Progressive Increase of Frontostriatal Brain Activation From Childhood to Adulthood During Event-Related Tasks of Cognitive Control

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Abstract: Higher cognitive inhibitory and attention functions have been shown to develop throughout adolescence, presumably concurrent with anatomical brain maturational changes. The relatively scarce developmental functional imaging literature on cognitive control, however, has been inconsistent with respect to the neurofunctional substrates of this cognitive development, finding either increased or decreased executive prefrontal function in the progression from childhood to adulthood. Such inconsistencies may be due to small subject numbers or confounds from age-related performance differences in block design functional MRI (fMRI). In this study, rapid, randomized, mixed-trial event-related fMRI was used to investigate developmental differences of the neural networks mediating a range of motor and cognitive inhibition functions in a sizeable number of adolescents and adults. Functional brain activation was compared between adolescents and adults during three different executive tasks measuring selective motor response inhibition (Go/no-go task), cognitive interference inhibition (Simon task), and attentional set shifting (Switch task). Adults compared with children showed increased brain activation in task-specific frontostriatal networks, including right orbital and mesial prefrontal cortex and caudate during the Go/no-go task, right mesial and inferior prefrontal cortex, parietal lobe, and putamen during the Switch task and left dorsolateral and inferior frontotemporoparietal regions and putamen during the Simon task. Whole-brain regression analyses with age across all subjects showed progressive age-related changes in similar and extended clusters of task-specific frontostriatal, frontotemporal, and frontoparietal networks. The findings suggest progressive maturation of task-specific frontostriatal and frontocortical networks for cognitive control functions in the transition from childhood to mid-adulthood. *Hum Brain Mapp 27:973–993, 2006.* © 2006 Wiley-Liss, Inc.

Key words: development; cognitive neuroscience; cognitive control; executive functions; fMRI

INTRODUCTION

Basic cognitive functions are established in childhood; more complex cognitive functions, however, such as organized and abstract thought, self-control, interference inhibition, and cognitive flexibility have been shown to develop throughout adolescence [Levin et al., 1991]. Concurrent with cognitive development are important brain maturational changes that continue into late adulthood such as synaptic pruning and reorganization, programmed cell death, and dendritic/axonal arborization [Changeux and Danchin, 1976; Huttenlocher, 1994]. Structural magnetic resonance imaging (MRI) studies have shown that these maturational changes co-occur with morphological changes in white to gray matter ratio in most brain areas from early childhood to

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late adolescence, presumably reflecting myelination [for overview, see Casey et al., 2000; Sowell et al., 2004]. More specifically, nonlinear increases in gray matter (GM) have been observed till adolescence, peaking at about 12–16 years (depending on the brain region), after which there is a reduction in total GM accompanied by a relatively more linear increase in white matter (WM) in frontal, temporal, and parietal brain regions [Giedd et al., 1999; Gogtay et al., 2004; Huttenlocher and Dabholkar, 1997; Schneider et al., 2004; Sowell et al., 1999a,b, 2004]. This nonlinear reduction in the GM/WM ratio has been related to progressive myelination processes by diffusion tensor imaging techniques [Huppi et al., 1998; Morriss et al., 1999; Schneider et al., 2004] and is characterized by regional heterogeneity and heterochronicity [Giedd et al., 1999; Sowell et al., 2004], with higher-order association cortices, in particular dorsal prefrontal, posterior parietal, and temporal lobes maturing relatively late in contrast with the early maturation of lower-order sensorimotor and occipital brain regions and the frontal pole [Casey et al., 2000; Giedd et al., 1999; Gogtay et al., 2004; Olesen, 2003]. Postadolescent development is characterized by a dramatic acceleration of frontal and striatal GM loss, parallel to a stabilization of GM loss in parietal lobes [Sowell et al., 1999b]. Increasing cognitive capacity during childhood and adolescence may therefore result from regressive changes such as synaptic pruning (thereby strengthening of relevant synaptic connections) together with progressive changes of myelination of connecting fibers, improving speed of connections and therefore cognitive efficiency [Casey et al., 2000; Sowell et al., 2004]. Cognitive functions that are mediated by the frontal lobes and frontostriatal connections are therefore thought to be particularly susceptible to late maturation during adolescence [Bjorklund and Harnishfeger, 1990; Casey et al., 2000; Dempster, 1992; Durston and Casey, 2005; Sowell et al., 2001].

Functional imaging has the advantage of elucidating the dynamic nature of cognitive development [Rubia, 2002]. Inhibitory and cognitive control functions have been of particular interest in the developmental functional imaging literature, as these functions are known to be mediated by the frontal lobes and their connections [Banich et al., 2000; Durston et al., 2002a; Garavan et al., 2001; Liu et al., 2004; Menon et al., 2001; Rubia et al., 2001, 2003; Smith et al., 2004], and have been shown to develop relatively late, peaking during adolescence [Anderson, 2002; Comalli et al., 1962; Daniel et al., 2000; Diamond, 1990]. As opposed to structural studies, however, the functional assessment of neuro-maturational processes of inhibitory and cognitive control has been less consistent. Developmental imaging studies investigating motor response inhibition in the Go/no-go or Stop task, for example, have differed in findings. Casey et al. [1997], examining only the frontal lobes, found no group differences between children and adults during a Go/no-go task in the magnitude of activation, but a negative correlation between age and the volume of activation in middle prefrontal cortex. Similarly, Booth et al. [2001], during Go/no-go task performance, also observed increased activation in children compared with adults in dorsolateral prefrontal cortex, in addition to other areas such as insula, superior temporal lobe, caudate, and thalamus. Other studies, however, have observed increased brain activation in adults compared with children with some showing alternative brain activation patterns for children. Durston et al. [2002b] found increased magnitude of signal change for children compared with adults for No-go compared with Go trials in bilateral inferior prefrontal cortex, dorsolateral prefrontal cortex, and parietal lobes. In adults, however, MR signal in performance-correlated brain regions of bilateral inferior prefrontal cortex and left anterior cingulate gyrus increased with increasing difficulty, an effect that was not observed in children, as they showed relatively large activation in these areas already during the easy trials. Rubia et al. [2000], comparing adolescents with adults during a Stop task, found increased activation in adults in left inferior and dorsolateral prefrontal cortex, areas that were also correlated linearly with age, but alternative brain activation in adolescents in right inferior prefrontal lobe and caudate. A linear increase in left inferior and orbital prefrontal activation with age during a Go/no-go task has also been observed in a younger age window between children and adolescents, with regressive changes in left dorsolateral prefrontal brain regions [Tamm et al., 2002]. The study with the largest subject numbers so far, 32 children and adults in Bunge et al. [2002], using an event-related Go/no-go task, showed increased activation for adults compared with children in right mesial, inferior, and dorsolateral prefrontal cortex, putamen, and temporoparietal areas.

While the developmental literature with respect to motor inhibition is rather inconsistent, developmental imaging studies investigating cognitive inhibition in the form of interference inhibition during stimulus-response incompatibility tasks have been more consistent, finding mostly increased brain activation in adults compared with children or adolescents in task-relevant brain regions with alternative activation patterns in children. Adleman et al. [2002], investigating children, adolescents, and adults during the Color-Word Stroop interference effect, found a positive correlation between age and activation in a left hemispheric network of lateral prefrontal lobe, anterior cingulate, and parietal brain regions with no findings of negative correlations with age. Similar to the study of Adleman et al., inhibition of distraction in a selective attention task showed increased brain activation in adults compared with children in anterior cingulate gyrus and thalamus [Booth et al., 2003]. Bunge et al. [2002] found hemispheric differences for the interference effect in the Eriksen Flanker task with children activating left prefrontal brain regions, in addition to posterior parietal and temporal areas, compared with adults, who showed right inferior prefrontal and putamen activation. A study of Casey et al. [2002] showed increased left middle frontal activation in adults, but increased volumes of activation in hippocampal/parahippocampal and basal ganglia in children. The only study, to our knowledge, that has investigated cognitive inhibition in the context of task switching found in-

creased activation in adults compared with children in frontal and parietal brain regions [Casey et al., 2004].

Overall, despite some differences in findings, it thus appears that during motor and cognitive inhibitory control functions, older subjects show increased activation in task-relevant focal brain regions, with younger age groups showing either less or more diffuse activation patterns in task-uncorrelated brain regions [for review, see Casey et al., 2000; Durston and Casey, 2005].

The majority of these developmental functional MRI (fMRI) studies on inhibitory functions were based on relatively small sample sizes and used block design fMRI (with the exception of the studies by Bunge et al. [2002] and Durston et al. [2002b], which may partly explain inconsistencies in findings. Performance differences in block design fMRI have been shown to be an important confound in the comparison of functional imaging of different age groups and to contaminate real findings of age-related brain activation differences [Murphy and Garavan, 2004]. This can be avoided by event-related designs, where only successful trials are being compared between groups. Furthermore, most of the previous imaging studies examined children up to 11 or 12 years, with only two of them comparing adolescents and adults [Adleman et al., 2002; Rubia et al., 2000]. Adolescence, however, is a particularly important age window for the development of these cognitive functions, given that these inhibitory functions have been shown to develop progressively into adolescence. Motor response inhibition in the Go/no-go task has been shown to peak at about 12 years [Levin et al., 1991], interference inhibition in the Color-Word Stroop or Simon task at about 17–19 years [Comalli et al., 1962; Daniel et al., 2000; Diamond, 1990], and cognitive flexibility at about 12 years [Anderson, 2002]. Adolescence is therefore a highly informative age range to investigate neuro-maturational changes of cognitive control and it has been suggested that major changes in functional neuroactivation occur between 12 and 19 years [Bunge et al., 2002].

The aim of this study, therefore, was to further clarify the relationship between the development of inhibitory control functions and underlying neural brain activation by comparing relatively large numbers of children/adolescents and adults in event-related fMRI paradigms that tapped into three different forms of inhibitory control: motor response inhibition, interference inhibition, and cognitive switching. The examination of the development of these different inhibitory processes in one study design should explore differences and similarities of the functional maturation of the specific frontostriatal and frontoparietal networks mediating these different processes of cognitive control. The event-related design should allow for post-hoc sampling of only correct performance trials, thus avoiding confounds due to potentially higher error rates in adolescents. Furthermore, a whole-brain regression analysis with age should examine developmental trajectories of the neural networks involved in these three inhibition functions across a relatively wide age range between late childhood and mid-adulthood.

All tasks were in the motor domain and designed as homogeneous as possible in motor requirements, visual stimulation, interstimulus intervals, and overall length in order to make them as comparable as possible. A Go/no-go task was used to measure selective motor response inhibition [Rubia et al., 2005]; a Simon stimulus-response incompatibility task was used to measure interference inhibition; a Switch task, demanding a cognitive switch between two different spatial dimensions, measured the ability to inhibit previously valid stimulus-response associations in order to switch set, thus measuring inhibition of irrelevance [Smith et al., 2004]. The tasks are thus measuring differing aspects of inhibitory control that have been shown to be mediated by different, although partly overlapping neural networks of frontostriatal and frontoparietal interconnections. Right inferior and orbital prefrontal cortex and its connections to the caudate have been shown to mediate motor response inhibition in Go/no-go and Stop tasks [Durston et al., 2002b; Konishi et al., 1998; Menon et al., 2001; Rubia et al., 2001, 2003]. Cognitive interference inhibition, by contrast, appears to be predominantly mediated by left hemispheric dorsolateral prefrontal, striatal, and parietal brain areas as shown for the stimulus-response incompatibility effects in the Color-Word Stroop [Banich et al., 2001, 2000; Carter et al., 2000; Fan et al., 2003] and the Simon tasks [Diamond, 2002; Liu et al., 2004]. Inhibition of irrelevant stimulus-response associations during task switching appears to be mediated by similar right inferior prefrontal and striatal brain regions as motor inhibition, but has been shown in addition to rely strongly on the parietal cortex and its connections to the frontal lobes [DiGirolamo et al., 2001; Konishi et al., 1999, 2002; Smith et al., 2004].

We hypothesized that there would be differences between adolescents and adults in these task-specific frontostriatal and frontoparietal neural networks mediating these three different inhibitory control mechanisms. In particular, we hypothesized that adults compared with children and adolescents would show increased activation in right inferior and orbital frontostriatal brain regions during the Go/no-go task, in right frontostriatal and parietal brain regions during the Switch tasks, and in a left hemispheric network of frontostriatal and frontoparietal areas during the Simon task. Second, extrapolating from evidence from previous studies for linear progressive changes during cognitive control during relatively narrow age ranges [Rubia et al., 2000; Adleman et al., 2002; Tamm et al., 2002], we hypothesized that a whole-brain regression analysis with age would show positive progressive changes from childhood to adulthood in task-relevant frontostriatal and frontoparietal brain activation.

SUBJECTS AND METHODS

Subjects

Fifty-two male right-handed subjects participated in the study, 23 adults and 29 adolescents. The adults were in the age range of 20–43 years (mean [SD] age, 28 [6]) and the

adolescents in the age range of 10–17 years (mean [SD] age, 15 [2]). Not all subjects performed all tasks due to several reasons such as time constraints, technical problems with the scanner, and scanner tiredness in some of the subjects. For the Go/no-go task, the comparison was between 23 adults and 25 adolescents, for the Simon task between 21 adults and 28 adolescents, and for the Switch task between 22 adults and 27 adolescents. There was an overlap of 20 adults and 17 adolescents who performed all three tasks. Between the Switch and the Simon task, there was an overlap between 20 adults and 26 adolescents. There were six adolescents who only performed the Go/no-go task, and there was an overlap between the Go/no-go and the Simon and Switch tasks, respectively, between 21 adults and 18 adolescents. There were significant group differences on the Raven's Standard Progressive Matrices Intelligence Questionnaire (IQ) [Raven, 1960], in some of the task-specific subgroup comparisons (Go/no-go task: adults mean [SD] IQ estimate: 112 [12], adolescents mean [SD] IQ estimate: 104 [11], $t = 2.4$, degrees of freedom [df] = 46, $P = 0.02$; Simon task: adults mean [SD] IQ estimate: 112 [12], adolescents mean [SD] IQ estimate: 105 [13], $t = 1.8$, df = 47, $P = 0.07$; Switch task: adults mean [SD] IQ estimate: 112 [12], adolescents mean [SD] IQ estimate: 105 [13], $t = 2$, df = 50, $P = 0.054$). The study was approved by the local Ethics Committee and subjects received £30 for their participation, which provided sufficient motivation.

fMRI Activation Task Design

A rapid, mixed trial, randomised presentation, event-related fMRI design was used for all tasks [Dale and Buckner, 1997; Dale, 1999]. Inter-stimulus intervals (ISIs) were randomly jittered between 1.6 and 2.0 for Go/no-go and Simon tasks, and between 1.8 s and 2.4 s for the Switch task to optimise statistical efficiency. It has been shown that both jittering of the ISI and randomization of stimulus type reduces or removes the response overlap distortions and therefore improves the efficiency of fast event-related fMRI designs monotonically with decreasing mean ISIs [Dale and Buckner, 1997; Dale, 1999; Burock et al., 1998].

The tasks were explained to the subjects and each subject was trained once in each task prior to scanning. In the scanner, the task instructions for each task were repeated to the subjects a few minutes before they performed the task. All tasks were written in visual basic programming and projected from a PC onto a mirror within the MRI scanner during the scan and response data were recorded onto a PC at the same time. All subjects received £30 for their participation. All tasks had a duration of about 6 min. Multivariate analysis of covariance (ANCOVA) was used with IQ as a covariate to test for group differences in performance using the statistical package of SPSS [Chicago, IL, 1994].

Go/no-go task

In the Go/no-go task a motor response has to be selectively inhibited or executed depending on whether a go signal or a no-go signal is displayed on the screen. It requires motor response inhibition and selective attention.

The basic task is a choice reaction time task. Arrows (of 500 ms duration each) pointing either to the left or right side appear on the middle of the screen. After the 500-ms stimulus duration, there is a blank screen of 1300 ms, so that each intertrial interval amounts to 1.8 s. The subject is instructed to press the left or right response button as fast as possible, depending on whether the arrow points left or right. Infrequently (in 12% of trials), arrows pointing to the top (no-go signals) appear in the middle of the screen with a 500-ms duration. Subjects have to inhibit their motor response to these arrows. In another 12% of trials (oddball trials), slightly slanted arrows pointing left or right appear, and subjects have to press a response button as fast as they can to either the left or right response button, corresponding to the direction of where the arrows point, just as to the go signals. The event-related analysis contrasted the activation related to successful no-go trials with activation related to successful go trials. Task duration was just over 6 minutes [for details of the task, see Rubia et al., 2005].

Simon task

We used an fMRI adaptation of the Simon task, also called the directional or motor Stroop task, involving a Stroop-like stimulus-response incompatibility effect, which is reflected in a typically slowed reaction time to the incongruent trials as compared with the congruent trials. The tendency to respond to the same side as the stimulus appearance has been documented as "spatial incompatibility" or the "Simon effect" [Simon and Berbaum, 1988, 1990].

The basic task is a choice reaction time task, where subjects have to press a left or right button depending on whether an arrow indicates left or right. In the congruent condition, the arrows pointing left appear on the left side of the screen and the arrows pointing right on the right side of the screen, i.e., they appear on the screen side corresponding to the direction where they point to. In the low frequency incongruent condition (12% of trials), an arrow pointing right appears on the left side of the screen or an arrow pointing left appears on the right side of the screen (incongruent conditions) and subjects have to press the button corresponding to the side where the arrow points, ignoring the conflict of the interfering information of the "wrong" (i.e., opposite) screen side of appearance. Twenty-four incongruent stimuli were thus interspersed with 160 high-frequency congruent stimuli. The event-related analysis compared the successfully performed incongruent trials with the successfully performed congruent trials. Task duration was about 6 minutes [Smith et al., 2005].

Switch task

Switch tasks require attentional flexibility and encompass both attentional and inhibitory functions. During the switch from one stimulus-response association set to a second one, interference from the previous stimulus-response association has to be inhibited in order to refocus the attention and

engage in the new stimulus response association. A modified version of the Meiran Switch task was used [Meiran, 1996; Smith et al., 2004].

Subjects used a keypad with four buttons in a diamond configuration in order to make responses. Subjects were presented with a grid divided into four squares, in the centre of which was a double-headed arrow positioned either horizontally or vertically. The grid with the double-headed arrow was presented for 1600 ms; 200 ms after presentation of the grid and arrows, a red dot appeared for 1400 ms in any one of the four squares of the grid. A horizontally pointing double-headed arrow indicated that the subject had to confirm whether the circle was in either of the two left or the two right squares of the grid, by pressing the left or right button. After the 1600 ms of presentation time, there was a blank screen for 800 ms. Subjects were instructed to make their responses as soon as possible after stimulus presentation. This presentation was repeated for several repeat trials with a total ISI of 2.4 s. A minimum of four repeat trials were followed by a switch trial where the double-headed arrows in the middle of the grid changed to a vertical position, and the subject had to indicate whether the circle was in either of the two upper or two lower squares of the grid by pressing the upper or lower button. This presentation pattern was maintained for several repeat trials followed by a switch trial where the arrow changed back to a horizontal position. Subjects thus had to switch their attention and response between the horizontal dimension (is the dot on the left or right side of the grid?) and the vertical dimension (is the dot on the upper or lower part of the grid?). The switch trials were separated by a minimum of four repetition times apart from each other (TR = ISI = 2.4 s), in order to allow optimal separation of the hemodynamic response. Switch trials thus appeared pseudorandomly either after 4, 5, or 6 repeat trials (i.e., every 9.6 s, 12 s, or 14.4 s) to avoid predictability. The 6-min task consisted of 152 trials with high-frequency repeat trials (79%) interspersed with 32 low-frequency switch trials (21%). Thus, on average, one in five trials was a switch trial. The event-related analysis contrasted activation associated with switch trials with that of repeat trials [for details of the task, see Smith et al., 2004].

MRI Image Acquisition

Gradient-echo echo-planar MR imaging (EPI) data were acquired on a GE Signa 1.5 T Horizon LX System (General Electric, Milwaukee, WI) at the Maudsley Hospital, London. Consistent image quality was ensured by a semiautomated quality control procedure. A quadrature birdcage head coil was used for radiofrequency (RF) transmission and reception. In each of 16 noncontiguous planes parallel to the anterior–posterior commissural, 208 T_2*-weighted MR images (154 T_2*-weighted MR images for the Switch task) depicting BOLD (blood oxygen level-dependent) contrast covering the whole brain were acquired with TE = 40 ms, TR = 1.8 s, flip angle = 90°, in-plane resolution = 3.1 mm, slice thickness = 7 mm, slice-skip = 0.7 mm. At the same time, a high-resolution inversion recovery EPI of the whole brain was acquired in the intercommissural plane with TE = 40 ms, TI = 180 ms, TR = 16,000 ms, in-plane resolution = 1.5 mm, slice thickness = 3 mm, slice-skip = 0.3 mm. This EPI dataset provided almost complete brain coverage.

Individual Analysis

The data were first realigned [Bullmore et al., 1999] to minimize motion-related artefacts and smoothed using a Gaussian filter (full-width at half-maximum, FWHM, 7.2 mm). Time series analysis was then carried out by first convolving each experimental condition with Poisson functions, modeling delays of 4 and 8 s, respectively (to allow variability within this range). The weighted sum of these two convolutions that gave the best fit (least-squares) to the time series at each voxel was then computed and a goodness-of-fit statistic computed at each voxel consisting of the ratio of the sum of squares of deviations from the mean intensity value due to the model (fitted time series) divided by the sum of squares due to the residuals (original time series minus model time series). This statistic is called the SSQ-ratio. The appropriate null distribution for assessing significance of any given SSQ-ratio was then computed using the wavelet-based data resampling method described in detail in Bullmore et al. [2001] and applying the model-fitting process to the resampled data. This process was repeated 20 times at each voxel and the data combined over all voxels, resulting in 20 "null" parametric maps of SSQ-ratio for each subject, which could be combined to give the overall null distribution of SSQ-ratio. The same permutation strategy was applied at each voxel to preserve spatial correlational structure in the data. Voxels activated at any desired level of type I error can then be determined by obtaining the appropriate critical value of the SSQ-ratio from the null distribution.

Mapping of Within-Group Activation

The observed and randomized SSQ-ratio maps were transformed into standard space by a two-stage process involving first a rigid body transformation of the fMRI data into a high-resolution inversion recovery image of the same subject followed by an affine transformation onto a Talairach template [Talairach and Tournoux, 1996]. A generic brain activation map (GBAM) can be produced for each experimental condition by calculating the median observed SSQ-ratio over all subjects at each voxel (median values were used to minimize outlier effects) at each intracerebral voxel in standard space [Brammer et al., 1997] and testing these median SSQ-ratio values against the null distribution of median SSQ-ratios computed from the identically transformed wavelet resampled data [Brammer et al., 1997]. In order to increase sensitivity and reduce the multiple comparison problem encountered in fMRI, hypothesis testing was carried out at the cluster level using the method developed by Bullmore et al. [1999], initially for structural image analysis, and subsequently shown to give excellent cluster-wise type I error control in both structural and functional fMRI analysis. In this particular analysis, <1 false-positive

activated clusters were expected at $P < 0.05$ at the voxel level and $P < 0.0025$ at the cluster level.

ANCOVA for Between-Group Differences in Activation

Following transformation of the statistics maps (SSQ-ratio) for each individual into standard space, it is possible to perform a randomization-based test for voxel or cluster-wise differences. First, the difference between the mean SSQ-ratio values in each group was calculated at each voxel. The mean ratio was then recalculated 1000 times at each voxel (to preserve spatial correlations) following random permutation of group membership and the difference in SSQ-ratios was calculated after each permutation. The probability of the original SSQ-ratio difference under the null hypothesis of no effect of group membership is the number of times we observed an SSQ-ratio difference as large or larger than the original difference during the permutation process divided by the total number of permutations. If this value exceeded our threshold for voxel level activation (normally $P < 0.05$), "activated" voxels were then used to identify connected clusters and subjected to cluster analysis as described in detail (with its validation) by Bullmore et al. [1999]. Briefly, first the data were thresholded on a voxel-wise basis at $P < 0.05$. As this alone would lead to an unacceptably high type I error rate over a whole brain, in a second step the data were assembled into 3-D clusters using a simply contiguity criterion. The "mass" of each cluster was then calculated by adding together the statistical values of all the cluster members. These cluster masses were then thresholded at any desired cluster-wise P value by applying an identical process to statistical maps produced following data permutation. The main advantage of the method is its use of cluster mass, which means that small, strongly responding clusters can survive thresholding, which is not the case with a simple cluster area/volume statistic. As the final thresholding is done at the whole-brain level (expectation of clusters per BRAIN) this clearly does not suffer from the problem of thresholding at each VOXEL (multiple comparison problem).

For this particular group comparison, less than 1 false-activated cluster was expected at $P < 0.05$ for voxel and $P < 0.01$ for cluster comparisons. IQ was covaried in the ANCOVA analysis for between-group comparisons.

Correlations with Age

Correlations between age and activation restricted to those brain regions that differed between the two groups

To test for linear correlations between age and brain activation over all subjects, independent of group status, in areas that differed between groups, the standardized fMRI BOLD response, i.e., the SSQ-ratios, were extracted for each subject in each of the 3-D clusters of significant group activation differences. Pearson correlations were then performed between age and the SSQ-ratios of all subjects, for each of the between-group activation clusters.

Whole-brain correlation analysis between age and activation

To test for a linear correlation between whole-brain activation and age across all subjects independent of their group status, the Pearson product-moment correlation coefficient was first computed at each intracerebral voxel in standard (Talairach) space between the age data and the BOLD response (% change in signal) over all subjects. The correlation coefficients were recalculated after randomly permuting the ages but not the fMRI data. Repeating the second step many times (50 times per voxel, then combining over all voxels) gives the distribution of correlation coefficients under the null hypothesis that there is no association between specific ages and specific BOLD effects. This null distribution can then be used to assess the probability of any particular correlation coefficient under the null hypothesis. The critical value of the correlation coefficient at any desired type 1 error level in the original (nonpermuted) data could thus be determined by reference to this distribution. Statistical analysis was extended to cluster level as described by Bullmore et al. [1999]. A $P < 0.05$ at voxel and $P < 0.01$ at cluster levels were chosen, allowing less than one error cluster.

Correlations with Performance

Correlations between behavioral performance and areas of brain activation differences

To investigate whether between-group activation differences resulting from the ANCOVA comparison between adolescents and adults were related to differences in behavioral performance, Pearson correlations were performed across all subjects between activation in those clusters that differed between groups and performance variables on the tasks. For this purpose, for each task, the standardized fMRI BOLD response, i.e., the SSQ-ratios, were extracted for each subject in each of the 3-D clusters of significant between-group activation differences. Pearson correlations were then performed between the performance variables of each task and the SSQ-ratios of all subjects for each of the between-group activation clusters.

Correlations between behavioral performance and areas that correlated linearly with age in the whole-brain regression analysis

The same procedure as above was applied to test for correlations between performance variables and brain activation clusters that correlated linearly with age in the whole-brain regression analysis. For each task, the SSQ-ratios were extracted for each subject in each of the 3-D clusters of significant positive or negative correlations with age. Pearson correlations were then performed between the performance variables of each task and the SSQ-ratios of all subjects for each of the age-correlated activation clusters.

TABLE I. Performance measures and group differences in performance on the three inhibition tasks for adolescents and adults

Task measure	Adults, mean (SD)	Adolescents, mean (SD)	F (df = 2)	*P*	Correlation with age *P* (r)
Go/no-go task					
P (I) (%)	97 (3)	89 (13)	5	0.015	0.03 (0.3)
MRT go (ms)	457 (81)	406 (55)	4	0.031	n.s.
Simon task					
Conflict effect (ms)	127 (67)	102 (43)	2.7	n.s.	0.016 (0.3)
MRT congr. (ms)	454 (83)	431 (96)	1.8	n.s.	n.s.
Incongr.errors (%)	10 (9)	21(15)	4	0.025	−0.03 (0.3)
Congr. errors (%)	0.3 (0.5)	2 (2)	6	0.004	−0.001 (0.5)
Switch task					
Switch effect (ms)	112 (71)	108 (60)	0.9	n.s.	n.s.
MRT congr.(ms)	700 (87)	694 (130)	0.8	n.s.	n.s.
Switch errors (%)	2 (3)	6 (6)	5	0.008	n.s.
Repeat errors (%)	2 (2)	3 (8)	2	n.s.	n.s.

P(I): probability of inhibition; MRT: mean reaction time; Congr.: congruent; Incongr.: incongruent; conflict effect: MRT to incongruent trials − MRT to congruent trials. Switch effect: MRT to switch trials − MRT to repeat trials.

RESULTS

Task Performance

Since IQ differed between groups in some of the tasks, for all tests multiple univariate ANCOVAs were conducted with IQ as covariate to test for group differences in the performance measures. There were significant group differences in the Go/no-go task (n = 48), in that adolescents (n = 25), compared with adults (n = 23), showed a higher speed-accuracy trade-off, favoring speed to accuracy. They showed faster mean reaction times and a lower probability of inhibition. There were also significant group differences in the Simon task (n = 49), with adolescents (n = 28) making more errors than adults (n = 21) on both incongruent and congruent trials. During the Switch task (n = 49), adolescents (n = 27) made more errors than adults (n = 22) to Switch trials (Table I).

Correlation Between Age and Performance

Regression analysis showed in the Go/no-go task (n = 48, age range 10–38) a significant positive correlation between age and probability of inhibition. In the Simon task (n = 49, age range 10–43), a significant negative correlation was observed between age and both congruent and incongruent errors and a positive effect of age on the conflict effect. For the Switch task (n = 49, age range 10–43), no significant correlations with age were observed for any of the Switch task measures (Table I).

Brain Activation Within Each Group

During all tasks, adults and adolescents showed brain activation in task-relevant brain areas. The results of significant brain activation for each group for the contrast of successful target trials with their respective control trials are reported below for each task at a voxel-wise $P < 0.05$, and cluster-wise $P < 0.0025$.

Go/no-go task

For the contrast of no-go with go trials, adults (n = 23) showed activation in right mesial and orbitofrontal cortex, anterior and posterior cingulate gyri, in right inferior parietal lobes, in caudate nucleus, and in left and right cerebellum. Adolescents (n = 25) showed group brain activation in ventrolateral prefrontal cortex and in right and left caudate nuclei (Table II, Fig. 1a).

Simon task

During incongruent contrasted with congruent trials, adults (n = 21) showed group activation in a predominantly left hemispheric network of dorsolateral prefrontal and inferior prefrontal cortices, reaching into premotor cortex and deep into the insula, in anterior cingulate gyrus, and in inferior parietal and superior temporal lobes. Adolescents (n = 28) showed group activation in predominantly right hemispheric brain regions of superior and inferior temporal and parietal lobes, with some additional activation in left parietal and temporal cortices and in bilateral cerebellum (Table II, Fig. 1b).

Switch task

During Switch contrasted with repeat trials, the adult group (n = 22) activated right and left postcentral and parietal brain regions reaching in the right hemisphere rostrally into right inferior prefrontal cortex, in right dorsolateral prefrontal cortex, anterior cingulate, and bilateral occipital gyri. Adolescents (n = 27) activated right and left inferior parietal and superior temporal brain regions (Table II, Fig. 1c).

Between-Group Differences in Brain Activation

The maximum and minimum displacement from the mean position was calculated for each subject in mm to

TABLE II. Within-group activation foci for adults and adolescents on the three tasks

Brain area (BA)	Peak Tal. coord. (*x*, *y*, *z*)	N voxels
Go/no-go task		
Adults		
R orbitofrontal cortex (BA 11)	32, 55, −18	9
R mesial frontal cortex (BA 10/32)	4, 59, 9	31
R rostrolateral prefrontal cortex (BA 10/46)	32, 52, 9	22
L inferior prefrontal cortex (BA 45)	−46, 25, 20	15
L anterior cingulate (BA 32)	−10, 40, −1	9
L inferior parietal lobe (BA 40)	− 47, − 26, 20	15
R caudate (head)	25, −18, 25	15
L posterior cingulate (BA 31)	−10, −62, 9	56
L inferior temporal gyrus (BA 22)	−22, 11, −7	7
L cerebellum	−36, −62, −12	41
R cerebellum	10, −77, 29	21
Adolescents		
R ventrolateral prefrontal cortex (BA 47)	36, 22, −12	30
L caudate (tail)	−26, −37, 4	7
L caudate (head)	−10, −11, 20	5
R caudate (head)	18, −7, 20	20
Simon task		
Adults		
L dorsolateral/inferior prefrontal/premotor cortex/insula (BA 46/44/6)	−49, 25, 8	532
L postcentral/superior temporal/parietal cortex (BA 4/22/40)	−38, −35, 8	509
R mesial frontal cortex (BA 10/47)	31, 47, −10	25
R inferior frontal cortex (BA 45)	51, 8, 12	20
L inferior frontal cortex (BA 45)	−37, 32, 11	28
L anterior cingulate gyrus (BA 24)	−25, 4, 27	14
R insula	29, −6, 11	68
R caudate/thalamus	7, −6, 14	21
R middle temporal lobe (BA 39)	30, −52, 13	32
Adolescents		
L superior temporal gyrus (BA 22)	−56, −16, 1	58
R superior/inferior temporal/parietal/occipital lobe (BA 21/39/19/40)	7; −54; −0	970
L premotor/parietal lobe (BA 6/40)	−51, −11, 40	110
L cerebellum	−1, 65, −20	150
R cerebellum	29, −40, 20	240
Switch task		
Adults		
R dorsolateral prefrontal cortex (BA 46)	27, 44, 20	15
R inferior frontal/insula/premotor/inferior parietal gyrus (BA 45/6/40)	44, −13, 23	502
R anterior/posterior cingulate (BA 24)	3, −8, 43	99
L postcentral/inferior parietal gyrus (BA 4/40)	−43, −24, 29	415
R putamen	20, 0, 15	29
R occipital gyrus (BA 18)	3, −8, 43	43
L occipital gyrus (BA 18)	−11, −75, 1	54
Adolescents		
R medial temporal lobe (BA 21)	28, −55, −0.3	83
R parietal/superior temporal lobe (BA 40/42)	48, −17, 20	229
L parietal/superior temporal lobe (BA 40/42)	−52, −21, 18	136
L inferior parietal lobe (BA 40)	− 32, −43, 49	18
R paracentral gyrus (BA 5)	5, −16, 43	29

GBAM: generic brain activation maps at $P < 0.05$ at voxel and $P < 0.0025$ at cluster-levels; Tal. Coord.: Talairach coordinates, shown for the peak of the 3-D activation cluster; BA: Brodmann area; N voxels: number of voxels.

assess the amount of subject motion. No significant group differences were observed in the extent of 3-D motion for the *x, y, z* rotation and *x, y, z* translation during any of the three tasks (Go/no-go task: adults mean [SD] 3-D motion in mm = −0.007 [0.002]; adolescents mean 3-D motion = −0.008 [−0.002], df = 46, P = n.s.; Simon task: mean 3-D motion adults = −0.0016 [0.002]; mean 3-D motion adolescents = −0.0002 [0.003], df = 47, P = n.s.; Switch task: mean 3-D motion adults = −0.0016 [0.002]; adults mean 3-D motion = −0.001 [0.0014]; adolescents mean 3D motion = −0.0015 [0.0034], df = 47, P = n.s.). In all tasks, adults showed significantly increased activation compared with adolescents in task-relevant frontal, striatal, and parietal brain regions. Only in the Simon task did adolescents show alternative increased activation in posterior cingulate gyrus/precuneus and in cerebellum.

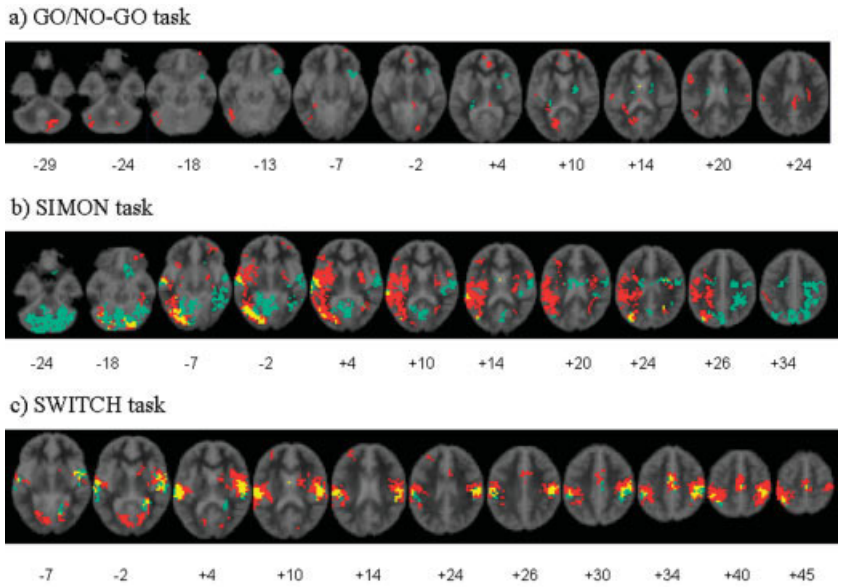

Figure 1.

Within-group brain activation maps for adults (red) and adolescents (green). Brain activation clusters that overlapped between the two groups are indicated in yellow. Shown are suprathreshold brain activation clusters at $P < 0.05$ at voxel, and $P < 0.0025$ at cluster levels. The z-coordinate is indicated in mm-distance from the anterior–posterior commissure. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Go/no-go task

There was increased brain activation in adults in mesial frontal cortex, including anterior cingulate gyrus, bordering orbitofrontal cortex and reaching caudally into the head of the caudate (Table III, Fig. 2).

Simon task

Adults showed increased brain activation in a left hemispheric network of dorsolateral and inferior prefrontal cortex reaching deep into the insula and dorsally into premotor cortex, in left anterior cingulate gyrus, left caudate, and in

TABLE III. Areas of brain activation differences between adults and adolescents for the three executive tasks

Brain area (BA)	Talairach coordinates (x, y, z)	Number of voxels	Correlation with age r (P)
Go/no-go task			
Adults > Adolescents			
R orbital/mesial frontal cortex/anterior cingulate/caudate (BA 11/10/32/24)	4, 48, 4	102	0.4 (0.003)
Simon task			
Adults > Adolescents			
L dorsolateral prefrontal cortex (BA 9)	−29, 37, 15	218	0.4 (0.03)
L inferior frontal/premotor cortex/insula (BA 47/6)	−32, 7, −2	393	0.5 (0.003)
L inferior parietal/superior temporal gyri (BA 40/22)	−50, −30, 26	135	0.3 (0.036)
L anterior cingulate gyrus (BA 32/24)	−18, 22, 26	38	n.s.
R putamen	25, −4, −2	108	0.4 (0.012)
Adolescents > Adults			
R posterior cingulate/precuneus/thalamus (BA23/30/31/7)	3, −74, 37	413	−0.4 (0.012)
R cerebellum	40, −59, −24	69	−0.4 (0.001)
Switch task			
Adults > Adolescents			
R anterior cingulate/putamen (BA 24/32/9)	14, 19, 26	123	0.24 (0.08)
R inferior prefrontal cortex/insula (BA 46/9/45)	32, 19, 9	126	0.4 (0.002)
L inferior parietal cortex (BA 40)	−40, −33, 53	65	0.3 (0.018)

For all group comparisons, ANCOVA were conducted at $P < 0.05$ for voxel and $P < 0.01$ for cluster comparisons. BA: Brodmann area. Only in the Simon task, adolescents showed increased activation compared with adults.

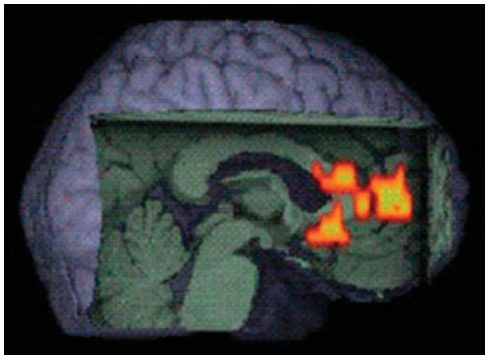

Figure 2.
Go/no-go task. Shown is increased BOLD fMRI response in adults compared with adolescents in anterior cingulate gyrus, orbitofrontal cortex, and caudate nucleus. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

left inferior parietal lobes, bordering superior temporal gyrus. There was also an activation increase in right putamen (Table III, Fig. 3a,b).

Over all subjects, the SSQ-ratios (standardized BOLD response) of all clusters of between-group differences (i.e., dorsolateral and inferior prefrontal cortex, anterior cingulate gyrus, caudate and inferior parietal lobes) were highly correlated with each other ($P < 0.0001$), pointing towards the possibility that these brain regions may form a network for task performance.

Adolescents compared to adults showed increased brain activation in two regional clusters, one comprising posterior cingulate gyrus and precuneus and the other one in the right lateral cerebellar hemisphere.

Switch task

During Switch contrasted with repeat trials, adults showed increased brain activation in right anterior cingulate gyrus, reaching caudally into the putamen, and in right inferior prefrontal gyrus, reaching deep into the insula (Table III, Fig. 4). There was also significantly increased activation in right inferior parietal lobe.

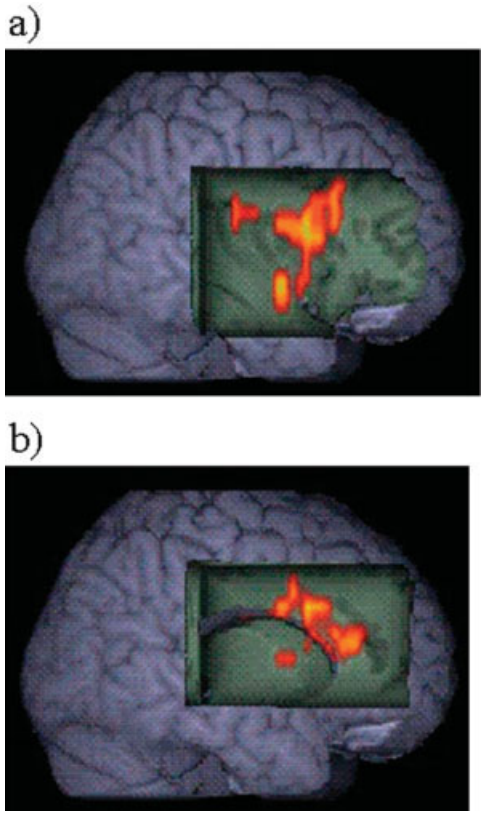

Figure 4.
Switch task. **a:** Increased BOLD fMRI response in adults compared with adolescents in right dorsolateral, inferior prefrontal, and premotor cortices. **b:** Anterior cingulate gyrus, reaching ventrally into anterior putamen. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

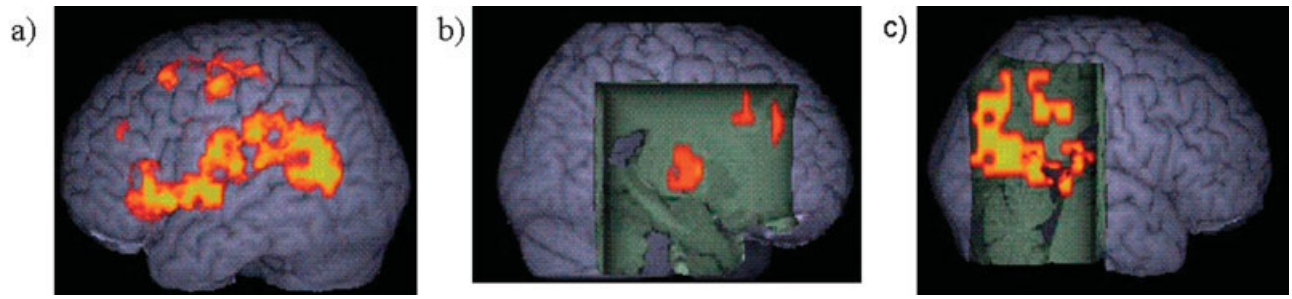

Figure 3.
Simon task. Shown is increased BOLD fMRI response in adults compared with adolescents in (**a**) left dorsolateral and inferior prefrontal cortices, premotor and inferior parietal cortices, and (**b**) in anterior cingulate gyrus and right putamen. **c:** Increased BOLD fMRI response in adolescents compared with adults in right cerebellum and in posterior cingulate gyrus/precuneus. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Over all subjects, the standardized BOLD response (SSQ-ratio) in anterior cingulate gyrus and in right inferior prefrontal cortex were significantly correlated with each other ($r = 0.7$, $P < 0.000$). The standardized BOLD response in right inferior prefrontal cortex correlated with the standardized BOLD response in inferior parietal lobe ($r = 0.3$, $P < 0.05$) and at a trend level with that of anterior cingulate gyrus ($r = 0.2$, $P < 0.09$). These three brain regions may form a network for task switching.

Correlations between Age and Activation Restricted to Those Brain Regions That Differed between the Two Groups

Go/no-go task

Across all subjects (n = 48, age range 10–38), there was a significant linear positive correlation between age and standardized BOLD response (SSQ-ratio) in the peak coordinates of the main cluster of between-group differences in anterior cingulate gyrus/orbitofrontal cortex (Table III).

Simon task

Across all subjects (n = 49, age range 10–43), there was a significant linear positive correlation between age and standardized BOLD response (SSQ-ratio) in the peak coordinates of all clusters of increased brain activation in adults in left dorsolateral and inferior prefrontal cortices, left inferior parietal/superior temporal lobe, and in right putamen, except for the cluster in left anterior cingulate gyrus (Table III).

There was also a significant negative linear correlation between age and standardized BOLD response (SSQ-ratio) in the peak coordinates of the two clusters of increased activation in adolescents in precuneus/posterior cingulate and cerebellum (Table III).

Switch task

The linear regression between age and those brain regions that differed between groups across all subjects (n = 49; age range, 10–43) showed a significant positive correlation between age and standardized BOLD response (SSQ-ratio) in all three clusters of between-group activation differences in anterior cingulate gyrus, right inferior prefrontal cortex/insula, and in left inferior parietal lobe (Table III).

Whole-Brain Regression Analysis Between Age and Activation

Go/no-go task

The whole-brain linear regression analysis with age over all subjects (n = 48, age range 10–38) and brain regions showed a positive linear correlation between age and activation in right and left anterior cingulate gyrus, right orbital/inferior prefrontal cortex, and in left inferior prefrontal cortex. A negative correlation with age was observed in right and left cerebellar vermis, a large bilateral cluster of posterior cingulate gyrus and precuneus that reached caudally into occipitotemporal gyrus and deep into thalamus, in left superior temporal, and right premotor/precentral gyri (Table IV, Fig. 5a).

Simon task

Across all subjects (n = 49, age range 10–43) and brain regions, a strong positive linear correlation between age and activation was observed over all subjects in a cluster of left inferior prefrontal and premotor gyrus reaching into superior temporal lobe, in right orbital and inferior prefrontal cortices reaching deep into the insula, in left dorsolateral prefrontal cortex, right putamen and thalamus, right superior temporal and left parietal lobes. Negative linear correlations with age were observed in predominantly right posterior cingulate gyrus bordering occipitotemporal brain regions, in bilateral cerebellum, right inferior parietal lobe, and precentral gyrus. A small cluster in right orbitofrontal cortex also showed a negative correlation with age (Table IV, Fig. 5b).

Switch task

The whole-brain linear regression analysis with age across all subjects (n = 48, age range 10–43) and brain regions showed a positive correlation between age and activation observed in a large cluster of right inferior prefrontal cortex, reaching deep into the insula, into precentral gyrus, and superior temporal lobe. Further areas that correlated positively with age were right orbitofrontal gyrus, left mesial frontal cortex, right and left caudate and putamen, and left tail of the caudate. Negative correlations with age were observed in right dorsolateral prefrontal cortex, left insula, mesial frontal gyrus, left superior and middle temporal lobes, right thalamus and hippocampus, left occipital cortex, and bilateral cerebellum (Table IV, Fig. 5c).

Correlations between Behavioral Performance and Areas of Brain Activation Differences

To investigate whether differences in between-group activation were related to differences in behavioral performance, Pearson correlations were tested between activation in those clusters that differed between groups and performance variables on the tasks.

For the Go/no-go task, no significant correlations were observed between any of the performance variables and the clusters of between-group difference in anterior cingulate gyrus/caudate.

For the Simon task (n = 49), there was a significant negative correlation between the number of errors to incongruent trials and the activation clusters in all areas of increased activation in adults except for anterior cingulate gyrus; i.e., in left dorsolateral prefrontal cortex (Table III; $r = -0.4$, $P < 0.005$), in left inferior prefrontal cortex (Table III; $r = -0.4$, $P < 0.004$), in left inferior parietal lobe (Table III; $r = -0.4$, $P < 0.002$), and in right putamen (Table III; $r = -0.4$, $P < 0.004$). There was also a significant negative correlation between errors and activation in the cluster of precuneus/posterior cingulate gyrus that was increased in adolescents (Table III; $r = 0.3$, $P < 0.018$).

TABLE IV. Whole-brain regression analysis showing brain areas of positive and negative linear correlations with age for the three executive tasks

Brain area (BA)	Talairach coordinates (*x*, *y*, *z*)	Number of voxels
Go/no-go task		
Positive correlations with age		
R + L anterior cingulate gyrus/mesial frontal lobe (BA 32/24/10)	4, 48, 4	194
R orbital/inferior prefrontal cortex (BA 11/47/46)	40, 52, −7	80
L inferior prefrontal cortex (BA 46)	−36, 48, 4	32
Negative correlations with age		
R + L vermis of cerebellum	4, −78, −18	309
L + R posterior cingulate/precuneus/occipito-temporal gyrus/thalamus (BA 23/30/31/39/22)	−36, −44, 20	980
L superior temporal gyrus (BA 22)	−60, −18, 4	16
R premotor cortex (BA 6)	47, −4, 20	17
Simon task		
Positive correlations with age		
L inferior prefrontal/insula/premotor/superior temporal (BA 45/6/4/22)	−43, −26, 25	515
R orbital & inferior prefrontal cortex/insula (BA 45)	43, 19, 9	237
L dorsolateral prefrontal cortex (BA 46)	−29, 37, 20	10
R putamen/thalamus	3, −13;,−12	45
R superior temporal lobe (BA 21)	58, −37, 20	11
R parietal lobe (BA 40)	32, −51, 37	34
Negative correlations with age		
R posterior cingulate/occipito-temporal cortex (BA 31/23/19/39)	7, −41, −13	524
R orbital frontal cortex (BA 11)	18, 41, −13	10
R cerebellum (lateral hemisphere)	43, −56, −18	79
L cerebellum (vermis)	−4, −82, −29	61
R inferior parietal lobe (BA 40)	50; − 22; 20	18
R premotor cortex (BA 6)	51; 4; 42	33
Switch task		
Positive correlations with age		
R inferior prefrontal cortex/insula/premotor/superior temporal lobe (BA 45/6/4/22)	40, −15, 15	998
R orbitofrontal cortex (BA 11)	29, 44, −13	19
L rostrolateral prefrontal cortex (BA 10)	−20, 48, 9	14
R + L caudate/putamen	14, 11, 4	76
L caudate (tail)/thalamus	−10, −37, 20	40
Negative linear correlations with age		
R dorsolateral prefrontal cortex (BA 46/45)	40, 48, 4	37
L insula	−36, 15, 42	36
Mesial frontal gyrus (BA 8)	0, 19, 48	22
L superior/middle temporal lobe (BA 22/37)	−47, −60, 9	41
R thalamus	3, −25, 3	18
L occipital cortex (BA 19)	−29, −67, 31	14
R hippocampus (BA 36)	29, −22, −24	29
R + L cerebellum	36, −52, −23	8

In order to examine whether the main group difference findings would be related exclusively to behavioral differences in performance, the group comparison between adults and adolescents for the Simon task was reanalyzed in an ANCOVA with errors to incongruent trials as covariates (in addition to IQ) at $P < 0.05$ for voxel and $P < 0.01$ for cluster analysis. All main clusters of between-group differences remained after covarying for errors.

For the Switch task, there was a marginal significant negative correlation between the number of Switch errors and brain activation in anterior cingulate gyrus that was increased in adults (Talairach coordinates: 14, 19, 26; Table III; $r = -0.3$, $P < 0.048$).

A reanalysis of the group comparison in an ANCOVA with Switch errors as covariate (in addition to IQ) at $P < 0.05$ for voxel and $P < 0.01$ for cluster analysis showed that only the cluster in left inferior parietal lobe remained when Switch errors were covaried. The clusters of increased activation in adults in right inferior prefrontal cortex and anterior cingulate gyrus, however, were still observed at a lower $P < 0.025$ for the cluster analysis.

Correlations Between Behavioral Performance and Areas That Correlated with Age in the Whole-Brain Regression Analysis

For the Go/no-go task, no correlations between performance and age-correlated brain activation clusters were observed.

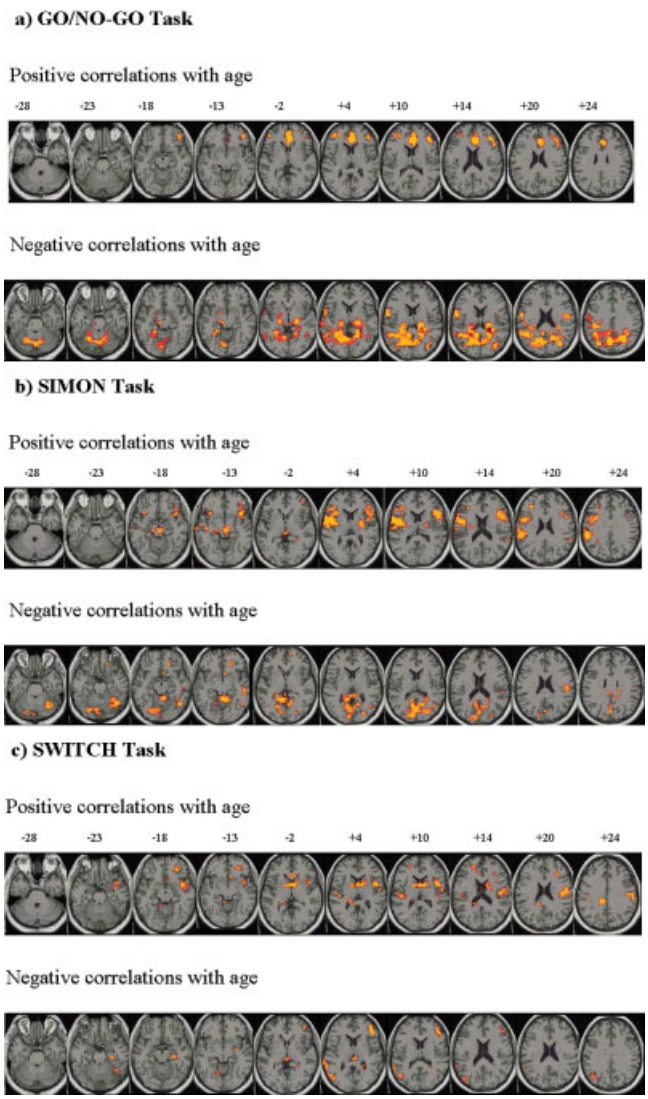

Figure 5.

Linear positive and negative correlations with age are shown on horizontal slices for (**a**) Go/no-go task, (**b**) Simon task, and (**c**) Switch task. The z-coordinate is indicated in mm-distance from the anterior–posterior commissure. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

For the Simon task, there was a significant negative correlation between the number of errors to the incongruent trials and the positive age-correlated cluster in left inferior prefrontal/superior temporal cortex (Talairach coordinates: −43, −26, 25; Table IV; $r = -0.4$, $P < 0.003$) and a significant positive correlation between errors to incongruent trials and the negative age-correlated cluster in right premotor cortex (Talairach coordinates: 51, 4, 42; Table IV; $r = 0.3$, $P < 0.047$).

To explore whether the performance correlated brain activation clusters would remain after covarying for performance, the whole-brain regression analysis was reanalyzed with errors to incongruent trials as covariate. The original findings remained essentially unchanged.

For the Switch task, there was a significant positive correlation between the Switch cost and the positive age-correlated activation cluster in right and left caudate and putamen (Talairach coordinates: 14, 11, 4; Table IV; $r = 0.4$, $P < 0.006$).

A reanalysis of the whole-brain regression analysis with the Switch effect as a covariate, however, resulted in essentially unaltered findings in the positive or negative linear age-correlations.

Group Differences in Heterogeneity of Activation

In order to investigate whether the increased brain activation in adults compared with adolescents in the three tasks was due to a larger spatial/functional heterogeneity in adolescents, for each cluster of between-group differences within each task we tested for group differences in dispersion. For this purpose, the *x, y, z* peak activation coordinates of the standardized BOLD response (SSQ-ratio) of the main clusters of group differences within each task were extracted for each subject. The respective group mean of these *x, y, z* coordinates was then subtracted from each individual's set of *x, y, z* coordinates in order to control for a bias from group membership. A principal component analysis was then performed on the standardized residuals of the coordinates, using an unrotated factor solution based on the correlation matrix. This resulted in one principal component for the *x, y, z* coordinates of all major clusters of brain activation differences, explaining between 50% and 65% of the variances. Levene's test for equality of variances was used to test for group differences in variance of the resulting principal component of each cluster for each task. No group differences were observed for the variances of the principal components of the residuals of the peak *x, y, z* coordinates of the standardized BOLD response in any of the tested group difference activation clusters for the Simon and the Switch tasks. Only for the Go/no-go task was there a significant group difference in the variances of the first principal component of the residuals of the peak coordinates of the main activation difference cluster in mesial frontal cortex ($F = 6.6$, df $= 46$, $P < 0.014$), showing that adolescents have less variance of activation than adults. This finding, however, did not survive Bonferroni correction for multiple testing and was not in the expected direction. The observed increase in activation in adults in the three tasks cannot be attributable, therefore, to greater heterogeneity of activation in adolescents compared with adults.

Group Differences in Extent of Activation

To test for the possibility that the group activation differences were due to a more diffuse or extensive activation pattern in one or the other group, we tested for group differences in extent of activation for the areas of between-group activation in each task. In a first step, we tested for each task for the amount of overlap between the areas of overlap between the two groups from the group activation

maps and the between-group difference maps from the ANOVA analyses, since a lack of overlap between activation of the two groups and the ANOVA difference map would suggest that areas that differed between groups were due to different activation patterns rather than differences in extent of activation in similar brain regions. In the Go/no-go task, there were only two voxels that overlapped between the two groups. The group activation differences were therefore not related to between-group differences in the extent of activation in identical brain regions, but to qualitatively different activation patterns in the two groups (Fig. 1a). In the Simon task, there was an overlap of 175 voxels between the two group maps (15% of areas activated in adults were also activated in adolescents). From these, only a small fraction, 19 voxels, overlapped with the ANOVA group difference map (which is 2% of the total amount of group activation differences). This suggests that 98% of areas that differed between groups were related to areas that showed a different activation pattern between groups, which excludes the possibility that areas of group difference were related to a more diffuse activation pattern in the same brain regions in one of the two groups (Fig. 1b). Only in the Switch task there was considerable overlap between the groups in 264 voxels (30% of areas that were activated in adults were also activated in adolescents). As can be seen from Figure 1c, this is due to the fact that adolescents activated a subgroup of areas that were activated in adults. From these, 53 voxels overlapped with the ANOVA group difference map. We therefore tested in this task for between-group differences in the extent of activation by comparing the amount of voxels activated in adults in areas of between-group differences with the amount of voxels activated in adolescents in areas of between-group differences. A t test showed that although adults showed a more extensive activation than adolescents in areas of between-group differences, the group difference was not significant (mean number of voxels activated in adults [SD], 42 [68]; in adolescents, 20 [27], df = 47, $t = 1.5$, $P < 0.2$).

Within-Subject Analysis

To explore whether a within-subject design would show different results, both the between-group ANOVA and the analysis of a correlation between brain activation and age were repeated, including only those subjects that performed all three tasks, i.e., 20 adults and 17 adolescents. The main findings remained essentially unaltered with the reanalysis.

Furthermore, a conjunction analysis across all three tasks was performed for the 20 adults and 17 adolescents that performed all tasks. Adults showed common brain activation across all tasks in left medial temporal and inferior parietal cortex (Brodmann Area (BA) 21/40; Talairach coordinates: −47, −19, −7; number of voxels: 204), in left occipitotemporal cortex (BA 18; Talairach coordinates: −29, −78, −2; number of voxels: 69), and in right medial temporal gyrus (BA 21; Talairach coordinates: 40, −30, −2; number of voxels: 16). Adolescents showed common brain activation across all three tasks in a small cluster in right inferior parietal lobe (BA 40; Talairach coordinates: 40, −26, 42; number of voxels: 9).

DISCUSSION

Adults and adolescents were compared in their neurocognitive networks during three tasks of motor and cognitive inhibitory control. Adolescents showed poorer performance than adults in all three tasks. During all tasks, adults compared with adolescents showed increased activation in task-relevant frontostriatal brain regions. During the Go/no-go task, adults showed increased brain activation in mesial prefrontal cortex, bordering right orbitofrontal cortex, and caudate. During the Simon task, adults showed increased activation in a left hemispheric network of dorsolateral, inferior prefrontal and parietal cortices, anterior cingulate, and right putamen, while during task switching the activation increase was in right inferior prefrontal and parietal cortices and in anterior cingulate gyrus reaching ventrally into right putamen.

The majority of brain areas of increased activation in adults showed a positive linear correlation with age. The whole-brain regression analysis with age confirmed and extended the region of interest (ROI)-based findings of a linear increase with age in task-relevant brain regions. The whole-brain regression analysis showed a strong linear positive correlation with age in right inferior prefrontal cortex and anterior cingulate gyrus during the Go/no-go task, in left and right inferior prefrontal cortex and putamen in the Simon task, and in a right inferior frontal-parietal network and basal ganglia during the Switch task. The findings suggest a progressive neurofunctional development in these task-specific prefrontal, striatal, and parietal brain regions, responsible for motor and cognitive inhibitory control. Negative linear regressive changes were observed during the three tasks in posterior brain regions such as cerebellum, posterior cingulate gyrus, and occipitotemporal brain regions. In the Simon and Switch tasks, some of the age-correlated brain regions from both the ROI and whole-brain regression analyses also correlated with performance, but remained when performance was covaried out, suggesting that the progressive functional maturation of these brain regions from childhood to adulthood is related to increased capacity of cognitive control functions.

The increase of mesial prefrontal brain activation in the Go/no-go task for adults and the linear correlation with age in this brain region in both the ROI and the whole-brain regression analysis extends the findings of Bunge et al. [2002] of an increase in anterior cingulate in adults compared with children in an event-related Go/no-go task to postadolescent development. Mesial frontal cortex, including anterior cingulate gyrus, has commonly been found to be activated in healthy adults during Go/no-go task performance [Durston et al., 2002b; Garavan et al., 1999; Kiehl et al., 2000; Liddle et al., 2001; Menon et al., 2001; Rubia et al., 2001] and may reflect the role of this brain region in selective attention and selective motor response inhibition [Kawashima et al., 1996; Rubia et al., 2001]. The linear age

correlation based on the whole-brain regression analysis in right and left inferior prefrontal cortex during motor inhibition extends previous developmental imaging studies that have found age-related brain activation in narrower age windows than this study in left [Rubia et al., 2000; Tamm et al., 2002], bilateral [Bunge et al., 2002], or right inferior prefrontal cortices [Durston et al., 2002b; Rubia et al., submitted] during Go/no-go and Stop tasks. A study of Durston et al. [2002b] found that performance-correlated right inferior prefrontal cortex and caudate were increased in adults compared with children in a Go/no-go task. We observed a linear correlation with age in right inferior prefrontal cortex in the same subjects as in this study during a stop task, published elsewhere [Rubia et al., submitted]. Inferior prefrontal cortex is a key area that has been related to motor response inhibition functions in Go/no-go [de Zubicaray et al., 2000; Kawashima et al., 1996; Konishi et al., 1998; Menon et al., 2001] and stop tasks [Rubia et al., 2001, 2003], and the positive age correlation in inferior prefrontal cortex and caudate from childhood to adulthood thus suggests a progressive maturation of the specific frontostriatal neural substrates of inhibitory control.

During performance on the Simon task, the increase of activation in adults and the positive age correlation (based on the whole brain and ROI regression) was in brain regions that have consistently been related to interference inhibition in the Stroop [Banich et al., 2000; Carter et al., 2000; Leung et al., 2000; Liu et al., 2004; Peterson et al., 1999, 2002] and Simon tasks [Bush et al., 2003; Dassonville et al., 2001; Fan et al., 2003; Iacoboni et al., 1998; Liu et al., 2004; Peterson et al., 2002]: namely, in a predominantly left hemispheric network of dorsolateral and inferior prefrontal cortices, basal ganglia, anterior cingulate gyrus, and inferior parietal lobes. These brain regions of progressive changes also correlated with each other, suggesting they form a network for task performance.

The findings of increased activation in adults in left dorsolateral prefrontal cortex and anterior cingulate gyrus during the Simon task are in line with findings of Adleman et al. [2002], who found increased activation in left dorsolateral prefrontal and inferior parietal cortex and anterior cingulate gyrus in adults compared with adolescents during a Color-Word Stroop task performance, which showed a linear age correlation for the age range of 12–22 years. Studying younger children than this study, increased activation in adults compared with children has been observed in left dorsolateral prefrontal cortex in a stimulus-response incompatibility task [Casey et al., 2002b] and during Color-Word Stroop task performance in a study using near infrared spectroscopy [Schroeter et al., 2004]. The age correlation findings between childhood and adulthood in right inferior prefrontal cortex, insula, and right putamen also further extend the findings of Bunge et al. [2002] of increased activation in the same brain regions for the contrast between adults and children during the Eriksen flanker task.

Despite the fact that the analysis used in this study only compared successful performance trials between groups, several of the brain areas that differed between groups and that correlated with age were also related to task performance. The progressive changes in the Simon task in left prefrontal, inferior parietal lobes, and putamen from both the ROI and the whole-brain regression analyses correlated negatively with the number of errors to incongruent trial, while the regressive changes in posterior cingulate (whole-brain regression analysis) and in premotor cortex (ROI analysis) correlated positively with the number of errors. This seems to reflect speed-accuracy-trade-off strategy differences between younger and older subjects, with the more reflective and accurate performance in the older subjects being mediated by increased activation in a task-specific left hemispheric frontostriatoparietal network and the relatively faster (shorter Simon effects) and more inaccurate response style of younger subjects being mediated by increased activation in posterior brain regions. The fact that the group activation differences remained when performance was covaried for implies that these brain activation differences were not exclusively performance related, but interact with brain maturation. Brain regions that develop functionally with age thus appear to improve cognitive efficiency.

During Switch task performance, adults showed increased activation in right inferior prefrontal and left parietal cortices, anterior cingulate, and putamen, areas that also showed a linear correlation with age in the ROI analysis. The whole-brain regression analysis confirmed progressive changes in almost identical brain regions of right inferior frontal cortex, reaching into insular and superior temporal brain regions, anterior cingulate gyrus, and the basal ganglia. Brain areas of progressive changes also correlated with each other, suggesting progressive maturation of right hemispheric inferior frontotemporal and frontostriatal networks for cognitive flexibility. Anterior cingulate, inferior prefrontal cortex, and the basal ganglia have consistently been found to be involved in task switching in the same task [Smith et al., 2004] and other paradigms of cognitive switching [DiGirolamo et al., 2001; Dove et al., 2000; Konishi et al., 1999, 2002; Monchi et al., 2001; Nagahama et al., 1999, 2001]. The findings of progressive postadolescent maturation of frontoparietostriatal activation during cognitive switching extends findings of frontal and parietal activation increases in adults compared with children in the only other published developmental study on switching in a relatively small number of subjects using block design [Casey et al., 2004]. In particular, the parietal lobes and basal ganglia seem to be crucial for maturation of task switching. In the ROI analysis, parietal lobe maturation was the most robust age-related finding after covarying for task performance, in line with evidence from normative adult studies that have suggested a specific role of the inferior parietal lobes for task switching [DiGirolamo et al., 2001; Glover et al., 2005; Smith et al., 2004]. Caudate and putamen correlated with the Switch cost, but remained after covarying for performance, suggesting that maturation of the basal ganglia is essential for improved capacity for cognitive flexibility in the transition from childhood to adulthood.

Interestingly, anterior cingulate gyrus, specifically Brodmann Area 24, was increased in adults during the three different tasks of cognitive control, suggesting that task-unspecific functions of executive attention and performance monitoring that are mediated by this brain region may be key functions underlying cognitive development. Anterior cingulate correlated linearly with age only in the Go/no-go task, in both the ROI and the whole-brain regression analyses. In the Switch task, however, anterior cingulate gyrus correlated negatively with errors and the age-correlated activation was only observable subthreshold when performance was covaried for.

Anterior cingulate gyrus has been suggested to be part of a generic midline attentional network providing "attention to action" [Fernandez-Duque et al., 2000; Luks et al., 2002; Luks and Simpson, 2004; Rubia et al., 1998, 2000], error detection [Ullsperger and van Cramon, 2004a,b; Rubia et al., 2003], and performance monitoring/conflict detection [Botvinick et al., 1999; Carter et al., 1999, 2000; van Veen and Carter, 2002], functions that were demanded by all three tasks. Progressive maturation of anterior cingulate activation with age may reflect the gradual establishment of performance monitoring functions from childhood to adulthood, leading to greater accuracy in performance. Although anterior cingulate correlated with errors in the Switch task, it should be noted that the linear progressive changes and group differences in anterior cingulate gyrus were only related to activation to successful performance trials, as errors were excluded from the analysis. This means that anterior cingulate activation could not have been related to error processing or error detection per se, but is more likely to reflect successful performance monitoring and conflict/interference detection, since greater activation correlated with fewer errors. This is in line with some evidence from normative adult imaging studies suggesting that error-related anterior cingulate activation is related to performance monitoring functions rather than to error detection per se [Botvinick et al., 1999; Carter et al., 1999, 2000; van Veen and Carter, 2002].

The hypothesis of progressive maturation of anterior cingulate gyrus as a reflection of maturation of task-independent conflict monitoring processes would explain why anterior cingulate has been shown in previous studies to be increased in adults compared with children or adolescents during a wide range of cognitive control functions such as motor inhibition in Go/no-go tasks [Bunge et al., 2002], interference inhibition in Color-Word Stroop tasks [Adleman et al., 2002], motor timing [Rubia et al., 2000], and Stop failures in the same subject group than the one tested in this study [Rubia et al., submitted].

One of the most interesting findings of this study is that of a progressive maturation from childhood to adulthood in the basal ganglia, concomitant with frontal maturation. During all three tasks, progressive changes in basal ganglia activation were observed, both when the data were clustered into two groups of adolescents and adults, as well as when whole-brain linear regression analyses were applied. Progressive changes were observed in the caudate during the motor inhibition task and in predominantly putamen during the two cognitive inhibition tasks, with additional caudate activation during task switching. These findings of maturation of frontostriatal activation networks for cognitive control functions parallel structural studies that have observed developmental changes in caudate and putamen concomitant with frontal lobe maturation [Castellanos et al., 2002; Giedd et al., 1996; Reiss et al., 1996; Sowell et al., 1999b; Thompson et al., 2000]. Although frontostriatal maturation for cognitive control functions have been hypothesized based on structural maturation findings and based on the fact that frontostriatal networks have been implicated in cognitive control [Durston and Casey, 2005; Casey et al., 2000], previous findings on functional basal ganglia maturation have not always been in line with this hypothesis. Increased putamen activation, in line with the findings of this study and the frontostriatal maturation hypothesis, has been observed in adults compared with children during tasks of stimulus-response incompatibility [Bunge et al., 2002; Casey et al., 2002] and in adults compared with adolescents during motor timing [Rubia et al., 2000]. Caudate activation, however, has been shown to be increased in adults compared with children in one study using motor inhibition in a Go/no-go task [Durston et al., 2002b], but to be decreased in adults compared to adolescents during two other studies of motor inhibition in a Go/no-go [Booth et al., 2003] and Stop task [Rubia et al., 2000] or not to differ between children and adults during a Go/no-go [Bunge et al., 2002] and Switch tasks [Casey et al., 2002a]. The relatively inconsistent findings of caudate maturation in previous developmental imaging studies of inhibitory control functions may be due to the use of small subject numbers; progressive changes in a relatively small brain region may only be observable with larger detective power in fMRI studies.

The progressive changes in temporal and parietal brain activation, which was particularly evident for the whole-brain age regression analysis during the Simon and Switch tasks, extends frontostriatal maturational models of cognitive control and are in line with recent anatomical studies showing late maturation of posterior parietal and temporal brain regions well into mid-adulthood [Gogtay et al., 2004]. Although some previous evidence exists for maturation of parietal brain regions during motor response inhibition [Rubia et al., 2000; Bunge et al., 2002], interference inhibition in stimulus-response incompatibility tasks [Adleman et al., 2002], and task switching [Casey et al., 2004], to our knowledge, temporal lobe maturation has not previously been related to age-related changes during inhibitory or cognitive control functions. The relatively large subject number of this study may have accounted for the rather robust findings in extrafrontal brain regions such as striatal, parietal, and temporal cortices.

Overall, the findings of linear progressive changes with age in task-relevant brain regions extend previous imaging studies on cognitive control that observed linear age-corre-

lations in narrower age windows than this study [Adleman et al., 2002; Rubia et al., 2000; Tamm et al., 2002] and are parallel to other developmental studies that found progressive linear changes in the context of other cognitive tasks such as working memory [Klingberg et al., 2002; Kwon et al., 1999], finger tapping, word-picture mapping, and verbal processing [Schapiro et al., 2004].

Linear regressive changes have also been shown in the whole-brain regression analysis with age in predominantly posterior brain regions including posterior cingulate gyrus and occipitotemporal brain regions, cerebellum, and premotor cortex. When subjects were grouped into adults and adolescents, however, only in the Simon task did adolescents show increased activation compared with adults in these posterior brain regions.

Areas that correlated negatively with age may reflect more immature networks for task performance. Posterior and anterior cingulate form part of the midline attentional system whereby posterior cingulate is particularly relevant for the dynamic reallocation of visual-spatial attention [Mesulam et al., 2001; Small et al., 2003]. The increased activation in posterior cingulate in adolescents during all three tasks might thus reflect a compensatory mechanism for the reduced activation in the anterior part of the cingulate gyrus, which is particularly plausible in the Simon task, where posterior cingulate activation correlated negatively with errors. The cerebellar hemispheres have been shown to be closely connected to the lateral prefrontal cortex [Kelly and Strick, 2003] and been implicated in cognitive functions, in particular, attention functions such as dual task interference [Marcantoni et al., 2003] and divided attention [Barrett et al., 2003]. Occipitotemporal brain regions seem to play role in visual-spatial attention [Iidaka et al., 2004; Vandenberghe et al., 1996]. The increased activation in younger subjects in posterior cingulate, cerebellum, and occipitotemporal brain regions may therefore reflect a more immature activation pattern, possibly compensating for the decreased activation in the prefrontal parts of anterior–posterior cingulate, frontocerebellar, or frontoparietotemporal networks for cognitive control functions. These findings of postadolescent regressive changes in posterior brain regions during three tasks of cognitive control extend previous imaging studies that have found increased activation in posterior brain regions in young children in temporal lobes and cerebellum during a Stroop [Booth et al., 2003; Bunge et al., 2002; Casey et al., 2002b] and in posterior cingulate gyrus during a Go/no-go task [Booth et al., 2003].

Minor regressive changes were observed in dorsolateral and mesial prefrontal cortices during the Switch task that may have been recruited by adolescents to compensate for the reduction in the rather large cluster in performance-correlated right inferior prefrontal cortex. The increased activation in dorsolateral prefrontal cortex in adolescents is parallel to findings of increased activation in this brain region in younger children compared with adults in the context of motor inhibition [Casey et al., 1997; Durston et al., 2002b].

Several mechanisms could have accounted for the observed age-related progressive and regressive changes in frontal, parietal, and cingulate brain regions. Functional maturation of frontostriatal and frontotemporoparietal brain regions may reflect relatively late linear and nonlinear progressive anatomical changes of myelination and GM loss, respectively, in these brain regions during the transition from childhood to adulthood [Gogtay et al., 2004; Sowell et al., 1999b]. Studies combining diffusion tensor imaging (to study WM maturation) and fMRI have shown evidence for parallel age-related maturational processes of progressive myelination of frontal and parietal association areas and functional development in the same brain areas in the context of working memory [Olesen et al., 2003]. The progressive changes observed in this study in the frontal lobes and their striatal and parietotemporal connections concomitant to regressive changes in posterior brain regions may thus parallel anatomical caudal to rostral maturational changes [Casey et al., 2000; Gogtay et al., 2004; Sowell et al., 2001, 2004]. Adolescents may rely more than adults on earlier maturing posterior brain regions to compensate for reduced activation in prefrontal brain regions that are still undergoing maturational changes in the transition from childhood to adulthood [Brown et al., 2005; Casey et al., 2000].

While it is commonly assumed that structural myelination processes underlie progressive functional specialization, a bidirectional causality between structural brain development and functional specialization is plausible, considering recent evidence of highly plastic bidirectional function–structure interrelations [Dettmers et al., 1999; Pantev et al., 2003, 2004], especially during development [Als et al., 2004; Draganski et al., 2004].

It has been argued that reduced activation in younger compared with older age groups may be a reflection of increased heterogeneity in activation patterns, possibly related to known individual differences in the developmental processes of GM and WM changes [Gaillard et al., 2001; Wilke and Holland, 2003]. This was, however, not the case in this study, since in none of the tasks did adolescents show a greater heterogeneity of brain activation than adults.

The conjunction analysis across tasks for those adults and adolescents that performed all three tasks showed an interesting laterality effect between age groups. Adults showed relatively strong conjunctive brain activation in a predominantly left hemispheric network of middle temporal, parietal, and occipital brain regions, presumably related to functions of visual-spatial attention common to all three tasks, while adolescents showed only small conjunctive activation in right inferior parietal lobe. Adults, more than adolescents, may have learned to use common attentional strategies for performance on different tasks of cognitive control. Differences between younger and older subjects in hemispheric laterality have been observed previously in the context of motor [Rubia et al., 2000] and interference inhibition [Bunge et al., 2002] and may imply maturational shifts in laterality.

A limitation of this study is the cross-sectional approach. Cross-sectional designs are confounded by interindividual

variance and cohort effects, which can weaken true developmental effects [Gogtay et al., 2004]. Future studies using repeated within-subject measurements across different ages in development would be more powerful to assess developmental trajectories of executive neurofunction.

CONCLUSIONS

To summarize, this study shows that during a range of inhibitory control functions including motor inhibitory control, interference inhibition, and cognitive set shifting, categorical and progressive linear developmental changes are observed between childhood and adulthood in task-specific functional neural networks of frontostriatal, frontoparietal, and frontotemporal brain regions with regressive changes in predominantly posterior brain regions. Despite the fact that only correct trials were compared between groups, a relationship with performance was observed in two of the tasks (the Simon and Switch tasks), where specific progressive and regressive activation changes correlated with both age and performance measures, and remained when performance was covaried for, suggesting that at least some of these neurofunctional maturational changes reflect improvement of cognitive capacity from childhood to adulthood.

The study thus demonstrates progressive age-related neurocognitive specialization of cognitive control that is not limited to the frontal lobes but extends to its connections to the basal ganglia and to parietal and temporal association areas.

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