The Neural Correlates of Declining Performance with Age: Evidence for Age-Related Changes in Cognitive Control

The neural system involved in cognitive control includes the anterior cingulate cortex (ACC) and the lateral prefrontal cortex (PFC). Neural activity within these structures is sensitive to aging. We investigated the hypothesis that decline in performance with age results in increased cognitive control, as indexed by greater activity within the ACC and lateral PFC. Using positron emission tomography we measured neural activity during a range of verbal decision-making tasks in 16 subjects aged 37–83 years. Conditions were separated behaviorally on the basis of their sensitivity to aging. This allowed the comparison of age-dependent and age-independent conditions, revealing the neural correlates of age-dependent decline in performance. We then modeled the relationship between age, decision type, performance, and frontal lobe activity. ACC activity was independently predicted by age and decision-making accuracy, indicating that in older individuals ACC response is more sensitive to declining performance. We also found strong functional connectivity between the ACC and lateral PFC and observed that activation of the lateral PFC was qualitatively different over time in different age groups. Thus, the ACC and lateral PFC show distinct responses to age-related decline in decision-making performance. This suggests that greater cognitive control is employed as individuals age and their performance declines.

Keywords: aging, cingulate, imaging, memory, prefrontal

Introduction

Aspects of cognitive processing decline with age (Park and others 1996). For example, age-related deficits have been reported in measures of working memory (Park and others 1996; Robbins and others 1998), in tasks requiring focused or selective attention (McDowd and Shaw 2000), and in general measures of processing speed (Salthouse 1996). These changes may lead to a decline in performance (Craik and Salthouse 2000), but their impact will depend, in part, upon the balance between supervisory systems that exert cognitive control and the subordinate systems that they influence.

Previous neuroimaging studies have demonstrated various patterns of age-related changes in neural activity that frequently include changes within the frontal lobes (Grady and others 1996, 2003; Cabeza and others 1997, 2002; McIntosh and others 1999; Grady and Craik 2000; Logan and others 2002). One observation has been that parts of the prefrontal cortex (PFC) in older individuals show reduced activation or under-recruitment when compared with similar regions in younger adults (Cabeza and others 1997; Madden and others 1999; Logan and others 2002; for a review, see Grady and Craik, 2000). For example, Cabeza and others (1997) observed that parts of the left PFC and occipitotemporal regions showed less activation for older than for younger adults during episodic memory encoding. Similarly, Logan and others (2002) found a reduction in activation of the left anterior inferior frontal gyrus (Brodmann area [BA] 45/47) in older adults compared with younger adults during the self-initiated encoding of words. This attenuated activation of prefrontal regions may partly underlie age-related cognitive decline (Madden and others 1999; Grady and Craik 2000; Logan and others 2002). However, in certain circumstances the underrecruitment is reversible, suggesting that the failure to recruit prefrontal systems may be in part context dependent (Logan and others 2002).

A second pattern of age-related changes has been a reduced asymmetry in the activation of the PFC in older compared with younger adults, a finding that has been observed across a number of different cognitive domains (Cabeza and others 1997, 2002; Madden and others 1999; Grady and Craik 2000; Reuter-Lorenz and others 2000; Logan and others 2002). It has been suggested that this pattern, which involves the recruitment of more extensive parts of the PFC in older subjects, may represent a form of compensation for age-related decline in cognitive processing. This hypothesis is supported by reports of improved behavioral performance in older adults who show more asymmetry in their pattern of activation (Reuter-Lorenz and others 2000; Cabeza and others 2002).

Neural activity within the anterior cingulate cortex (ACC) as well as the lateral PFC is sensitive to the effects of aging (Cabeza and others 1997; Madden and others 1999; Band and Kok 2000; Falkenstein and others 2000; Grady and Craik 2000; Rypma and D’Esposito 2000; Milham and others 2002; Park and others 2003). For example, the response of the ACC in older adults is more sensitive to the presence of conflict during a Stroop task (Milham and others 2002). As the ACC and lateral PFC both form part of the cortical network involved in cognitive control (MacDonald and others 2000; Paus 2001; Shallice 2002), these changes may reflect changes in cognitive control that accompany aging.

Cognitive control involves the support of relevant processing and the monitoring of potential and actual behavior (Shallice 1988). As individuals age, increased levels of control may compensate for age-related decline in other aspects of information processing. The behavior of older individuals suggests that they continue to monitor their performance accurately (Rabbitt 1979) but exert increased cognitive control following errors (Band and Kok 2000). This strategic change in task performance may be driven by an increased sensitivity within the ACC to declining performance (Milham and others 2002) and is likely to be associated with age-related modulation of activity within both the ACC and lateral PFC.

The ACC and lateral PFC have distinct yet complementary roles in cognitive control (MacDonald and others 2000; Schall and others 2002). The ACC appears to be involved primarily in...
the assessment of responses, detecting both errors (Gehring and others 1993; Falkenstein and others 2000) and the presence of conflict between potential responses (Carter and others 2000). In contrast, the lateral PFC appears to be involved in more strategic processing, through the support of task-relevant processes and the high-level monitoring of ongoing behavior (MacDonald and others 2000; Shallice 2002). Hence, the ACC is thought to signal the optimal level of cognitive control, with changes in the level of control implemented through an interaction between the ACC and the lateral PFC.

Frontal lobe damage results characteristically in a difficulty coping with novel situations, a change that is expressed clinically in perseverative and stereotyped responses (Shallice 1988). In functional imaging studies, the amount of frontal lobe activity is related to the novelty of a task. Activity within the ACC and lateral PFC has been shown to decline with practice (Raichle and others 1994; Jansma and others 2001); a pattern that has been interpreted as resulting from a reduction in the requirement for cognitive control, accompanying a shift from controlled to more automatic information processing (Jansma and others 2001). Older individuals frequently show less cognitive flexibility (Mutter and Pliske 1994; Chasseigne and others 1997; Robbins and others 1998), and the neural system involved in cognitive control may reflect this change. This area has received little attention in previous neuroimaging studies of aging, although age-related differences in the pattern of change in neural activity over time have previously been demonstrated (Madden and others 1999).

In our study, 19 subjects aged between 37 and 83 years made 2 types of verbal decision: semantic decisions required the retrieval of associative knowledge, whereas syllable decisions required comparison of the number of syllables within heard words. Further, the perceptual clarity of the words was manipulated by presenting them as either clear or degraded speech. We predicted that aging would differentially affect behavioral performance on these tasks, providing conditions where performance either declined with age (i.e., an age-dependent condition) or where performance was unrelated to age (i.e., an age-independent condition).

Semantic knowledge is acquired throughout life, and the storage and use of this type of information appears to be relatively unimpaired by aging (Salthouse 1982, 1996; Nyberg and others 1996; Burke and Mackay 1997). Thus, we predicted that semantic decisions made on clear speech stimuli would be the most resistant to aging. In contrast, the controlled processing of word syllabic structure involves focusing attention on the surface sound structure of words, which, unlike attending to the meaning of a word, is not a feature of normal automatic speech perception and comprehension (Scott and Johnsrude 2003). As older individuals frequently show less cognitive flexibility (Mutter and Pliske 1994; Chasseigne and others 1997; Robbins and others 1998), we predicted that this type of verbal decision making would be more sensitive to aging. In addition, the perception of degraded speech undergoes a noticeable decline beginning in the fifth decade of life (Bergman and others 1976; Gordon-Salant and Fitzgibbons 1993), and we expected that age-related impairment in peripheral auditory function (Baltes and Lindenberger 1997) would contribute to a decline in performance in the conditions that involved the presentation of degraded speech stimuli.

We predicted that age-dependent decline in performance would be associated with age-dependent changes in neural activity. The location of such a change in neural activity should inform the nature of any cognitive response to declining performance as individuals age. One way of attempting to improve performance would be to increase the level of cognitive control involved in decision making. Increased levels of cognitive control are known to be associated with increased activation within the ACC and lateral PFC (Cohen and others 1997; MacDonald and others 2000; Paus 2001; Shallice 2002). Therefore, increased activation of the ACC and lateral PFC as individuals age would suggest an age-dependent increase in the level of cognitive control involved in decision making.

In addition, using a different type of analysis, we examined the effect of task repetition upon neural activity to identify any time-dependent effects present in different age groups. Older individuals may show difficulty adapting to novelty, and we predicted that this would be associated with a different level of activation over time within the network that supports cognitive control. Specifically, on the basis of previous work (Madden and others 1999), we predicted that activation within the ACC and lateral PFC would fall more slowly with experience in older subjects relative to younger subjects. This would provide evidence for a higher level of cognitive control in older individuals maintained over time.

Materials and Methods

Subjects

Nineteen English speaking, right-handed, normal volunteers (7 females), aged between 37 and 83 years, gave informed, written consent for the study. Subjects were excluded if they had neurological illness, psychiatric illness, or showed signs of dementia mini mental state examination (MMSE < 28). Subjects were also excluded if they had risk factors for cerebrovascular disease. Structural magnetic resonance imaging (MRI) scanning was used to exclude brain abnormalities. Prior testing demonstrated that subjects were capable of hearing the stimuli clearly. The study was approved by the Administration of Radioactive Substances Advisory Committee (Department of Health, UK) and the research ethics committee at The Hammersmith Hospital (London, UK).

Two subjects with behavioral performance in the scanner greater than 2 standard deviations from the mean of the whole group were excluded from imaging analysis. Another subject was excluded from further analysis as a result of a failure to complete the study. One further subject was not entered into analyses requiring the use of performance data due to technical problems leading to a failure to record behavioral data while in the scanner. As a result, 16 subjects (37-83 years old) were included in the overall analyses of aging effects, and 15 subjects (41-83 years old) were included in those analyses that involved performance data.

Study Design

Brain activation was measured using positron emission tomography (PET). The use of PET has 2 distinct advantages over functional MRI (fMRI) for this type of study. In contrast to fMRI, stimuli are routinely presented in a quiet auditory environment in PET studies. This factor was particularly important for our study because subjects are unable to perceive the degraded speech against a background of fMRI scanner noise. In addition, PET allows a more accurate estimation of neural activation in a number of brain regions that are critical for language processing, the result of fMRI susceptibility artifacts found at air-tissue interfaces (Devlin and others 2000). Conversely, there are also limitations of PET compared with fMRI. For example, event-related designs are not possible using PET, as conditions must be presented as a block. In our study this means that correct and incorrect trials cannot be analyzed separately, limiting the temporal resolution of the analysis.

Verbal decisions were made on triplets of single heard words. Different combinations of the same words were used in the 2 tasks (semantic and syllable decision making). Stimuli were presented either as clear or degraded speech. Stimulus presentation was paced with an
interstimulus interval of 6 s. Subjects made a right-handed button press to signify their word choice and online recordings of responses and reaction times (RTs) were made.

**Semantic Decision**

Subjects made semantic decisions (Sem) on heard word triplets following a standard question asked once at the onset of each scanning block (e.g., “which word has more in common with beach: island or mountaintop?”). After the first triplet of each block, stimuli were presented without the preceding question. The triplets were selected on the basis of a pilot study performed on 10 normal subjects who did not subsequently participate in the scanning study. This study was used to identify word triplets for the semantic task where there was a greater than 90% agreement on the “correct” response.

**Syllable Decision**

Subjects made a syllabic judgment (Syll) on heard word triplets following a standard question (e.g., “which word has the same number of syllables as hammer: tool or trailer?”). As with the semantic condition, the question was asked once at the start of each block of syllable decision making. Pilot data were used again to define triplets with a greater than 90% agreement on the correct response.

**Clear and Noise-Vocoded Stimuli**

Subjects made the Sem and Syll decisions on stimuli presented either as clear speech (SemSp and SyllSp) or as 8-channel noise-vocoded speech (8VoCo) (Shannon and others 1995) spoken by a female British English speaker (SemVoCo and SyllVoCo). The method of constructing noise-vocoded speech has been described previously (Shannon and others 1995; Scott and others 2001). After such manipulation, 8-VoCo sounds like a harsh whisper but can be understood after a brief period of training.

For the purposes of this study, training consisted of a single session held immediately prior to scanning. Subjects were trained on examples of semantic and syllable decision making as well as in comprehending degraded speech. The examples of decision-making were not used subsequently during scanning. Toward the end of the training period subjects heard 54 single-8-VoCo words and were scored on the accuracy of their repetition of these words. The period of training was adjusted until each subject was repeating with >90% accuracy (range, 55.3-85.6). The correlation between age and repetition performance after training approached significance (Pearson’s correlation coefficient = –0.49, P = 0.067). This correlation was performed upon 15 subjects due to the loss of data for 1 subject. By the end of scanning, all subjects fully understood and were competent at decision-making.

**PET Scanning**

Subjects were scanned on a Siemens HR++ (966) PET camera (Spinks and others 2000). Water, labeled with a positron-emitting isotope of oxygen ($^{15}O$), was used as the tracer to demonstrate changes in regional cerebral blood flow (rCBF), equivalent to changes in tissue concentration of $^{15}O$. Positron emissions are integrated over the course of each scan to provide a single measure of rCBF for each voxel from each scan. Analysis involved relating changes in local tissue activity (normalized for global changes in perfusion across scans). Scan order was entered as a nuisance variable.

To identify the neural correlates of age-related decline in performance, conditions where decision-making performance was dependent upon the age of the subject (age-dependent decision making) were compared with those where decision-making performance was independent of age (age-independent decision making). Individual contrast images for age-dependent versus age-independent decision making were defined at a fixed-effects level and then entered into a random-effects correlation analysis using the individual’s age as a covariate of interest. A condition with age-independent decision making provides an appropriate baseline for this analysis because the level of cognitive control will be similar across subjects of different ages, as performance in such a condition does not systematically vary with age. In contrast, in a condition with age-dependent decline in decision-making accuracy, greater cognitive control will be required as individuals age. Thus, the comparison of age-dependent and age-independent conditions reveals the neural correlates of age-related increases in cognitive control relative to a well-controlled baseline. In addition, the main effect of age-dependent versus age-independent decision making across all individuals was demonstrated.

A separate analysis was also performed to identify brain regions where neural activity correlated with performance. In this analysis, the effects of condition and performance were modeled separately, with the percentage accuracy for each condition entered as a covariate of interest. For both these whole-brain analyses we employed a threshold of $P < 0.05$ corrected for multiple comparisons across the volume of the brain, except for activations that fell within the ACC and PFC, about which we had a priori hypotheses. For these activations we employed small-volume corrections using the volumes of the ACC and the PFC derived from a neuroanatomical probabilistic atlas (Hammers and others 2003).

A multiple regression analysis was employed to investigate further the relationship between decision-making performance, age and neural activation. Using a region of interest (ROI) approach, we derived estimates of mean activation for the contrast of age-dependent and age-independent decision making from within the whole of the ACC, the middle frontal gyrus, and the inferior frontal gyrus. We again used regions defined from a neuroanatomical probabilistic atlas (Hammers and others 2003) and obtained subject-specific mean activation values from these regions by using an ROI analysis toolbox implemented within SPM99 (Brett and others 2002). Mean activation values were obtained for the contrast of conditions showing age-dependent performance with SemSp, where performance was age-independent (i.e., [SyllSp – SemSp], [SyllVoCo – SemVoCo], and [SemVoCo – SemSp]). The mean activation values for these contrasts were entered as the dependent variable into a stepwise multiple regression analysis with the age of the subject, the percentage accuracy of decision making, and the type of decision making as independent predictors.

We also investigated the effect that repeating each condition on 4 separate occasions (task repetition) had upon neural activation in the age-dependent and age-independent conditions. Our hypotheses related to the neural response within the lateral PFC and ACC, as outlined in the Introduction, and therefore we examined the patterns of activation within these regions. As this analysis was orthogonal to the other analyses we performed, the pattern of activity was examined using ROIs centered on peaks of activation within the lateral PFC and ACC taken from this study. In the ACC, 1 ROI was used, centered on the peak of activation from the age-related activation observed in the ACC. In the lateral PFC, 2 ROIs were used, centered on the peaks of activity in the right dorsolateral PFC and ventrolateral PFC shown in the main effect of the individual PET scans. These were then spatially transformed (normalized) into standard MNI (Montreal Neurological Institute) stereotactic space (Evans and others 1993). This transformation allowed comparisons to be made across individuals. The scan data were then smoothed using an isotropic 16-mm, full width at half-maximum Gaussian kernel to account for the individual variation in gyral anatomy found within the PFC (Rajkowska and Goldman-Rakic 1995) and to improve the signal-to-noise ratio. Specific effects were investigated using appropriately weighted linear contrasts and covariates to create statistical parametric maps of the T-statistic (which were subsequently transformed into Z scores). We used a blocked analysis of covariance with global counts as confounds to remove the effect of global changes in perfusion across scans. Scan order was entered as a nuisance variable.

**Data Analysis**

SPM99 software (Wellcome Department of Cognitive Neurology, Queen Square, London: http://www.fil.ion.ucl.ac.uk/spm) was used to realign the PET Scanning images and to perform spatial smoothing of the data.
age-dependent versus age-independent decision making (i.e., [SemVoCo + SyllSp + SyllVoCo] − [SemSp]). rCBF values, adjusted for effects of interest, were extracted from spherical ROIs with a radius of 10 mm. The use of extracted rCBF values allowed age-dependent and age-independent conditions to be analyzed separately. To allow statistical analysis using analysis of variance (ANOVA), subjects were split around the mean age of the whole group into 2 groups containing the same number of subjects: a younger group (aged between 37 and 54 years, mean age 44.5) and an older group (aged between 60 and 83 years, mean age 70). A mixed ANOVA was performed using mean activation values as the dependent variable, with the type of decision making and scan order as within-subjects effects and age group as a between-subjects effect. Mean activation values from the right dorsolateral PFC and ventrolateral PFC were included in the same analysis, adding region as a further between-subjects effect for this analysis. In addition, the accuracy of decision making was added to the model to assess whether there was a significant relationship between changes in neural activation and performance over time.

The functional connectivity between the ACC and the lateral PFC was investigated. The activity across all scans (adjusted for confounds), taken from the peak voxels from the ACC of the correlational analyses using subjects accuracy and age, were used as covariates of interest in separate functional connectivity analyses (Friston and others 1997). These analyses revealed neural regions where activity covaried with ACC activation. We employed a threshold of $P < 0.05$ corrected for multiple comparisons across the volume of the whole brain, except for activations that fell within the ACC and PFC, where we again employed a small-volume correction for these regions. To identify any differences in functional connectivity from the peaks of activity in the accuracy and aging analyses were directed compared using a random-effects paired $t$ test analysis.

Online records of behavioral performance across time were analyzed using mixed ANOVA. This involved entering percentage accuracy and RT as dependent measures, with scan order and the type of decision making as within-subjects factors and age group as a between-subjects factor.

### Results

#### Behavioral Results

Behavior recorded during scanning is summarized in Table 1. Errors were classed as incorrect responses according to either the criterion established in the pilot study (at least 90% agreement) or due to a failure to respond during the 6-s interstimulus interval. RTs were taken from the offset of the last word of a triplet.

#### Behavioral Performance across All Subjects

Over the whole group, irrespective of age, condition-related differences in accuracy were present. Main effects of task ($F_{1,14} = 11.114, P = 0.0005$) and stimulus type ($F_{1,14} = 71.50, P < 0.0005$) were observed, the result of more errors when decisions were based on word meaning or were made on degraded stimuli. There was also an interaction between task and stimulus type ($F_{1,14} = 34.7, P < 0.0005$), the result of more errors in the SemVoCo than the SyllVoCo conditions, with no difference between the SemSp and SyllSp conditions. This interaction was expected, as even single-channel noise-vocoded speech (the amplitude envelope of speech filled with band-passed noise) retains information about the syllabic structure of the original word in the absence of intelligibility (Rosen 1992). There were also main effects of task ($F_{1,14} = 21.33, P < 0.0005$) and stimulus type ($F_{1,14} = 27.30, P < 0.0005$) on RT, the result of slower responses for decisions based on word meaning and for decisions made on degraded stimuli. No interaction was observed between task and stimulus type. In addition, RTs were slower for the response that followed an error ($F_{1,14} = 19.311, P = 0.001$).

#### The Effects of Aging upon Behavioral Performance

Examining the effects of age upon decision-making performance showed that, as predicted, the performance of decisions based on the meaning of heard words presented as clear speech (SemSp) was age-independent (Table 1). In contrast, the 3 other types of decision making were age-dependent, that is, decision-making accuracy declined with age when decisions were based on the meaning of heard words presented as degraded speech (SemVoCo) or when they were based on the sound structure of heard words presented both as clear speech and degraded speech (SyllSp and SyllVoCo). No correlations between aging and RT were observed in any condition. The lack of an effect of age on RTs is likely to have resulted from the paced nature of stimulus presentation. To ensure that the same number of trials was presented in each block, stimuli were presented every 6 s, leading to the RTs associated with some responses being limited by the timing of the following stimulus.

To investigate the effect of task repetition in different age groups, subjects were split into 2 groups around the mean age of the group (Fig. 1). For age-dependent conditions, by definition, a main effect of age group on accuracy was present ($F_{1,13} = 39.2, P < 0.0005$). However, there was no effect of age group on RT and no interactions of task repetition and age group for either accuracy or RT. Thus, there were no significant changes in within-group performance as subjects repeated the tasks. In the age-independent condition (SemSp) there was a significant effect of task repetition on the RT of SemSp.

### Table 1

Demographic and performance data

<table>
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<th>Whole-group data</th>
<th>Two-group data</th>
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<tr>
<td></td>
<td>Mean (±SE)</td>
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<td>Corr with age</td>
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<td>Age range</td>
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<td>Mean years of education</td>
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<td>Degraded speech repetition</td>
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<tr>
<td>Digit span</td>
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<td>8.1 (0.40)</td>
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<tr>
<td></td>
<td>Backward 6.0 (0.37)</td>
<td>6.4 (0.53)</td>
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<td>Accuracy (%)</td>
<td>119.8 (0.89)</td>
<td>119.5 (1.4)</td>
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</table>

Note: Mean: whole group of mean, ± standard error (±SE), and correlations calculated as Pearson’s correlation coefficient (corr). NART = National Adult Reading Test.

*Denotes significance at the 0.05 level (2 way).

### Table 2

Demographic and performance data

| Digit span            | Clear Speech    | Syllable decisions | 962 (110) | −0.15 (0.591) | 891 (177) | 1024 (145) |
|                       | Semantic decisions | 1210 (108) | −0.01 (0.695) | 1278 (183) | 1166 (132) |
|                       | Vocoder speech   | 1210 (110) | −0.05 (0.874) | 1212 (181) | 1210 (144) |
|                       | Syllable decisions | 1711 (134) | −0.02 (0.936) | 1617 (135) | 1794 (227) |

Mean (±SE) Mean (±SE) Mean (±SE)
decisions, the result of faster responses as subjects repeated the task \( (F_{3,30} = 4.714, P < 0.007) \). There was no significant effect of age group and no interactions of age group and task repetition on RT for the SemSp condition. In addition, there were no effects of age group or task repetition and no age by repetition interactions on accuracy for the SemSp condition.

**Imaging Results**

The prefrontal systems involved in the controlled processing of semantic and syllabic information, irrespective of subject age, have been addressed in an earlier article (Sharp and others 2004). Comparing semantic and syllable decision making showed that activation within the left PFC was dependent upon the type of decisions made, with greater activation within the left rostral PFC (BAs 8 and 9) and left ventrolateral PFC (BAs 45 and 47) observed during decisions made on the basis of word meaning. In addition, the level of activation within the left rostral PFC was dependent upon whether the clear or degraded speech stimuli were presented, with greater activation observed during decisions made upon clear speech stimuli. In contrast, the activation of the right lateral PFC (BAs 9 and 46) was sensitive to the type of stimulus rather than the task, with greater activation observed in this region when decisions were made upon degraded stimuli. This is compatible with a role for the right lateral PFC in implementing an increased requirement for cognitive control when decisions are made more demanding. Importantly, task-specific activation was not observed within the ACC, indicating that the type of decision making was not critical in determining activation within this region.

**Correlation between Age and ACC Activity**

The behavioral distinction between age-dependent and age-independent decision making formed the basis for the initial part of our imaging analysis. For the contrast of age-dependent and age-independent conditions, the level of activation within the ACC was predicted by age; as age increased, the activation of the ACC increased in magnitude (Table 2). The peak of this positive correlation between age and neural activity fell in the paralimbic division of the rostral ACC (BA 32) (Fig. 2). No other regions showed a positive correlation between age and activity, nor were there regions showing a negative correlation.

Whole-brain analysis also showed that for age-dependent conditions relative to age-independent conditions, neural activity correlated negatively with the accuracy of decision making in the ACC (BA 32) (Table 2). At a less conservative threshold \( (P < 0.001, \text{uncorrected for whole-brain comparisons}) \) other peaks of activation were also observed in the accuracy correlation within the left superior frontal gyrus (BA 8) and the right inferior parietal cortex (BA 40). Within the ACC, the peaks of activation in the age and accuracy analyses were anatomically close, however at a threshold of 0.001 uncorrected, there was no overlap in the spatial extent of significant activations in the 2 analyses (Fig. 2). In addition, the main effect of age-dependent versus age-independent decision making showed peaks of

![Figure 1](image-url)
activity within the right dorsolateral PFC and ventrolateral PFC as well as the right inferior parietal lobe.

We employed a ROI analysis to investigate further the relationship between age, decision-making performance, and neural activation. This analysis confirmed that mean neural

<table>
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<th>T-score</th>
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<td>L VLPFC/OFc</td>
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<td>36 14 12</td>
<td>5.95</td>
</tr>
<tr>
<td></td>
<td>R DLPFC</td>
<td>8/9</td>
<td>34 30 32</td>
<td>4.40</td>
</tr>
<tr>
<td></td>
<td>L frontal pole</td>
<td>10</td>
<td>20 58 10</td>
<td>4.47</td>
</tr>
</tbody>
</table>

Note: Approximate BAs are taken from the Talairach and Tournoux Atlas after transforming MNI coordinates into Talairach space (www.mrc-cbu.cam.ac.uk/Imaging/Common/brodmann_areas.shtml) (Hammers and others 2003; Paus and others 1996) used for additional anatomical localization. L = left; R = right; anterior cingulate cortex (ACC); dorsolateral prefrontal cortex (DLPFC); ventrolateral prefrontal cortex (VLPFC); frontal pole (FP); SFG = superior frontal gyrus; inf PL = inferior parietal lobule; OFC = orbitofrontal cortex.

Figure 2. The correlation between age, accuracy of decision-making, and ACC activation. (i) Regions, rendered on to coronal and axial slices of a group MRI template, where neural activity increased with age (red) or with a declining accuracy of decision-making (blue). The correlation with age is shown for the contrast of age-dependent versus age-independent conditions (i.e., [SylVoCo + SyIIVoCo + SemVoCo] – [SemSp]). The correlation with accuracy is shown for the 3 age-dependent conditions. The figures are displayed in neurological convention. The threshold was set at 0.001 uncorrected for whole-brain comparisons, excluding clusters with a spatial extent of <10 voxels. Peaks of activation are observed within the rostral ACC. (ii) Subject’s age plotted against the mean effect size from the peak voxel of the age correlation taken from within the ACC. Units of effect size are relative to whole-brain mean activity values and are normalized around zero. The units of effect size represent the percentage change of whole-brain activity, and the increasing values with age indicate that the ACC is activated more for age-dependent conditions relative to age-independent conditions as subjects age.

The Effects of Task Repetition

For age-dependent conditions, the activation pattern within the right lateral PFC across time differed in the younger and older age groups (Fig. 3). Subjects repeated the same decision-making condition 4 times, and in the older group increasing activation of the right lateral PFC was associated with the maintenance of stable behavioral performance. This effect was shown in a mixed ANOVA using activation values extracted from the right dorsolateral PFC (BA 46) and ventrolateral PFC (BA 44) as the dependent variables. This demonstrated an interaction between age group and task repetition in both regions (F₁₈,₇₄ = 18.74, P = 0.013). There were no significant main effects of region, type of decision making, or overall effects of task repetition and no other significant interactions. Planned post hoc comparisons for within-subjects effects revealed an effect of task repetition of borderline significance in the older group (F₃,₂₁ = 2.91, P = 0.059), where neural activity in both the right dorsolateral PFC (DLPFC) and ventrolateral PFC (VLPFC) increased with age.
repetition of the same age-dependent task. There was no significant effect of task repetition in the younger group ($F_{3,18} = 1.45, P = 0.262$). Post hoc tests for between-subjects effects revealed a significant difference between the 2 groups on the final performance of the 3 age-dependent conditions ($F_{1,13} = 9.67, P = 0.008$) but no significant difference in activity for the 3 previous trials. This was due to greater activity for the older group on the final repetition of the tasks. A separate mixed ANOVA analysis showed no significant relationship between task repetition and activity within the ACC. A similar analysis was carried out for SemSp, the age-independent condition. This demonstrated no significant relationship in either the ACC or lateral PFC between neural activity, task repetition, and age group. In addition, no significant time-dependent relationship was observed between behavioral performance and activation within these areas.

**Functional Connectivity between the ACC and Lateral PFC**

The ACC showed extensive functional connectivity with bilateral frontal cortical regions (Fig. 4). The pattern of connectivity was similar when the starting point for the analysis was taken either from the peak of the relationship with accuracy in the ACC or from the peak of the relationship with aging. Analyzing connectivity from the accuracy-related analysis demonstrated peaks of covariation, significant at $P < 0.05$ corrected for multiple comparisons across the whole brain, within bilateral ventrolateral PFC, right dorsolateral PFC, bilateral orbitofrontal cortex, and the frontal poles. Additional peaks were present at a lower threshold ($P < 0.001$ uncorrected for multiple comparisons) within the thalamus and right inferior parietal lobe. Analyzing connectivity from the aging-related peak within the ACC demonstrated peaks of covariation, again significant at $P < 0.05$ corrected for multiple comparisons, in bilateral VLPFC, DLPFC, orbitofrontal cortex, and the frontal poles. In addition, at this threshold there was an extensive area of covariation within the thalamus and also a peak of covariation within the right inferior
Discussion

Our results show how an age-related decline in performance is associated with distinct responses within the ACC and lateral PFC. In the ACC neural activity increases with age, whereas in the right lateral PFC activity shows a time-dependent increase in older subjects. As the ACC and lateral PFC are known to be involved in evaluating the need for and implementing cognitive control, these results suggest that greater cognitive control is employed in older individuals as performance declines with age.

The first part of our analysis involved the comparison of decision making with age-dependent and age-independent performance. This comparison allowed the identification of activation associated with an age-dependent decline in performance. Semantic decision making on clear speech (SemSp) was used as the baseline for these analyses, providing a condition where behavioral performance was age-independent. This condition provided an appropriate control for aspects of complex decision-making that were not directly related to the age-related decline in accuracy. The comparison of age-dependent and age-independent decision-making showed that activity within the ACC was predicted by subjects’ age as well as by the accuracy of their decision-making. Activation within these regions is likely to be related to changes in the age-dependent conditions, although, as with all contrasts that involve cognitive subtraction, it is not possible to exclude a contribution from activation changes in the baseline condition that are independent of behavioral performance.

The neural system that provides cognitive control is thought to comprise evaluative and strategic components that are, to some extent, anatomically separable (MacDonald and others 2000). The ACC appears to be predominantly evaluative and is sensitive to aspects of response generation, including the degree of conflict between potential responses (Carter and others 1998; Schall and others 2002) and the number of errors produced. Event-related potential studies have demonstrated a midline error-related negativity (Falkenstein and others 2000), thought to originate from the ACC (Dehane and others 1994), which varies in magnitude with age (Band and Kok 2000); whereas fMRI studies have shown that the level of ACC activity is related to the amount of “response conflict” across a range of different tasks (Carter and others 1998), an effect that may be greater in older individuals (Milham and others 2002).

In our study, for those conditions that showed an age-related decline in performance, activity within the rostral ACC increased with increasing age. This result supports the proposal that a greater requirement for cognitive control as individuals age is signaled by the ACC. As the accuracy of decision making also correlated directly with ACC activity, one explanation for this correlation is that older subjects tended to produce more errors that in turn resulted in increased ACC activity. The blocked nature of experimental design in PET studies means that correct and incorrect trials cannot be modeled separately. However, modeling the relationship between age, accuracy, and mean ACC activity across the whole of each block showed that age continued to predict ACC activity even after controlling for accuracy, indicating that the relationship between age and ACC activity cannot be explained simply by a simple linear relationship between age and accuracy.

Separate peaks of age and accuracy-related activity were observed within the rostral ACC. One explanation for this observation is that a functionally distinct region within the ACC is increasingly recruited with age and provides an additional evaluative signal relating to an increased requirement for cognitive control in older individuals. This type of functional specialization for subregions within the ACC has previously been described in other contexts (Paus 2001). Alternatively, the results could represent age-related differences in the recruitment of a common ACC system. This is more compatible with observation of anatomically close locations for peaks of activation in the age and accuracy correlations, despite very different analyses being used to derive these results, and also the similarity of the functional connectivity from these parts of the ACC to lateral frontal regions. An increased sensitivity of the ACC to response conflict has previously been observed in older individuals during a Stroop task (Milham and others 2002). Therefore, the differential involvement of a common functional ACC system in individuals of different ages could be explained by an increased sensitivity of the ACC to declining performance as individuals age.

In nonhuman primates, the control of eye movements has been used as a model for investigating interactions between the supervisory system involved in cognitive control and the subordinate systems involved in programming actions (Schall and others 2002). Neurons within the ACC have been shown to code the consequences of an action; for example, separate neurons responding to eye-movement errors or to the presence of rewards have been identified (Ito and others 2003). These evaluative signals appear to influence behavior through an interaction between the ACC and the PFC, and this interaction is thought to provide a feedback circuit that can bias the preparation of a motor response and allow a more adaptive match between behavior and environmental demands (Schall and others 2002). In humans, changes to the level of cognitive control are also thought to be implemented through interaction between the ACC with the lateral PFC (Carter and others 2000), and the importance of this interaction is supported by the extensive functional connectivity we observed between the ACC and lateral PFC. Thus, it appears that the level of ACC activity signals the requirement for ongoing cognitive control and that changes in this signal can be adaptive for the control of behavior. The age-related increase in ACC response observed in this study provides a physiological mechanism for adapting to age-related decline in aspects of information processing, by exerting increased cognitive control over action.

Implementing cognitive control requires a system capable of representing the current task demand, monitoring the contents of working memory in the context of this task demand, and focusing attention upon relevant information or processing (Koechlin and others 2003). The lateral PFC is thought to be central to this type of processing (Shallice 2002), and the right dorsolateral PFC has been specifically implicated in monitoring the information retrieved into working memory (Stuss and others 1994; Henson and others 1999, 2000). We observed increased right lateral PFC activation in age-dependent conditions, a result that is compatible with a role for this area in supporting the increased monitoring demands associated with...
tasks where the relationship between information held in working memory, task demand, and response selection is unclear (Sharp and others 2004).

Within the right lateral PFC a very different pattern of activation over time was observed in the 2 age groups. Unlike the younger group, neural activity in the older group increased with the repetition of age-dependent conditions, and by the time of the final block of decision making, activity in the right lateral PFC was greater in the older group than in the younger group. This pattern of activation was not observed in the ACC for the age-dependent conditions or in either the ACC or lateral PFC for the age-independent condition. In addition, a similar pattern was not observed in the behavioral data. Thus, the maintenance of a stable level of behavioral performance over time was associated with qualitatively different patterns of lateral PFC recruitment in the 2 age groups in conditions where performance declined with age. This suggests that age-related differences exist in the level of cognitive control involved in decision-making over time.

This time-dependent difference in the activation of the lateral PFC for the old and young groups could occur for a number of reasons. One possible explanation is that less cognitive control is required in the young group as subjects gained more experience on the tasks, but subjects in the older group failed to learn from experience in the same way. Previous studies using young subjects have demonstrated practice-related reductions in activation within lateral PFC across a range of different cognitive tasks (Raichle and others 1994; Jansma and others 2001). These studies used repetition of the same stimulus items during practice, resulting in behavioral changes, that is, faster RTs, less error, and less variance in responses, suggestive of a shift from controlled to more automatic information processing (Shiffrin and Schneider 1977). In our study we presented only novel stimuli, and there was no behavioral evidence to indicate age-dependent changes in the nature of processing over time. In addition, although the mean level of activation did decrease over time in the right lateral PFC of the young group, this effect did not reach significance. Therefore, there is little behavioral or neuroimaging support for a shift from controlled to more automatic processing in the young group to explain the age-dependent difference in activation within this region.

An alternative explanation for the time-dependent difference in activation within the lateral PFC is that the amount of cognitive control involved in decision making increases with task repetition in the older group, in keeping with the pattern observed in our neuroimaging data. An increased level of cognitive control toward the end of the experiment could be a direct response to the relatively poor overall level of performance in the older group. In the model we have articulated, poor performance results in an increased level of ACC activation, which signals the requirement for an increased level of control. This is implemented via an interaction with the lateral PFC that results in changes such as the allocation of more resources to the maintenance and monitoring of task-relevant information held within working memory in an attempt to improve the level of performance.

A further explanation is that aspects of age-related cognitive decline may make it more difficult for older individuals to maintain their level of performance over time. For example, age-related impairments in sustained attention and inhibitory processing have been reported (e.g., Hasher and Zacks 1988; West 1999) as well as sizeable increases in task switching costs in older individuals (Kray and Lindenberger 2000; Meiran and others 2001). Koechlin and others (2003) have demonstrated the involvement of the anterior DLPC in the episodic control of behavior, and this region is sensitive to the amount of interference that may occur between instructions given to participants in different experimental episodes. In the current experiment, task repetition require sustained attention, task switching, and the inhibition of inappropriate processing, which, in the case of our conditions, involves the inhibition of either semantic or phonological stimulus processing. The potential impact of these factors on performance varies over time, being greatest toward the end of the experiment. Hence, in older subjects, the impact of an age-related decline in sustained attention and inhibitory processing would be expected to be greatest after task repetition. As a result of these time-dependent factors, greater levels of cognitive control would be required in the older group to produce a similar level of behavioral performance at the end of a series of task repetitions.

The temporal resolution of PET limits our ability to separate the effects of these factors on neural activity. However, these last 2 explanations make different predictions about behavioral changes over time. An increased level of cognitive control in response to static levels of poor performance would be expected to lead to performance improvements over time. In contrast, age-dependent impairments in sustained attention and inhibitory processing would be expected to progressively impair performance over time, an effect that may not be fully compensated for by an increased level of overall cognitive control. The behavioral results do not clearly discriminate between these possibilities but are more in keeping with the former model, as both RT and error rate shows a trend toward improving in the older group with task repetition, although no significant linear relationship between behavioral performance, task repetition, and lateral PFC activity is observed when these factors were formally modeled.

The current results suggest that age-related increases in frontal lobe activation may result in part from a "selective" increase in activation within the neural system involved in cognitive control. Decline in information processing, possibly the result of task-specific underrecruitment of other frontal resources (Logan and others 2002) or a reduced functional connectivity between elements of the recruited network (McIntosh and others 1999; Logan and others 2002), results in a greater need for cognitive control. We propose that this changing requirement leads to an age-related increase in the response of the ACC to errors and a time-dependent increase in the response of the right lateral PFC. These changes could be adaptive in nature, reflecting increased attentional support for processing that is relevant to current behavior.

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References
Age and Cognitive Control


