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Frontal Function and Executive Processing in Older Adults: Process and Region Specific Age-Related Longitudinal Functional Changes

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Abstract

Longitudinal studies on aging brain function have shown declines in frontal activity as opposed to the over-recruitment shown in cross-sectional studies. Such mixed findings suggest that age-related changes in frontal activity may be process- and region-specific, having varied associations across different frontal regions involved in distinct cognitive processes, rather than generalized across the frontal cortex. Using data from the Baltimore Longitudinal Study of Aging (BLSA), we examined individual differences through cross-sectional associations at baseline evaluation and longitudinal changes in regional cerebral blood flow (rCBF) in relation to different executive abilities in cognitively normal older adults. We found that, at baseline, greater rCBF in middle frontal regions correlated with better performance in abstraction and chunking, but greater rCBF in the insula and a distinct middle frontal region correlated with poorer inhibition and discrimination, respectively. In addition, increases in frontal rCBF over time were associated with longitudinal declines in abstraction, chunking, inhibition, discrimination, switching, and manipulation. These findings indicate process- and region-specific, rather than uniform, age-related changes in frontal brain-behavior associations, and also suggest that longitudinally high-levels of frontal engagement reflect declining rather than stable cognition.

Keywords

Aging; Longitudinal; Cross-Sectional; Brain Function; Executive Processing

INTRODUCTION

Cross-sectional studies on aging show that older adults exhibit higher, and more bilateral, task-related frontal lobe functional activity than younger adults across various cognitive tasks involving working memory and executive function (Reuter-Lorenz & Cappell, 2008; Schneider-Garces et al., 2010), episodic memory (Cabeza, Anderson, Locantore, &

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McIntosh, 2002), and even basic perceptual processing (Goh, Suzuki, & Park, 2010; Grady et al., 1994). These greater levels of frontal activity in older adults have also been generally associated with better behavioral performance, leading to the heuristic that greater frontal activity may be an indicator of cognitive health and may reflect engagement of compensatory processes to maintain cognitive function with advancing age (Park & Goh, 2009; Park & Reuter-Lorenz, 2009). It is not clear, however, whether greater frontal activity accompanying better performance in older adults is a generalized phenomenon across the many frontal regions that engage different neurocognitive processes. It is also unclear whether age-related increases in frontal function support longitudinal stability of cognitive function. Indeed, in a recent longitudinal study, Nyberg et al. (2010) found that age-related changes in prefrontal activity were characterized more by functional reduction over time rather than the over-recruitment evident in cross-sectional findings. In the present study, we evaluate the cognitive implications of age-related changes in frontal function during verbal memory performance by considering both the cross-sectional and longitudinal associations between individual differences in frontal brain activity and different domains of executive processing.

Recent studies have begun to fractionate the frontal cortex into distinct regions involved in separable components of executive processing. For example, distinct and increasingly abstract levels of associative rule processing engage regions progressing from posterior to anterior regions within the dorsolateral prefrontal cortex (Badre & D'Esposito, 2009). In addition, different aspects of inhibitory and attentional control, and task goal processing are associated with activity in different ventrolateral prefrontal/insula areas and in the anterior cingulate gyrus (Chikazoe, 2010; Dosenbach et al., 2006).

Given such diversity in frontal regional processing, it is likely that age-related differences in brain-behavior associations in frontal areas would be process- and region-specific, rather than uniformly reflecting greater activity with better performance (Turner & Spreng, 2012). Thus, age-related increases in functional activity in some frontal regions may reflect additional recruitment of neural processing, not typically necessary at younger ages, to compensate for age-related cognitive decline and aid task performance in older adults. However, increases in other frontal regions may also reflect declines in executive control functions such as non-selective neural recruitment related to reduced inhibition of task-irrelevant and even interfering neural activity, greater attentional effort, or reduced processing efficiency (requiring longer or more elaborate processing to perform computations) (Reuter-Lorenz & Cappell, 2008; Rypma et al., 2006).

Compared to cross-sectional studies that generally show greater frontal activity with age is associated with better performance, longitudinal imaging studies have revealed a less consistent pattern of frontal functional changes associated with aging. For example, in the Nyberg et al. study (2010), greater cross-sectional age was associated with greater frontal functional responses due to a select higher-performing sample that remained in the six-year longitudinal study. However, longitudinal evaluations of this sample revealed declines over time in prefrontal activation. In addition, Beason-Held et al. (2008) reported both longitudinal increases and decreases in specific regions of frontal activity in participants who maintained a high level of memory performance. Thus, unlike cross-sectional findings, longitudinal findings demonstrate more heterogeneous trajectories across different frontal regions with advancing age. Longitudinal studies have also suggested that not all age-related changes in brain activity reflect compensatory processing and some changes may signal cognitive decline that occurs in normal aging.

In this study, we used mixed-model analyses (Laird & Ware, 1982) to obtain individual estimates of longitudinal changes in neuropsychological test measures of different executive

abilities (abstraction, chunking, inhibition, discrimination, switching and manipulation; see Goh, An, & Resnick, 2011), as well as changes in voxel-wise rCBF measures of neural activity during a verbal recognition memory task in cognitively normal older adults followed over an 8-year interval. These measures of executive abilities were previously shown to have substantial individual variability in longitudinal trajectories that also dissociated participants with eventual cognitive impairment from those who remained clinically normal (Goh et al., 2011). Thus, these measures show both individual differences and between-task variation in longitudinal trajectories for a variety of measures of executive function involving frontal processing (Badre & D'Esposito, 2009) and provide the opportunity for investigation of age effects on brain-behavior associations for specific executive tasks which may have clinical relevance. In addition, the availability of longitudinal functional imaging data acquired during performance of verbal recognition memory tasks in these Baltimore Longitudinal Study of Aging (BLSA) participants also afforded the evaluation of frontal executive processes related to episodic retrieval (Buckner, 2004; Buckner, Kelley, & Petersen, 1999). Specifically, recognition of studied words requires selection, comparison, and matching of cue to memory traces, inhibition and discrimination between competing alternatives, and is facilitated by encoding strategies such as abstraction and chunking that help to group items into more meaningful representations.

The present investigation has two broad goals. First, for cross-sectional data at baseline, we evaluated whether higher baseline frontal activity in cognitively normal older adults reflects generalized compensatory recruitment or more process-specific associations across different aspects of executive function. If age-related increase in frontal activity represents more generalized compensatory recruitment, then higher baseline activity across all frontal regions would be associated with better performance across all executive domains assessed. Moreover, higher frontal activity should not be associated with poorer performance with any executive ability. However, if age-related increases in frontal activity are region- and process-specific as detailed above, we predicted that higher baseline activity should be associated with better baseline performance in some frontal regions but poorer performance in other regions across the different specific executive processes.

Second, for the longitudinal data, we evaluated whether increasing (or decreasing) frontal activity over time would be associated with longitudinal improvement or declines in executive processing in those who show performance changes but still remain cognitively normal. We hypothesized that a longitudinal pattern of chronic high-levels of frontal activity, measured as sustained or increasing levels of rCBF over time, reflects the need for continued compensatory engagement or effortful processing, and could be associated with age-related cognitive decline. Conversely, individuals with relatively stable cognitive function would learn from repeat testing of the verbal memory task and require less compensatory and attentional effort over time, reflected as longitudinally decreasing frontal rCBF. As such, we expected that sustained or increasing longitudinal frontal blood flow would be associated with longitudinal decline in executive performance, while decreasing frontal activity would be associated with longitudinally improving performance over repeated testing.

MATERIALS AND METHODS

Participants

Data in this study were obtained from the neuroimaging sub-study of the BLSA, which consisted of a total of 160 participants (Resnick et al., 2000). Exclusion criteria for the BLSA neuroimaging sub-study were the presence or history of neurological impairment, metastatic cancer, or severe cardiovascular disease (treated hypertension was not exclusionary) at baseline neuroimaging evaluation. Within this sample, we excluded 23

participants who were diagnosed with cognitive impairment (mild cognitive impairment or MCI, dementia, or Alzheimer's Disease) over the course of the ongoing BLSA study and 1 participant who had an autoimmune deficiency disease. Cognitive impairment was determined by regular case conferences and consensus diagnosis using results of neurological assessments, neuropsychological diagnostic tests and clinical data (Driscoll et al., 2006 and Kawas, Gray, Brookmeyer, Fozard, & Zonderman, 2000). All participants were followed annually and reviewed at a consensus conference if they screened positive on the Blessed Information Memory Concentration score (score ≥ 4), if their Clinical Dementia Rating score was ≥ 0.5 using subject or informant report. Diagnosis of dementia was based on the Diagnostic and Statistical Manual of Mental Disorders Third Edition, Revised (DSM-III-R) (1987) criteria for dementia, diagnosis of Alzheimer's disease used the National Institute of Neurological and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria (McKhann et al., 1984), and diagnosis of mild cognitive impairment followed the Petersen criteria (Petersen et al., 1999).

Of the remaining 136 participants, we excluded 37 participants who had less than 5 serial follow-up test sessions of both neuropsychology and imaging data to ensure reliable longitudinal estimates. Follow-up test sessions were separated by approximately one to two years. The final sample included 99 participants whose demographic and follow-up details are listed in Table 1. In contrast to most cross-sectional studies of aging, the regular and longitudinal assessment of cognitive status in this present study resulted in a participant sample that had remained free from cognitive impairment over a considerable number of years, reducing the effect of undetected incipient cognitive impairment, such as MCI, on our results. The local Institutional Review Board approved the research protocol for this study, and written informed consent was obtained at each visit from all participants.

Neuropsychological Test Battery and Component Executive Domains

Table 2 lists the neuropsychological test outcome measures acquired at each follow-up session and the component executive domains assessed by the measures. Details about each test and formation of each executive component have been previously described in Goh et al. (2011). Briefly, the different components were labeled based on the main cognitive processes assessed by the neuropsychological tests as conceptualized in previous literature (Lezak, Howieson, & Loring, 2004). Moreover, because our interest was in evaluating whether different aspects of executive processing would show equivalent associations with frontal brain function, we investigated the measures for each component as distinct variables rather than form a general executive factor. Test scores were all transformed to z-scores based on the means and standard deviations of each measure, computed across baseline and follow-up performance. Composite scores were formed only when the cognitive processes assessed were conceptually similar and were computed by averaging across the normalized test scores associated with that domain. Increasing values on all executive component scores always reflect better performance.

Executive Performance Mixed Model Analysis

Mixed model analysis (Laird & Ware, 1982) was applied to the executive performance scores using R version 2.11.1 with the package lme4 version 0.999375-37. For each executive domain, we applied the following mixed-effects models to evaluate the effects of cross-sectional baseline age and longitudinal follow-up interval:

$$y_{ij} = \beta_0 + \beta_1 \text{Age}_i + \beta_2 \text{Interval}_{ij} + \beta_3 (\text{Age}_i \times \text{Interval}_{ij}) + b_{0i} + b_{1i} \text{Interval}_{ij} + \varepsilon_{ij}. \quad (\text{Eq. 1})$$

$$y_{ij} = \beta_0 + \beta_1 \text{Interval}_{ij} + b_{0i} + b_{1i} \text{Interval}_{ij} + \varepsilon_{ij} \quad (\text{Eq. 2})$$

In the above models, y_{ij} is the score on the executive domain for the j^{th} subject on the i^{th} follow-up test visit. Age indicates participants' baseline age at the first neuroimaging visit centered to age 55 yrs. Interval is defined as the longitudinal predictor coded as the time (yrs) from baseline age (1st interval is 0). β denotes fixed effects estimates, b denotes subject specific random effects estimates, and ε is the residual error. Statistical significance of β_1 in Eq. 1 indicates a cross-sectional effect of age on the executive domain, and significance of β_3 indicates a dependency of longitudinal change on baseline age at first assessment. Statistical significance of β_1 in Eq. 2 indicates an effect of longitudinal change on the cognitive domain, regardless of participant age. Individual estimates of the slope of longitudinal changes in executive performance were obtained using Eq. 2 ($\beta_1 + b_{1i}$) and subsequently used in the analysis with rCBF data.

Verbal Memory Task During PET Scanning

At each follow-up session, participants performed a verbal recognition memory task during a functional PET scanning experiment. There were two word lists, each with 20 target words, used for the recognition task. Words lists were alternated every other follow-up session (repeated every 2 to 4 years) to reduce repetition-learning effects. In the study phase approximately 30 min before scanning, participants studied the 20 target words serially presented on a computer screen (Beason-Held et al., 2008; Resnick & Maki, 2001). During the recognition phase, which was performed during PET scanning, participants serially viewed the 20 target words with 20 novel words randomly intermixed and indicated with button presses whether or not they had seen each of the words earlier. Recognition accuracy was computed as the d' sensitivity score based on hits and false alarm rates. Reaction times were also recorded. There was also a PET scan during a resting condition during which participants saw a blank screen and remained still with eyes open.

PET Scanning Parameters

$[^{15}\text{O}]$ water PET measures of rCBF were obtained using a GE 4096+ scanner. For each scan, 75 mCi of $[^{15}\text{O}]$ water were injected as a bolus. For each of the recognition memory and resting conditions, 15 axial slices of 6.5 mm thickness were acquired for 60s from the time total radioactivity counts in the brain reached threshold level. Attenuation correction was performed using a transmission scan acquired prior to the emission scans.

PET Image Preprocessing and Mixed Model Analysis

Image preprocessing was done using Statistical Parametric Mapping (SPM5; Wellcome Department of Cognitive Neurology, London, England). For each participant across follow-up sessions, PET images were realigned to the first session, spatially normalized to the MNI (Montreal Neuroscience Institute) template space with $2 \times 2 \times 2$ mm resolution, and smoothed using a full width at half maximum of 12 mm. Voxel rCBF values for all images were ratio adjusted and scaled to a mean global flow of 50 ml/100 g/min. Images were then masked to include only voxels that significantly modulated rCBF responses during the verbal recognition memory task relative to rest (positive and negative contrasts), with threshold $p < .001$ and cluster size correction of at least 50 voxels (400 mm^3) (see Fig. S1). All subsequent whole-brain analyses operated on the masked images, reducing the number of voxels in consideration.

Mixed model analysis of PET images was implemented using the R package AnalyzeFMRI version 1.1-12 in addition to the lme4 package mentioned above. To obtain voxel-wise

individual estimates of longitudinal changes in rCBF, Eq. 2 was applied to each voxel with y_{ij} being the rCBF value of that voxel for the i^{th} subject on the j^{th} follow-up test visit. Thus, for each participant, we computed an image in which each voxel consisted of the slope estimate ($\beta_1 + b_{1i}$ from Eq. 2) of the effect of interval on rCBF for that voxel. These images were individual estimates of voxel-wise longitudinal changes in rCBF subsequently used in the analysis with the executive performance data.

Associations Between Executive Performance and rCBF

To evaluate the relationships between cross-sectional baseline differences and longitudinal changes in executive performance and functional brain activity, we performed the following voxel-wise whole-brain regression analyses, adjusted for baseline age and sex. First, to evaluate the relationship between baseline brain activity and baseline executive performance, for each executive domain, we regressed participants' performance scores at baseline onto the baseline rCBF images. Second, to evaluate the relationship between longitudinal changes in brain activity and longitudinal changes in executive performance, for each executive domain, we regressed participants' slope estimates of longitudinal change in executive performance onto the slope images of longitudinal change in rCBF.

For all whole-brain analyses, voxels that showed significant associations of interest were defined as those that surpassed a statistical threshold of $p < .005$, as recommended by the PET Working Group of the NIH/NIA Neuroimaging Initiative (<http://www.nia.nih.gov/about/events/2011/positron-emission-tomography-working-group>), with cluster-size correction of at least 50 voxels (400 mm^3), as used in previous PET studies (Beason-Held et al., 2008). For selected findings, rCBF activations were extracted from regions-of-interest (ROIs) and plotted to aid data visualization. ROIs were spheres with 5 mm radius, centered on the MNI coordinates of peak voxels from the analyses.

RESULTS

Age Effects on Executive Domains and Verbal Recognition Memory

Mean performance raw scores and longitudinal changes for the neuropsychological measures are shown in Table 3. Regression coefficients of the mixed-model analysis of baseline age and longitudinal interval effects on the executive components derived from these measures (z-scores; see Methods) are illustrated in Fig. S2. Higher baseline age was significantly associated with poorer performance for switching (z-score difference/yr $\pm 95\%$ CI = -0.030 ± 0.016 , $t(97) = -4.121$, $p < .01$), with a similar general trend for the other domains although these were not significant. In addition, there were significant longitudinal declines in inhibition (z-score change/yr $\pm 95\%$ CI = -0.027 ± 0.024 , $t(97) = -2.576$, $p < .05$) and manipulation (z-score change/yr $\pm 95\%$ CI = -0.036 ± 0.026 , $t(97) = -3.185$, $p < .01$), but improvement in discrimination (z-score change/yr $\pm 95\%$ CI = 0.023 ± 0.018 , $t(97) = 2.919$, $p < .01$) over time. These cross-sectional baseline age and longitudinal interval effects on executive performance generally were consistent with the differential longitudinal trajectories of specific executive abilities we reported previously in the broader sample (Goh et al., 2011). Whereas participants showed learning through repeated testing in discrimination performance, inhibition and manipulation were less amenable to repetition learning and age-related declines were more pronounced than possible learning.

Performance for the verbal recognition memory task administered during the PET scan had a mean (SD) sensitivity score of 0.41 (0.20) and a mean (SD) response time of 1383 (350) ms at baseline. There were no significant effects of age or longitudinal change on sensitivity scores. However, older compared with younger baseline age was associated with longer response time (additional time per year $\pm 95\%$ CI = $12.9 \pm 10.9 \text{ s/yr}$; $t(97) = 2.71$, $p < .01$),

and responses were faster with longitudinal repeated testing indicating learning effects (response time change per year $\pm$ 95% CI = -12.7 ± 3.4 s/yr; $t(97) = -3.70$, $p < .01$). These findings were consistent with our prior observations (Beason-Held et al., 2008), which investigated the neural correlates of verbal recognition memory performance in a more selected sample of very healthy BLSA participants.

In the present study, we evaluated the associations between verbal recognition memory performance in the PET scanner and different components of executive function. At baseline, higher sensitivity score was weakly but significantly correlated with better performance in discrimination ($r = 0.22$, $p < .05$), consistent with the commonality of processes tapped by these two measures that involve detecting and dissociating targets and distractors. There were no significant associations between baseline recognition memory response time and executive performance. For longitudinal change, improving manipulation correlated with improving sensitivity ($r = 0.23$, $p < .05$) and reduced response times ($r = -0.21$, $p < .05$) on the verbal memory task. Overall, better verbal recognition memory was associated with better executive ability, supporting our evaluation of the association between the executive measures and rCBF during the recognition task.

Associations between rCBF and Executive Performance at Baseline

As shown in Fig. 1 and Table 4a, baseline levels of rCBF across different frontal regions showed both positive and negative associations with baseline performance across different executive domains (non-frontal associations are not focal to this study but are listed in Table S1). Higher baseline rCBF in the left middle and superior medial frontal regions, and right rolandic operculum correlated with better baseline performance for abstraction. Higher baseline rCBF in the left inferior (pars triangularis) frontal gyrus also correlated with better baseline chunking performance.

In contrast, higher baseline rCBF in the left insula and right inferior (pars triangularis) frontal regions correlated with poorer baseline inhibition performance. Higher baseline rCBF also correlated with poorer discrimination performance in a region of the left middle frontal gyrus that is separate from the region associated with abstraction. These negative associations suggest that higher activity in these distinct frontal regions does not necessarily facilitate task performance and may reflect greater non-selective or effortful control processing. There were no significant frontal associations between baseline rCBF and performance for manipulation or switching.

Overall, we observed that higher rCBF at baseline was not uniformly associated with better performance across all executive abilities. Rather, higher rCBF in some frontal regions was associated with better performance whereas higher rCBF in other frontal regions corresponded with poorer performance across different executive abilities.

Longitudinal rCBF and Longitudinal Executive Performance

Across all executive domains examined, we found negative correlations between longitudinal changes in frontal rCBF and longitudinal changes in executive performance (Fig. 2; Table 4b). Specifically, greater longitudinal stability or improvement in abstraction performance was correlated with decreasing rCBF in the left insula, and inferior (pars opercularis) frontal gyrus. The same negative association with longitudinal rCBF trajectories was present for chunking in bilateral medial orbital frontal gyri, and left insula, for discrimination in the left insula, for inhibition in the left inferior (pars triangularis, pars opercularis) frontal and precentral gyri, for manipulation in the left superior medial frontal gyrus, and finally, for switching in the left insula, and right anterior cingulate gyrus and rolandic operculum. Scatter plots in Fig. 2 also show that annual changes in rCBF were

mostly negative (rCBF change slopes < 0), indicating overall longitudinal reduction in activity in these frontal regions. Critically, individuals who demonstrated greater rates of longitudinal reduction in rCBF also showed relatively stable or less declines in longitudinal executive performance (z -score slopes negative but approaching 0; see plots for inhibition, switching¹, and manipulation), and even improvement (z -score slopes > 0 ; see abstraction, chunking, and discrimination). Conversely, individuals whose rCBF was sustained or increasing over time (rCBF change negative and approaching or greater than 0) in the above frontal regions tended to show declining executive performance. The only positive association in the frontal region was in the right superior orbital frontal for inhibition (Fig. S3).

DISCUSSION

Our findings show a heterogeneous pattern of brain-behavior associations in the frontal regions of older adults when considering cross-sectional baseline data. Higher baseline rCBF in some frontal regions correlated with better performance, but higher rCBF in other distinct frontal regions correlated with poorer performance for select executive domains. In addition, our longitudinal findings suggest that chronic high-levels of frontal rCBF over an extended period, particularly in the left insula/inferior frontal regions, may reflect more effortful processing associated with declines in executive ability rather than stability or improvement. These findings dissociate longitudinal brain-behavior associations from the heuristic derived from cross-sectional findings that there is generalized age-related increase in frontal activity that is compensatory. Together, these results suggest that a more complex framework is required to sufficiently account for both cross-sectional and longitudinal findings on age-related changes in frontal function.

Studies of executive processing suggest that dorsolateral prefrontal regions are involved in processing abstract rules during cognitive tasks (Badre & D'Esposito, 2009). In our study, we found that higher activity at baseline in regions within the dorsolateral prefrontal cortex correlated with better performance in abstraction, the ability to identify abstract semantic relationships between items, and chunking, the ability to organize stimuli into meaningful groups. As suggested in Goh et al. (2011), it is plausible that these processes can facilitate recognition during the verbal memory task by aiding the retrieval and organization of memory engrams. Thus, greater activity in these specific frontal regions may reflect the compensatory nature of these specific executive processes in facilitating episodic retrieval performance in older adults.

In contrast, greater baseline activity in the left insula and in a different, more anterior and medial, middle frontal region did not facilitate behavior, but were instead associated with poorer performance in inhibition and discrimination, respectively. These executive domains involve attentional effort to suppress irrelevant information and select relevant ones. A possible account for this finding is that greater blood flow in these frontal regions may reflect non-selective neural engagement due to neurotransmitter dysregulation or reduced efficacy of inhibitory frontal white-matter connections with age (Li, Lindenberger, & Bäckman, 2010; Persson et al., 2006). Such non-selective engagement might impede the ability to inhibit or discriminate different types and sources of information during episodic retrieval. In this view, age-related increases in neural activity in these regions are not compensatory, but rather detrimental to cognitive processing and task performance, particularly when signal detection is involved.

¹The negative association between longitudinal rCBF and longitudinal switching performance remained ($r_{\text{adj}} = -0.48$) even after the possible outlier on the bottom right area of the plot in Fig. 4 was removed.

A complementary account is that greater blood flow in these regions may also indicate greater neural effort to suppress or control competing processes due to underlying declines in other brain memory and perceptual processing regions (Fabiani, 2012; Goh et al., 2010; Gutchess et al., 2005; Reuter-Lorenz & Cappell, 2008). From this perspective, age-related frontal increases are still compensatory, but the additional recruitment may involve inefficiency or is insufficient to overcome age effects on task performance. In either case, our finding of greater blood flow levels within these frontal regions at baseline that were associated with poorer executive processing is not consistent with the view that higher frontal activity is uniformly associated with better cognitive ability.

The notion that higher activity in ventrolateral frontal regions reflects greater attentional effort (Chikazoe, 2010; Dosenbach et al., 2006) is consistent with our longitudinal findings. As mentioned, other studies of frontal executive processing have implicated the insula and inferior frontal regions in attentional effort, and higher activity in these regions in older adults is more likely to occur when there are task processing errors, more interference, and greater need for attentional control (Langenecker, Nielson, & Rao, 2004; Nielson, Langenecker, & Garavan, 2002; Zhu, Zacks, & Slade, 2010). In our study, older adults who chronically engaged high-levels of frontal activity in the left insula and inferior frontal regions also showed longitudinal performance decline across all executive domains examined. Thus, age-related sustained or increases in frontal activity over a long period of time are not necessarily associated with benefits to performance, but may be a marker of executive decline. Instead, reductions in frontal activity, presumably associated with learning from repeated testing, are aligned with stable or improving performance over time in the present study. This suggests that some older adults in our sample maintained the neural capacity to learn from experience, much like younger adults, by reducing the need for processing whenever possible.

We note that our sample consists of older adults who are above 55 years of age, and that the cross-sectional data spanned approximately 30 years, while the longitudinal period spanned approximately a decade. In this sample of older adults with a broad range of baseline brain and cognitive responses, we identified associations between longitudinal functional imaging and cognitive changes that are already detectable within a decade of follow-up. Thus, our study focuses on a finer temporal resolution of age-related changes compared to prior cross-sectional studies that detect functional differences associated with an age gap of about 40 years or more. It is possible that the individual differences we see in our results might show a different trend in a younger sample or a longer longitudinal follow-up period equivalent or greater than the cross-sectional range we evaluated. Nevertheless, the biological effects of aging are arguably accentuated in older adults relative to younger adults, making our sample ideal for evaluating brain and cognitive differences between individuals who show susceptibility to age-related cognitive declines versus those who are resilient over time.

In our study, abstraction, chunking, and switching were assessed using single measures rather than composite scores, which may limit the certainty of whether the measures truly reflect these executive domains. Nevertheless, these measures of executive processing were selected based on conceptual as well as empirical validation from previous studies (Lezak et al., 2004). Moreover, one of the goals of this study was to determine if higher frontal activity would be uniformly associated with better performance across measures of different aspects of executive processing. In this respect, using composite scores or a more reduced set of measures of general executive function would limit our ability to detect heterogeneous involvement across different frontal areas. We also note that differences between the memory test in the scanner and the neuropsychological tests of executive ability outside of the scanner may have contributed to a relatively weak correspondence between these behavioral measures. The scanner task involved studying a list of words presented once and

subsequently recognizing the words with limited time to respond. By contrast, the neuropsychological tests of discrimination (from the CVLT) were self-paced, with the word list studied 5 times as per the CVLT procedure, and involved both recall and recognition. In addition, the tests of manipulation involved rearranging sequences of letters and numbers rather than words. Regardless of these differences, the consistent significant correlations observed between in-scanner memory test and executive test performances, along with previous literature implicating frontal involvement in executive processing (see Introduction), provide joint support that the longitudinal changes in frontal rCBF responses in this study relate to executive processes.

Finally, participants in our study showed learning-related improvements over repeated testing for the in-scanner recognition memory task, despite the use of alternating word lists, as well as in the neuropsychological tests of discrimination, which may have dampened our ability to accurately estimate age-related effects on these abilities. However, the extent to which an executive domain displays stability or learning-related improvement over time indicates that this ability is more resilient to the effects of aging relative to other abilities. Indeed, our findings showed that some abilities, such as inhibition and manipulation, were not as amenable to learning through repeated testing. Moreover, even within the abilities that benefited from repeat testing, our longitudinal findings showed that there were participants who declined in performance and continually engaged high levels of frontal activity over follow-up whereas those who showed learning and improvement tended to reduce frontal engagement over time. It is still possible, nonetheless, that there is a non-linear relationship between frontal activity levels and executive ability. For example, cases of more severe cognitive decline may be associated with levels of frontal activity that are even lower or reduced compared to those observed in the higher performers in our sample. Future studies that compare rCBF between clinically normal participants and those with clinical diagnosis of cognitive impairment (such as dementia) are ongoing to address this issue.

Whereas many cross-sectional studies on neurocognitive aging suggest that age-related increases in functional activity in frontal regions are a general phenomenon and play a compensatory role, our findings indicate that frontal processes are more heterogeneous in this regard. Whether age changes in frontal responses reflect compensatory recruitment, effortful, or non-selective, activity with respect to a given task varies, depending on the processes and regions involved. Our findings also indicate that chronically high-levels of frontal engagement, at least in the ventral-lateral area, are associated with declining executive performance rather than improved or sustained performance. Thus, optimal cognitive aging may involve the ability to engage additional task-related compensatory resources when the need arises, as well as the ability to rapidly learn and adapt so that further resource consuming compensatory processes are minimized.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

There are mixed findings on age-related increase in frontal activity and cognition.
We examine longitudinal changes in frontal rCBF and different executive abilities.
Baseline frontal rCBF had mixed correlations with different abilities and regions.
Sustained or improving performance correlated with decreasing frontal rCBF.
Aging frontal activity changes is process and region specific and not generalized.

Fig. 1.

Functional slices overlaid on an MNI anatomical template showing frontal areas with significant associations between cross-sectional baseline rCBF and baseline performance across different executive domains, thresholded at $p < .005$, with cluster-size = 50. Warm colors show regions where higher baseline rCBF was associated with higher baseline performance. Cool colors show regions where higher baseline rCBF was associated with lower baseline performance.

Fig. 2.

Functional slices overlaid on an MNI anatomical template showing frontal areas where better performance over time is associated with longitudinal rCBF reductions across different executive domains. Statistical maps are thresholded at $p < .005$, with cluster-size 50. Scatterplots show estimated longitudinal change slopes for executive performance plotted against rCBF change estimated from each ROI. Regression lines and r values are adjusted for age and sex. Dashed lines demarcate zero change points for each axis.

Table 1

Demographic and follow-up details of the 99 participants (55 males, 44 females; 88 Caucasians, 11 African Americans).

	Mean (SD)	Min.	Max.
Baseline age in yrs	69.0 (7.3)	56.1	85.9
Baseline MMSE	28.9 (1.4)	23	30
Years of education	16.2 (2.8)	8	20
Follow-up interval in yrs	7.8 (0.9)	4.9	9.4
No. of follow-up sessions	8.3 (1.1)	5	9

Table 2

List of component executive domains, definitions, and test outcome measures.

Domains	Definitions	Tests (Outcome Measures)
Abstraction	Formation of conceptual associations.	Similarities [†] (No. of correct conceptual associations between items).
Chunking	Strategic organization of information into meaningful categories.	CVLT [‡] (Semantic clustering ratio during word list recall).
Discrimination *	Distinguishing between targets and distractors.	CVLT [‡] (Short-delay recall after interference); CVLT [‡] (D' recognition score).
Inhibition *	Suppressing information or responses.	Category Fluency [§] (Total perseverations); Letter Fluency [§] (Total perseverations).
Manipulation *	Reordering and rearrangement of item information in mind.	Alpha Span [¶] ; Digit Span Backwards [‡] .
Switching	Alternating between different task goals.	Trail Making ^{//} (Difference between trails A and B).

* Composite scores.

[†] (Wechsler, 1981).[‡] (Delis, Kramer, Kaplan, & Ober, 1987).[§] (Spree & Benton, 1969).[¶] (Crain, 1990).^{//} (Reitan, 1992).

Table 3

Mean performance raw scores for neuropsychological test measures at baseline, and longitudinal performance changes over follow-up sessions.

Test Measures	Baseline		Longitudinal Change	
	Mean (SD)	Range	Mean (SD)	Range
Similarities	22.13 (3.31)	8 to 26	0.041 (0.087)	−0.12 to 0.40
CVLT Semantic Clustering Ratio	2.58 (0.92)	0.25 to 4.12	0.0011 (0.039)	−0.087 to 0.12
CVLT % Decrement in Short-Delay Recall after Interference	12.63 (15.55)	−20 to 62.5	−0.59 (0.82)	−3.14 to 1.67
CVLT D' Recognition Score	3.37 (0.51)	1.60 to 3.96	0.0069 (0.0052)	0.0062 to 0.0085
Category Fluency Total Perseverations	1.16 (1.61)	0 to 9	0.017 (0.028)	−0.084 to 0.10
Letter Fluency Total Perseverations	1.60 (1.82)	0 to 8	0.087 (0.13)	−0.34 to 0.84
Alpha Span	5.82 (1.55)	3 to 9	−0.093 (0.076)	−0.35 to 0.052
Digit Span Backwards	7.72 (2.04)	4 to 13	−0.019 (0.016)	−0.052 to 0.025
Trail Making A-B Difference	−43.65 (26.47)	−126 to 31	−0.50 (0.85)	−3.63 to 0.68

Table 4

Peak MNI coordinates of frontal regions showing significant associations between rCBF and executive performance.

Associations	Domains	Regions	BA	x	y	z	t	No. of voxels
a. Baseline rCBF and Baseline Executive Performance								
Abstraction		L Middle Frontal	44	-38	24	34	4.09	102
		L Superior Medial Frontal	10	-4	62	2	3.21	108
		R Rolandic Operculum	48	54	-14	22	3.30	57
Chunking		L Inferior Frontal (Pars Triangularis)	48	-42	26	24	3.64	164
Discrimination		L Middle Frontal	46	-28	42	28	-4.45	120
Inhibition		L Insula	48	-42	14	-6	-3.21	256
		R Inferior Frontal (Pars Triangularis)	48	48	30	20	-3.47	149
b. Longitudinal rCBF and Longitudinal Executive Performance								
Abstraction		L Insula	48	-44	8	-4	-3.68	203
		L Inferior Frontal (Pars Opercularis)	48	-56	16	10	-3.33	67
Chunking		L Medial Orbital Frontal	10	0	62	-8	-3.31	96
		R Medial Orbital Frontal	10	14	46	-2	-3.58	59
		L Insula	47	-34	18	-6	-3.29	84
Discrimination		L Insula	47	-34	22	-4	-3.20	63
Inhibition		L Inferior Frontal (Pars Triangularis)	45	-44	42	6	-3.94	103
		L Inferior Frontal (Pars Opercularis)	48	-52	12	6	-4.55	256
		L Precentral	44	-46	10	40	-3.53	63
		R Superior Orbital Frontal	11	26	56	-2	3.35	100
Manipulation		L Superior Medial Frontal	10	0	54	22	-2.97	71
Switching		L Insula	48	-30	16	8	-3.72	196
		R Rolandic Operculum	48	56	-6	10	-3.51	62
		R Anterior Cingulate	11	8	42	2	-3.77	162