy elderly subjects: a threshold effect. *Arch Neurol* **6**: 215–223.

Boone KB, Miller BL, Lesser IM. 1993. Frontal lobe cognitive functions in aging: methodologic considerations. *Dementia* **4**(3–4): 232–236.

Buchner A, Faul F, Erdfelder E. 1997. G•Power: A priori, post-hoc, and compromise power analyses for the Macintosh (Version 2.1.2) [Computer program]. University of Trier: Trier.

Bullmore E, Horwitz B, Honey G, et al. 2000. How good is good enough in path analysis of fMRI data? *NeuroImage* **11**: 289–301.

Cabeza R, McIntosh AR, Tulving E, Nyberg L, Grady CL. 1997. Age-related differences in effective neural connectivity during encoding and recall. *Neuroreport* **8**(16): 3479–3483.

Cabeza R, Anderson ND, Locantore JK, McIntosh AR. 2002. Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage* **17**(3): 1394–1402.

Casey BJ, Cohen JD, Jezzard P, et al. 1995. Activation of prefrontal cortex in children during a nonspatial working memory task with functional MRI. *Neuroimage* **2**(3): 221–229.

Cohen MS. 1997. Parametric analysis of fMRI data using linear systems methods. *Neuroimage* **6**(2): 93–103.

Colcombe SJ, Kramer AF, Erickson KI, Scalf P. 2005. The implications of cortical recruitment and brain morphology for individual differences in inhibitory function in aging humans. *Psychol Aging* **20**(3): 363–375.

Cook IA, Leuchter AF, Morgan ML, et al. 2002. Cognitive and physiologic correlates of subclinical structural brain disease in elderly healthy control subjects. *Arch Neurol* **59**(10): 1612–1620.

Cook IA, Leuchter AF, Morgan ML, et al. 2004. Longitudinal progression of subclinical structural brain disease in normal aging. *Am J Geriatr Psychiatry* **12**(2): 190–200.

David AS, Cutting JC. 1990. Affect, affective disorder and schizophrenia. A neuropsychological investigation of right hemisphere function. *Br J Psychiatry* **156**: 491–495.

Davidson RJ, Lewis DA, Alloy LB, et al. 2002. Neural and behavioral substrates of mood and mood regulation. *Biol Psychiatry* **52**(6): 478–502.

D'Esposito M, Postle BR, Rypma B. 2000. Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies. *Exp Brain Res* **133**(1): 3–11.

D'Esposito M, Deouell LY, Gazzaley A. 2003. Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging. *Nat Rev Neurosci* **4**(11): 863–872.

de Groot JC, de Leeuw FE, Oudkerk M, et al. 2000. Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. *Ann Neurol* **47**: 145–151.

de Marco G, de Bonis M, Vrignaud P, et al. 2006. Changes in effective connectivity during incidental and intentional perception of fearful faces. *Neuroimage* **30**(3): 1030–1037.

Della-Maggiore V, Sekuler AB, Grady CL, et al. 2000. Cortico-limbic interactions associated with performance on a short-term memory task are modified by age. *J Neurosci* **20**(22): 8410–8416.

Della-Maggiore V, Grady CL, McIntosh AR. 2002. Dissecting the effect of aging on the neural substrates of memory: deterioration, preservation or functional reorganization? *Rev Neurosci* **13**(2): 167–181.

Drevets WC. 2003. Neuroimaging abnormalities in the amygdala in mood disorders. *Ann N Y Acad Sci* **985**: 420–444.

Duffy FH, Mcanulty GB, Albert MS. 1996. Effects of age upon interhemispheric EEG coherence in normal adults. *Neurobiol Aging* **17**(4): 587–599.

Dunkin JJ, Osato S, Leuchter AF. 1995. Relationships between EEG coherence and neuropsychological tests in dementia. *Clin Electroencephalogr* **26**(1): 47–59.

Dunkin JJ, Leuchter AF, Cook IA, et al. 2000. Executive dysfunction predicts nonresponse to fluoxetine in major depression. *J Affect Disord* **60**(1): 13–23.

Ekman P, Friesen WV. 1976. *Pictures of Facial Affect*. Consulting Psychologists Press: Palo Alto, CA.

Fazekas F, Schmidt R, Kleinert R, et al. 1998. The spectrum of age-associated brain abnormalities: their measurement and histopathological correlates. *J Neural Transm Suppl* **53**: 31–39.

Ferro JM, Madureira S. 2002. Age-related white matter changes and cognitive impairment. *J Neurol Sci* **203–204**: 221–225.

Fischer HW, Ketonen L. 1991. *Radiographic Neuroanatomy: A Working Atlas*. McGraw-Hill, Health Professions: New York.

Fu CH, McIntosh AR, Kim J, et al. 2006. Modulation of effective connectivity by cognitive demand in phonological verbal fluency. *Neuroimage* **30**(1): 266–271.

Fuster JM. 2001. The prefrontal cortex–an update: time is of the essence. *Neuron* **30**(2): 319–333.

Geschwind N. 1965a. Disconnexion syndromes in animals and man. I. *Brain* **88**(2): 237–294.

Geschwind N. 1965b. Disconnexion syndromes in animals and man. II. *Brain* **88**(3): 585–644.

Geschwind N, Kaplan E. 1962. A human cerebral deconnection syndrome. A preliminary report. *Neurology* **12**: 675–685.

Glabus MF, Horwitz B, Holt JL, et al. 2003. Interindividual differences in functional interactions among prefrontal, parietal and parahippocampal regions during working memory. *Cereb Cortex* **13**(12): 1352–1361.

Gootjes L, Bouma A, Van Strien JW, et al. 2006. Attention modulates hemispheric differences in functional connectivity: evidence from MEG recordings. *Neuroimage* **30**(1): 245–253.

Grady CL, McIntosh AR, Bookstein F, et al. 1998. Age-related changes in regional cerebral blood flow during working memory for faces. *Neuroimage* **8**(4): 409–425.

Grady CL, McIntosh AR, Craik FI. 2003. Age-related differences in the functional connectivity of the hippocampus during memory encoding. *Hippocampus* **13**(5): 572–586.

Greicius MD, Krasnow B, Reiss AL, Menon V. 2003. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci USA* **100**(1): 253–258.

Gunning-Dixon FM, Raz N. 2000. The cognitive correlates of white matter abnormalities in normal aging: a quantitative review. *Neuropsychology* **14**: 224–232.

Gunning-Dixon FM, Raz N. 2003. Neuroanatomical correlates of selected executive functions in middle-aged and older adults: a prospective MRI study. *Neuropsychologia* **41**(14): 1929–1941.

Gunning-Dixon FM, Gur RC, Perkins AC, et al. 2003. Age-related differences in brain activation during emotional face processing. *Neurobiol Aging* **24**(2): 285–295.

Gur RE, McGrath C, Chan RM, et al. 2002. An fMRI study of facial emotion processing in patients with schizophrenia. *Am J Psychiatry* **159**(12): 1992–1999.

Guttmann CR, Benson R, Warfield SK, et al. 2000. White matter abnormalities in mobility-impaired older persons. *Neurology* **54**: 1277–1283.

Hariri AR, Bookheimer SY, Mazziotta JC. 2000. Modulating emotional responses: effects of a neocortical network on the limbic system. *Neuroreport* **11**(1): 43–48.

Hickie I, Scott E. 1998. Late-onset depressive disorders: a preventable variant of cerebrovascular disease? *Psychol Med* **28**(5): 1007–1013.

Honey GD, Suckling J, Zelaya F, et al. 2003. Dopaminergic drug effects on physiological connectivity in a human cortico-striato-thalamic system. *Brain* **126**(8): 1767–1781.

Horwitz B. 2003. The elusive concept of brain connectivity. *Neuroimage* **19**(2 Pt 1): 466–470.

Inzitari D. 2000. Age-related white matter changes and cognitive impairment. *Ann Neurol* **47**: 141–143.

Kaplan EF, Goodglass H, Weintraub S. 1983. *The Boston Naming Test*, 2nd edn. Lea & Febiger: Philadelphia, PA.

Ketonen LM. 1998. Neuroimaging of the aging brain. *Neurol Clin* **16**: 581–598.

Kikuchi M, Wada Y, Koshino Y, et al. 2000. Effect of normal aging upon interhemispheric EEG coherence: analysis during rest and photic stimulation. *Clin Electroencephalogr* **31**(4): 170–174.

Kondo H, Morishita M, Osaka N, et al. 2004. Functional roles of the cingulo-frontal network in performance on working memory. *Neuroimage* **21**(1): 2–14.

Koshino H, Carpenter PA, Minshew NJ, et al. 2005. Functional connectivity in an fMRI working memory task in high-functioning autism. *Neuroimage* **24**(3): 810–821.

Krishnan KR, McDonald WM. 1995. Arteriosclerotic depression. *Medic Hypotheses* **44**: 111–115.

Krishnan KR, Hays JC, Blazer DG. 1997. MRI-defined vascular depression. *Am J Psychiatry* **154**(4): 497–501.

Kumar A, Cook IA. 2002. White matter injury, neural connectivity and the pathophysiology of psychiatric disorders. *Dev Neurosci* **24**(4): 255–261.

Kumar A, Bilker W, Jin Z, Udupa J. 2000. Atrophy and high intensity lesions: complementary neurobiological mechanisms in late-life depression. *Neuropsychopharm* **22**: 264–274.

Kumar A, Schweizer E, Jin Z, et al. 1997. Neuroanatomical substrates of late-life minor depression: a quantitative magnetic resonance imaging study. *Arch Neurol* **54**(5): 613–617.

Kumar A, Jin Z, Bilker W, et al. 1998. Late-onset minor and major depression: early evidence for common neuroanatomical substrates detected by using MRI. *Proc Natl Acad Sci USA* **95**(13): 7654–7658.

Kumar A, Thomas A, Lavretsky H, et al. 2002. Frontal white matter biochemical abnormalities in late-life major depression detected with proton magnetic resonance spectroscopy. *Am J Psychiatry* **159**(4): 630–636.

Lamar M, Yousem DM, Resnick SM. 2004. Age differences in orbitofrontal activation: an fMRI investigation of delayed match and nonmatch to sample. *Neuroimage* **21**(4): 1368–1376.

Langenecker SA, Nielson KA, Rao SM. 2004. fMRI of healthy older adults during Stroop interference. *Neuroimage* **21**(1): 192–200.

Lavretsky H, Lesser IM, Wohl M, et al. 1999. Clinical and neuroradiologic features associated with chronicity in late-life depression. *Am J Geriatr Psychiatry* **7**(4): 309–316.

Lavretsky H, Lesser IM, Wohl M, et al. 2000. Apolipoprotein-E and white-matter hyperintensities in late-life depression. *Am J Geriatr Psychiatry* **8**(3): 257–261.

Lee L, Harrison LM, Mechelli A. 2003. A report of the functional connectivity workshop, Dusseldorf 2002. *Neuroimage* **19**(2 Pt 1): 457–465.

Lenze E, Cross D, McKeel D, et al. 1999. White matter hyperintensities and gray matter lesions in physically healthy depressed subjects. *Am J Psychiatry* **156**: 1602–1607.

Lesser IM, Boone KB, Mehringer CM, et al. 1996. Cognition and white matter hyperintensities in older depressed patients. *Am J Psychiatry* **153**: 1280–1287.

Leuchter AF, Newton TF, Cook IA, et al. 1992. Changes in brain functional connectivity in Alzheimer-type and multi-infarct dementia. *Brain* **115**(5): 1543–1561.

Leuchter AF, Dunkin JJ, Lufkin RB, et al. 1994. Effect of white matter disease on functional connections in the aging brain. *J Neurol Neurosurg Psychiatry* **57**(11): 1347–1354.

Longstreth WT, Manolio TA, Arnold A, et al. 1996. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people: the Cardiovascular Health Study. *Stroke* **27**: 1274–1282.

Lowe MJ, Mock BJ, Sorenson JA. 1998. Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. *Neuroimage* **7**(2): 119–132.

Madden DJ, Turkington TG, Provenzale JM, et al. 1999. Adult age differences in the functional neuroanatomy of verbal recognition memory. *Hum Brain Mapp* **7**(2): 115–135.

Mantyla R, Aronen HJ, Salonen O, et al. 1999. The prevalence and distribution of white-matter changes on different MRI pulse sequences in a post-stroke cohort. *Neuroradiology* **41**(9): 657–665.

Marshall JC, Fink GR. 2003. Cerebral localization, then and now. *Neuroimage* **20** (Suppl. 1):S2–S7.

Mayberg HS. 2003. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. *Br Med Bull* **65**: 193–207.

McIntosh AR, Grady CL, Haxby JV, et al. 1996. Changes in limbic and prefrontal functional interactions in a working memory task for faces. *Cereb Cortex* **6**(4): 571–584.

Noppeney U, Friston KJ, Price CJ. 2004. Degenerate neuronal systems sustaining cognitive functions. *J Anat* **205**(6): 433–442.

O'Brien J, Ames D, Chiu E, et al. 1998. Severe deep white matter lesions and outcome in elderly patients with major depressive disorder: follow up study. *BMJ* **317**(7164): 982–984.

O'Sullivan M, Jones DK, Summers PE, et al. 2001. Evidence for cortical 'disconnection' as a mechanism of age-related cognitive decline. *Neurology* **57**(4): 632–638.

O'Sullivan M, Morris RG, Huckstep B, et al. 2004. Diffusion tensor MRI correlates with executive dysfunction in patients with ischaemic leukoaraiosis. *J Neurol Neurosurg Psychiatry* **75**(3): 441–447.

Park DC, Welsh RC, Marshuetz C, et al. 2003. Working memory for complex scenes: age differences in frontal and hippocampal activations. J Cogn Neurosci 15(8): 1122–1134.

Phillips ML, Drevets WC, Rauch SL, Lane R. 2003. Neurobiology of emotion perception II: Implications for major psychiatric disorders. Biol Psychiatry 54(5): 515–528.

Quintana J, Fuster JM. 1993. Spatial and temporal factors in the role of prefrontal and parietal cortex in visuomotor integration. Cereb Cortex 3(2): 122–132.

Rajah MN, D'Esposito M. 2005. Region-specific changes in prefrontal function with age: a review of PET and fMRI studies on working and episodic memory. Brain 128(Pt 9): 1964–1983.

Ramnani N, Behrens TE, Penny W, Matthews PM. 2004. New approaches for exploring anatomical and functional connectivity in the human brain. Biol Psychiatry 56(9): 613–619.

Reuter-Lorenz PA, Jonides J, Smith EE, et al. 2000. Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. J Cogn Neurosci 12(1): 174–187.

Rubinow DR, Post RM. 1992. Impaired recognition of affect in facial expression in depressed patients. Biol Psychiatry 31(9): 947–953.

Rypma B, D'Esposito M. 2000. Isolating the neural mechanisms of age-related changes in human working memory. Nat Neurosci 3(5): 509–515.

Rypma B, Prabhakaran V, Desmond JE, Gabrieli JD. 2001. Age differences in prefrontal cortical activity in working memory. Psychol Aging 16(3): 371–384.

Rypma B, Prabhakaran V, Desmond JE, et al. 1999. Load-dependent roles of frontal brain regions in the maintenance of working memory. Neuroimage 9(2): 216–226.

Rypma B, Berger JS, Genova HM, et al. 2005. Dissociating age-related changes in cognitive strategy and neural efficiency using event-related fMRI. Cortex 41(4): 582–594.

Saxena S, Brody AL, Ho ML, et al. 2002. Differential cerebral metabolic changes with paroxetine treatment of obsessive–compulsive disorder vs major depression. Arch Gen Psychiatry 59(3): 250–261.

Saxena S, Brody AL, Maidment KM, et al. 2004. Cerebral glucose metabolism in obsessive–compulsive hoarding. Am J Psychiatry 161(6): 1038–1048.

Sheline YI, Barch DM, Donnelly JM, et al. 2001. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. Biol Psychiatry 50(9): 651–658.

Shindy WW, Posley KA, Fuster JM. 1994. Reversible deficit in haptic delay tasks from cooling prefrontal cortex. Cereb Cortex 4(4): 443–450.

Smith CD, Snowdon DA, Wang H, Markesbery WR. 2000. White matter volumes and periventricular white matter hyperintensities in aging and dementia. Neurology 54: 838–842.

Soderlund H, Nyberg L, Adolfsson R, et al. 2003. High prevalence of white matter hyperintensities in normal aging: relation to blood pressure and cognition. Cortex 39(4–5): 1093–1105.

Steffens DC, Krishnan KR. 1998. Structural neuroimaging and mood disorders: recent findings, implications for classification, and future directions. Biol Psychiatry 43(10): 705–712.

Talairach J, Tournoux P. 1988. Coplanar Stereotaxic Atlas of the Human Brain: 3 Dimensional Proportional System: An Approach to Cerebral Imaging. Georg Thieme Verlag: New York.

Taylor WD, Payne ME, Krishnan KR, et al. 2001. Evidence of white matter tract disruption in MRI hyperintensities. Biol Psychiatry 50(3): 179–183.

Taylor WD, Steffens DC, MacFall JR, et al. 2003. White matter hyperintensity progression and late-life depression outcomes. Arch Gen Psychiatry 60(11): 1090–1096.

Vandenbroucke MW, Goekoop R, Duschek EJ, et al. 2004. Inter-individual differences of medial temporal lobe activation during encoding in an elderly population studied by fMRI. Neuroimage 21(1): 173–180.

Vataja R, Pohjasvaara T, Mantyla R, et al. 2005. Depression-executive dysfunction syndrome in stroke patients. Am J Geriatr Psychiatry 13(2): 99–107.

Velanova K, Lustig C, Jacoby LL, Buckner RL. 2006. Evidence for Frontally Mediated Controlled Processing Differences in Older Adults. Cereb Cortex (doi: 10.1093/cercor/bhl013).

Williams D, Tijssen M, Van Bruggen G, et al. 2002. Dopamine-dependent changes in the functional connectivity between basal ganglia and cerebral cortex in humans. Brain 125(7): 1558–1569.

Woods RP, Cherry SR, Mazziotta JC. 1992. Rapid automated algorithm for aligning and reslicing PET images. J Comput Assist Tomogr 16(4): 620–633.

Woods RP, Grafton ST, Holmes CJ, et al. 1998a. Automated image registration: I. General methods and intrasubject, intramodality validation. J Comput Assist Tomogr 22(1): 139–152.

Woods RP, Grafton ST, Watson JD, et al. 1998b. Automated image registration: II. Intersubject validation of linear and nonlinear models. J Comput Assist Tomogr 22(1): 153–165.

Wyckoff N, Kumar A, Gupta RC, et al. 2003. Magnetization transfer imaging and magnetic resonance spectroscopy of normal-appearing white matter in late-life major depression. J Magn Reson Imaging 18(5): 537–543.