Maturation of Brain Function Associated With Response Inhibition

LEANNE TAMM, PH.D., VINOD MENON, PH.D, AND ALLAN L. REISS, M.D.

ABSTRACT

Objective: To investigate the developmental trajectory of response inhibition and, more specifically, whether there is a dissociation of function in the prefrontal cortex over the course of development of executive function and associated response inhibition abilities. **Method:** Nineteen typically developing subjects, ranging in age from 8 to 20, performed a Go/NoGo task while behavioral and functional magnetic resonance imaging (fMRI) data were collected. **Results:** All subjects performed the task with few errors of omission and commission. No relationship between accuracy and age emerged, but the ability to inhibit responses *more quickly* significantly improved with age. Analyses of fMRI data revealed a positive correlation between activation and age in the left inferior frontal gyrus/insula/orbitofrontal gyrus, and a negative correlation between activation and age in the left middle/superior frontal gyri. **Conclusion:** These data provide the first evidence of dissociable processes occurring in the prefrontal cortex during development of executive functions associated with response inhibition: (1) Younger subjects activate more extensively than older subjects in discrete regions of the prefrontal cortex, presumably due to increased demands and inefficient recruitment of brain regions subserving executive functions including working memory. (2) Older subjects show increasingly focal activation in specific regions thought to play a more critical role in response inhibition. *J. Am. Acad. Child Adolesc. Psychiatry*, 2002, 41(10):1231–1238. **Key Words:** development, fMRI, inhibition, Go/NoGo, executive function.

Inhibitory control, the ability to withhold a preplanned response, interrupt a process that has already started, avoid interference, and delay a response (Harnishfeger and Bjorklund, 1993; Rubia et al., 1998), is fundamental to successful executive function, behavior, and social adaptation. Failure to inhibit responses may result in impaired ability to sustain attention, marked distractibility, or behavioral dyscontrol. Furthermore, significant deficits in response inhibition are prominent in a variety of psychiatric disorders, including attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, and Tourette's disorder (Garavan et al., 1999). As such, the development of intact and proficient inhibitory function is critical to adaptive function. Knowledge of the typical developmental trajectory of this function will inform our understanding of atypical response inhibition in psychiatric and behavioral disorders.

Developmental studies suggest that by the age of 7, typically developing children have the conceptual understanding of when to inhibit responses, but that this may not always translate into successful/efficient procedural behavioral performance (Dowsett and Livesey, 2000). Specifically, children younger than 6 years old appear to be able to verbalize when a response should be inhibited but not necessarily make the related motor response (Bell and Livesey, 1985; Livesey and Morgan, 1991). There are, however, marked developmental gains in the ability to inhibit prepotent responses throughout childhood that continue into early adulthood (Band et al., 2000; Harnishfeger and Bjorklund, 1993; Schachar and Logan, 1990; Williams et al., 1999). In particular, reaction time improvements for both response execution and response inhibition (the latter being a mathematically derived estimate) are observed between the ages of 6 and 20 (Band

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From the Department of Psychiatry and Behavioral Sciences, Stanford School of Medicine, Stanford, CA. Drs. Menon and Reiss are with the Program in Neuroscience and Stanford Brain Research Center.

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Correspondence to Dr. Tamm, Department of Psychiatry and Behavioral Sciences, 401 Quarry Road, Stanford University School of Medicine, Stanford, CA 94305-5717; e-mail: leannet@stanford.edu.

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et al., 2000; Williams et al., 1999). Researchers have speculated that improvements in inhibitory control correspond with increasing metacognitive abilities (Zelazo et al., 1996), as well as with maturation of brain regions thought to underlie working memory and inhibitory control, and, in particular, the prefrontal cortex (Carver et al., 2001; Harnishfeger and Bjorklund, 1993; Passler et al., 1985). However, until recently, it has been difficult to investigate the neural bases of these hypotheses because of the invasive nature of imaging methodologies.

The advent of functional magnetic resonance imaging (fMRI) has substantially increased our ability to examine the neural mechanisms underlying age-related improvements in inhibitory control. To date, however, only two fMRI studies have investigated developmental changes associated with different types of response inhibition (Casey et al., 1997; Rubia et al., 2000). These studies have reported dissimilar and potentially inconsistent findings, leaving unclear the precise developmental trajectory of response inhibition.

Casey et al. (1997) compared the extent of activation in the prefrontal cortex of children (n = 9, ages 7–12) and adults (n = 9, ages 21–24) during a Go/NoGo response inhibition task. Their investigation of brain activation was limited *a priori* to five broad regions of the prefrontal cortex (i.e., inferior frontal, middle frontal, orbital frontal, superior frontal, and anterior cingulate cortices). Significantly larger mean volumes of activation were observed in children than adults within the dorsal and lateral prefrontal cortices (Casey et al., 1997).

In contrast, Rubia et al. (2000) investigated differences in functional brain activation between adolescents (n = 9, ages 12–19) and adults (n = 8, ages 22–40) on a stop-signal inhibition task, and conducted both group comparisons and regression analyses. Rubia et al. reported that adults showed greater activation than adolescents in the left middle and inferior frontal gyri, and regression analyses showed increasing activation with age in the left inferior frontal gyrus. Adolescents also showed greater activation in the right caudate nucleus and right inferior frontal gyrus relative to adults, but no negative age-related changes via regression analyses emerged for these regions.

These somewhat divergent results may have arisen from methodological differences between the studies. One obvious difference is that the two studies examined participants from different age groups, with Casey et al. excluding adolescents and Rubia et al. excluding children. Furthermore, the types of tasks used in the two studies assessed different forms of response inhibition. Specifically, the Go/NoGo task used by Casey et al. requires inhibition of a prepotent response prior to its initiation, whereas the stop-signal task involves inhibition of a response that has already begun (Rubia et al., 2001). Thus, the specific type of inhibition measured in each study may be quite different. Comparison between the two studies also is complicated because Casey et al. utilized broad regions of interest in the prefrontal cortex encompassing entire gyri (making it difficult to discern the precise regions involved in response inhibition). Casey et al. examined the extent of activation in the prefrontal cortex, whereas Rubia et al. examined the whole brain and the fundamental power quotient of each voxel. Although the Rubia et al. study conducted regression analyses over a wide range of ages (i.e., 12–40), children, who arguably might show the largest developmental changes and variation in behavioral performance (Band et al., 2000), were excluded. In addition, the inclusion of older adults may have obscured potential positive age-related findings because of decreases in gray matter with age (Pfefferbaum et al., 1994; Sowell et al., 1999).

Thus, our knowledge regarding the development of response inhibition remains incomplete, and the following questions remain to be addressed. First, what is the developmental trajectory of response inhibition, as assessed via voxel by voxel regression analyses of the whole brain, in a group of subjects spanning from childhood to young adulthood? Second, do linear changes in task performance correspond with linear changes in brain activation? The primary objective of this study was to address these issues by examining the performance and brain activation of children, adolescents, and young adults on the Go/NoGo task. It has been argued that this task most directly assesses the construct of inhibitory control because it requires an all-or-none decision about action or nonaction (compared with cognitive forms of inhibitory control, such as interference control) (Rubia et al., 2001). Based on the findings of the two previous developmental neuroimaging studies of response inhibition, we had three questions related to activation in the prefrontal cortex: (1) Are there specific areas in the prefrontal cortex that show decreasing activation with age, such as reported by Casey et al. (1997)? (2) Are there discrete brain regions that show increasing activation with age, as reported by Rubia et al. (2000)? (3) Is there a dissociation of function in the prefrontal cortex, such that distinct regions might show age-related decreases, whereas other regions might show age-related increases,

over the course of development of executive function and associated response inhibition abilities?

METHOD

Subjects

Nineteen subjects, ranging in age from 8 to 20 (mean age 14.41, SD = 3.08; 8 male), participated in the study after giving written informed consent. These subjects were recruited as typically developing controls for neurodevelopmental studies. Of the 19 subjects, 13 identified themselves as Caucasian, 3 as Asian, 1 as Latino, and 2 did not report their ethnicity. They were all right-handed and were screened for neurological, developmental, and psychiatric disorders via telephone interview with the primary caregiver. All participants were rated in the "normal" range on the Child Behavior Checklist (Achenbach, 1991). Cognitive functioning was assessed utilizing the Wechsler Intelligence Scale for Children, Third Edition (WISC-III; ages 7–16) and the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III, ages 16 and up). The mean full-scale IQ score for the sample was 112.00 (SD = 12.74).

Experimental Task

The Go/NoGo experiment consisted of a 30-second rest epoch, 12 alternating 26-second epochs of Go and Go/NoGo conditions, followed by a 30-second rest epoch. A standard blocked design (Casey et al., 1997) was used in this study as a way to provide and maintain a high level of prepotent response since randomly presenting an equal number of Go and NoGo stimuli might have eliminated build-up of such a response. During the rest condition, subjects passively viewed a blank screen. During the experimental condition, subjects viewed a series of letters once every 2 seconds and responded with a key press to every letter except the letter X to which they were instructed to withhold response. In the Go (control) condition, subjects were presented a random sequence of letters other than the letter X. In the Go/NoGo (experimental) condition, subjects were presented with the letter X 50% of the time, thus requiring response to half the trials (Go trials) and response inhibition to the other half (NoGo trials). At the beginning of each epoch, a 2-second instruction warned the subject about the new task condition. All subjects responded using the forefinger of the right hand. Errors of omission (misses), errors of commission (false alarms), and reaction time to correct trials during the experimental condition were recorded.

fMRI Acquisition

Images were acquired on a 1.5T GE Signa scanner with Echospeed gradients, using a custom-built whole head coil that provides a 50% advantage in signal-to-noise ratio over that of the standard GE coil (Hayes and Mathias, 1996). A custom-built head holder was used to prevent head movement. Eighteen axial slices (6 mm thick, 1 mm skip) parallel to the anterior and posterior commissure covering the whole brain were imaged with a temporal resolution of 2 seconds by using a T2* weighted gradient echo spiral pulse sequence (TR = 2000 ms, TE = 40 ms, flip angle = 89° and 1 interleave) (Glover and Lai, 1998). The field of view was 240 mm and the effective in-plane spatial resolution was 4.35 mm. To aid in localization of functional data, high-resolution T1-weighted spoiled grass gradient recalled (SPGR) 3D MRI sequence with the following parameters was used: TR = 24 ms; TE = 5 ms; flip angle = 40°; 124 slices in sagittal plane; 256 × 192 matrix; acquired resolution = 1.5 × 0.9 × 1.2 mm. The images were reconstructed as a 124 × 256 × 256 matrix with a 1.5 × 0.9 × 0.9 mm spatial resolution.

The task was programmed using Psyscope (*http://poppy.psy.cmu.edu/psyscope*). Initiation of scan and task was synchronized using a TTL pulse delivered to the scanner timing microprocessor board from a "CMU Button Box" microprocessor (*http://psyscope.psy.cmu.edu*) connected to the computer. Letters were presented visually at the center of a screen using a custom-built magnet compatible projection system (Resonance Technology, Northridge, CA).

Image Preprocessing

Images were reconstructed, by inverse Fourier transform, for each of the 120 time points into 64 × 64 × 18 image matrices (voxel size: 3.75 × 3.75 × 7mm). fMRI data were preprocessed using SPM99 (*http://www.fil.ion.bpmf.ac.uk/spm*). Images were corrected for movement by using least square minimization without higher-order corrections for spin history, and normalized to Montreal Neurological Institute template provided with SPM. Images were then resampled every 2 mm using sinc interpolation.

Statistical Analysis

Statistical analysis was performed on group data by using a random effects model (Holmes and Friston, 1998) along with the theory of Gaussian random fields as implemented in SPM99. This method takes advantage of multivariate regression analysis and corrects for temporal and spatial autocorrelations in the fMRI data (Friston et al., 1995).

Confounding effects of fluctuations in global mean were removed by proportional scaling where, for each time point, each voxel was scaled by the global mean at that time point. Low-frequency noise was removed with a high-pass filter (0.5 cycles/minute) applied to the fMRI time series at each voxel. A temporal smoothing function (4-mm Gaussian kernel corresponding to dispersion of 8 seconds) was applied to the fMRI time series to enhance the temporal signal-to-noise ratio. Voxel-wise t statistics were computed using the random effects model and normalized to Z scores to provide a statistical measure of activation independent of sample size. Finally, to determine the presence of significant clusters of activation, the joint expected probability distribution of height ($Z > 1.67$; $p < .05$) and extent ($p < .05$) threshold (Poline et al., 1997) was used to correct for spatial correlations in the data.

For group analysis, a random effects model was used to determine voxel-wise t statistics contrasting specific conditions of interest. This model estimates the error variance for each condition of interest across subjects, rather than across scans (Holmes and Friston, 1998). The random effects model provides better generalization to the subject population, albeit with some loss in power due to averaging in the time domain. This analysis proceeded in two steps. In the first step, adjusted images corresponding to the conditions/events of interest were determined. For each condition, a weighted average of the images was computed taking into account the hemodynamic response. In the second step, these condition-specific images were contrasted in a general linear model to determine appropriate t statistics. The t statistics were normalized to Z scores to determine significant clusters of activation. The following contrasts were examined: NoGo minus Go (experimental minus control conditions) and Go minus NoGo (control minus experimental conditions).

Linear regression was used to determine the voxels showing positive or negative age-related changes during the Go/NoGo task. Subject age was used as a covariate of interest. Voxel-wise t statistics were computed using regression analysis, which were then normalized to Z scores. Significant clusters of activation were determined using the joint expected probability distribution of height and extent of Z scores, with height ($Z > 2.33$, $p < .01$) and extent threshold ($p < .01$). After the identification of clusters in which age-related correlations with

brain activation were found, an analysis of whether activation in these clusters was correlated with reaction time was conducted. Specifically, the two voxel clusters (left inferior frontal gyrus and left superior frontal gyrus) showing significant age-related changes in activation were identified as functional regions of interest (fROIs). Pearson correlations between percentage of voxels activated (height threshold $Z > 2.33$) within the fROIs and reaction time were then computed.

Neuroanatomical locations of activation were first determined using the standard Talairach atlas (Talairach and Tournoux, 1988) and then refined using the more detailed and thorough Duvernoy atlas (Duvernoy et al., 1999).

RESULTS

BEHAVIORAL

The primary aim of the behavioral analyses was to examine the relationship, if any, between performance and age. Linear regression analyses were conducted regressing age on performance (accuracy and reaction time). The results of these analyses, as well as means and standard deviations, are reported in Table 1.

Accuracy

Errors of Omission (Misses). A log transformation was applied to the errors of omission dependent variable due to the presence of two outliers. The regression analysis did not indicate a significant relationship between errors of omission and age.

Errors of Commission (False Alarms). As with the errors of omission variable, there was no significant relationship between errors of commission and age.

Reaction Time

Reaction Time to Correct Trials in the Experimental Condition. Regression analysis of reaction time for correct trials during the experimental condition revealed a significant correlation between age and reaction time ($R^2 = 0.30$, $p = .02$). Specifically, reaction times decreased with age.

BRAIN ACTIVATION

Regression analyses examining which brain areas showed age-related changes were conducted after an initial comparison of brain activation during the experimental condition versus brain activation during the control condition for all subjects (pooled). Finally, a follow-up investigation correlating percent voxels activated and reaction time in two age-related fROIs (for positive and negative activation) was conducted.

TABLE 1
Regression Analyses for Dependent Variables of Interest

Variable	Mean (SD)	Model	*df*	β	R^2
Errors of omission	1.32 (2.00)	Age	1,17	–.23	.05
Errors of commission	4.11 (2.49)	Age	1,17	–.28	.08
Reaction time to correct trials in experimental (inhibition) condition	556.86 (129.53)	Age	1,17	–.55	.30*

* $p < .05$.

TABLE 2
Brain Areas Showing Significant Activation ($p < .05$) for the Experimental Minus Control Condition

Activated Region	No. of Voxels	Z_{max}	Peak Location
Experimental minus control (NoGo – Go)			
Right frontal operculum/inferior frontal gyrus	772	4.83	48, 12, 2
Left middle frontal gyrus (BA 8/9)	524	4.44	–32, 40, 34
Right superior frontal gyrus (BA 6)	2534	4.30	16, –2, 66
Right posterior middle temporal gyrus bordering occipital gyrus (BA 21/22)	634	3.71	48, –42, –2

Note: BA = Brodmann area; no. of voxels = number of voxels activated; Z_{max} = maximum Z score; peak location is listed by Talairach coordinates.

Experimental Minus Control (Go/NoGo Minus Go). Group activation associated with the experimental condition was found bilaterally in the middle frontal gyrus and inferior frontal gyrus (pars triangularis). In the right hemisphere, the superior frontal gyrus, orbitofrontal gyrus, insula, middle temporal gyrus bordering on the occipital gyrus, and cingulate showed significant activation in the experimental condition (Table 2, Fig. 1).

Age-Related Increases in Activation. The regions in which there was a positive correlation between activation and age in the Go/NoGo condition were the left inferior frontal gyrus/insula, extending to the orbitofrontal gyrus (Table 3, Fig. 1).

Age-Related Decreases in Activation. The regions in which there was a negative correlation between activation and age in the Go/NoGo condition were predominantly in the left superior frontal gyrus and middle frontal gyrus, extending into the cingulate (Table 3, Fig. 1).

Functional Regions of Interest. Correlation analyses between the percentage of voxels activated and reaction time to correct trials in the experimental condition for the two fROIs (i.e., left inferior frontal gyrus and left superior frontal gyrus) were conducted. The correlation between the left inferior frontal gyrus fROI and reaction time was $r_{19} = 0.38$, not significant. The correlation between the left superior frontal gyrus fROI and reaction time was $r_{19} = –0.28$, not significant.

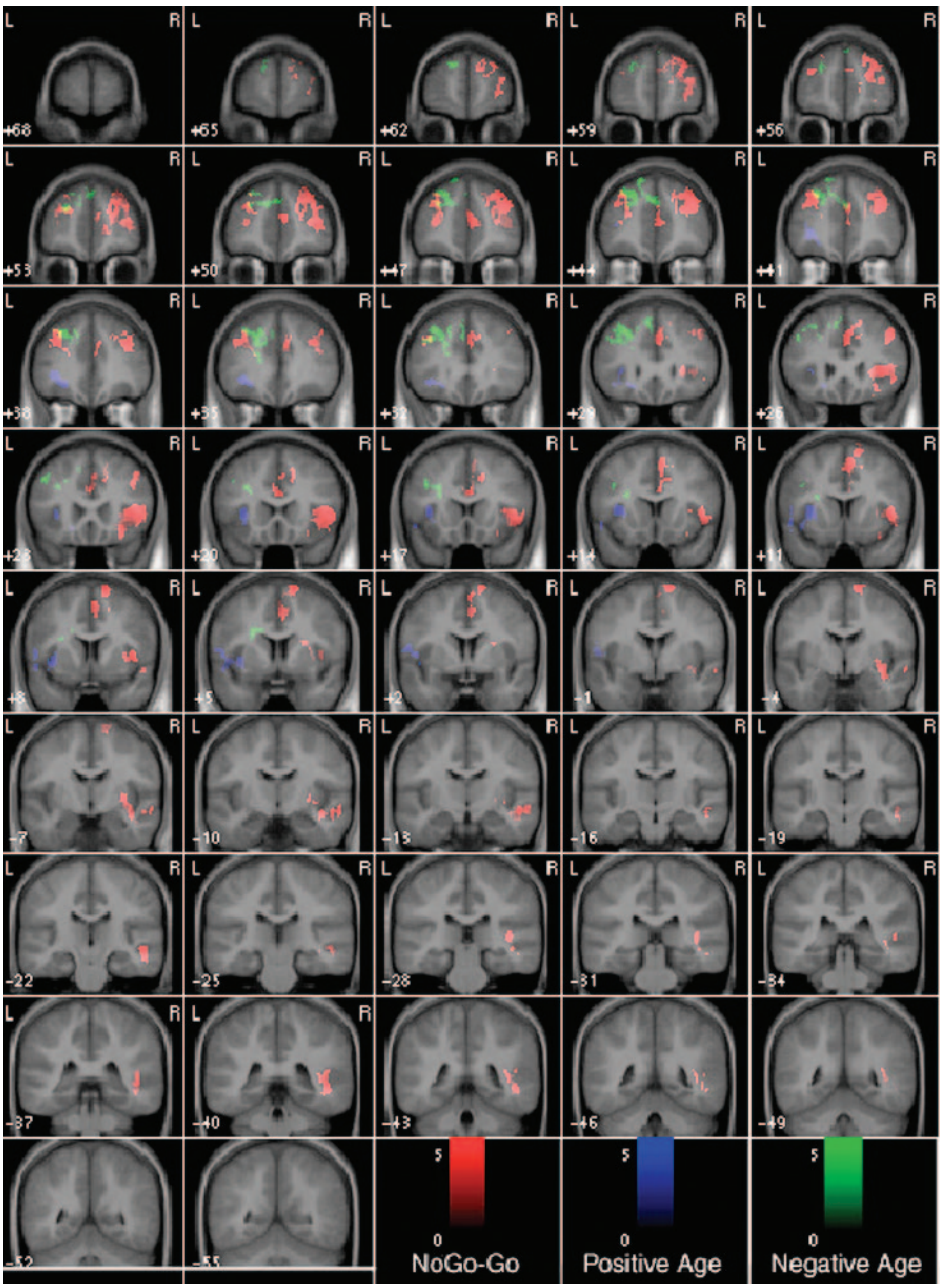

Fig. 1 Activation associated with the experimental minus control contrast (NoGo – Go) for all 19 subjects is depicted in red. Areas showing increasing activation with age via regression analyses are depicted in blue (positive age), and areas showing decreasing activation with age via regression analyses are depicted in green (negative age). Activations are depicted on an averaged group image in the coronal plane from front to back.

DISCUSSION

Our results indicate that there are significant developmental changes associated with the process of response inhibition, as conceptualized by the Go/NoGo task used in this study. Specifically, analyses of behavioral variables obtained during the experimental condition of the task (NoGo – Go) revealed that reaction times significantly decreased with age, indicating more rapid response execution (and therefore more efficient response inhibition) during correct NoGo trials for older subjects. Errors of omission and errors of commission, however, did not show

TABLE 3
Brain Areas Where (1) Participants Show Increasing Activation with Age and (2) Participants Show Decreasing Activation With Age

Activated Region	No. of Voxels	Z_{max}	Peak Location
Positive correlation between activation and age			
Left inferior frontal gyrus/insula extending to orbitofrontal gyrus	515	3.48	–34, 12, 6
Negative correlation between activation and age			
Left superior frontal gyrus (BA 8) extending to middle frontal gyrus and cingulate	1040	3.42	–14, 46, 46

Note: BA = Brodmann area; no. of voxels = number of voxels activated; Z_{max} = maximum Z score; peak location is listed by Talairach coordinates.

significant age-related changes, indicating that subjects of all ages were able to perform the task adequately at the presented level of difficulty. The neuroimaging results demonstrate that there are both positive and negative age-related changes in specific brain regions associated with response inhibition. Specifically, younger subjects recruited the left superior and middle frontal gyri more than older subjects to perform the task adequately. In contrast, older subjects showed increased focal activation in the left inferior frontal gyrus, a region thought to be critically involved in inhibitory control (Konishi et al., 1999; Liddle et al., 2001; Menon et al., 2001; Rubia et al., 2001). Thus, our study provides evidence for dissociation between the prefrontal cortex regions involved in the development of inhibitory control.

The results from the present study provide clarification regarding the somewhat inconsistent results reported by the two previous developmental neuroimaging studies of response inhibition (Casey et al., 1997; Rubia et al., 2000). Consistent with the findings of Casey et al. (1997), we also observed a negative correlation between activation in the left prefrontal cortex (i.e., superior/middle frontal gyri and cingulate) and age. Furthermore, congruent with the findings of Rubia et al. (Rubia et al., 2000), who observed positive age-related changes in the left middle-inferior and left infero-opercular frontal gyri, we found a positive correlation between age and activation in the left inferior frontal gyrus/insula/orbitofrontal cortex. We suggest methodological differences accounted for the disparate findings reported by Casey et al. and Rubia et al. Specifically, the fact that Casey et al. utilized broad regions of interest and did not use regression analyses likely obscured the finding of positive age-related changes in the left inferior frontal gyrus. The fact that Rubia et al. did not observe negative age-related changes (in their regression analyses) may have arisen from sample characteristics, specifically, the failure to include children younger than twelve years old.

Together these studies suggest that age-related changes in the prefrontal cortex may be regional in nature and that there are at least two distinct processes related to response inhibition occurring with development. (1) During tasks requiring response inhibition, younger subjects activate more extensively than older subjects in discrete regions of the prefrontal cortex (i.e., middle and superior frontal gyri); and (2) older subjects have more focal activation in specific regions of the prefrontal cortex (i.e., inferior frontal gyrus).

More diffuse prefrontal activation in younger subjects may arise because children lack the cognitive resources to efficiently organize, monitor, and strategize behavioral actions to maximize response inhibition (Luciana and Nelson, 1998). Thus, although all subjects performed the task adequately, it is likely that younger subjects used less efficient strategies that required recruitment of more widespread regions of the prefrontal cortex. The Go/NoGo task requires multiple executive functions including working memory (i.e., "remember not to press for X"), avoiding interference, and withholding responses that have been established as prepotent responses. Studies suggest that the left middle frontal gyrus is involved in nonspatial working memory tasks (Belger et al., 1998; Collette et al., 1999; D'Esposito et al., 1998) and that the superior frontal gyrus (BA8) subserves working memory maintenance functions (Rowe and Passingham, 2001; Rowe et al., 2000). Furthermore, the left middle frontal gyrus may play a role in attentional set-shifting during tasks of motor selection (Omori et al., 1999). The cingulate, particularly the anterior region, has been implicated in conflict monitoring and response competition (Braver et al., 2001; Lee et al., 2001); i.e., perhaps playing a role in processing the conflict between executing or inhibiting a high frequency response in the Go/NoGo task). Neuropsychological evidence suggests that when the prefrontal cortex is called upon to perform multiple executive functions, performance deteriorates (Luciana and Nelson, 1998). We suggest that children are less efficient at integrating executive functions partly served by these prefrontal regions, resulting in poorer performance, which in this case is evidenced by slower reaction times during task performance and greater activation in these brain regions likely reflecting greater reliance on executive functions served by these regions (i.e., compensatory strategies).

Our findings suggest that the left inferior frontal gyrus, orbitofrontal gyrus, and the adjoining insula become increasingly specialized for response inhibition with development. To examine whether the increasing activation with age observed in this cluster was related to improvements in behavioral performance, a correlation between reaction time and percent voxels activated in this functional region of interest was conducted. The results of this analysis did not, however, suggest a specific role for these regions in decreased reaction time with age.

Although age-related increases in activation in the left inferior frontal gyrus/orbitofrontal gyrus/insula did not appear to be directly related to decreases in reaction time, it is possible that these regions play a role in the use of strategies or perhaps in a more extensive network involved in inhibitory control, thereby yielding or contributing to improvements in reaction time and the refinement of executive function. Alternatively, there may be nonlinear changes that have not been explored in the current study. Studies have suggested that the orbitofrontal cortex plays a specific role in controlling voluntary goal-directed behavior (Schoenbaum et al., 1998; Tremblay and Schultz, 2000), an essential skill for response inhibition. Furthermore, the left orbitofrontal cortex is thought to play a role in strategic memory and supporting the mobilization of behavioral strategies for cognitive tasks (Savage et al., 2001). The left insula has also been shown to play a role in learning and acquisition of inhibitory avoidance behavior (Bermudez-Rattoni and McGaugh, 1991), self-monitoring (Blakemore et al., 1998), and the formation of an articulatory plan (Wise et al., 1999). It is possible that older subjects may have adopted a more verbal strategy for task completion (i.e., mentally articulating "don't press for X") corresponding with increased activation in the left inferior frontal gyrus/insula. In sum, the ability to reflect on one's performance and use that information to enhance strategy and task performance appears to improve with age, and this may coincide with increasingly focal activation of specific prefrontal regions (i.e., the left inferior frontal gyrus, insula, and orbitofrontal cortex).

Taken together, the behavioral and neuroimaging findings suggest that the ability to inhibit responses is available early in development and that broad regions of the dorsolateral prefrontal cortex (middle and superior frontal gyri) are recruited to facilitate response inhibition, possibly via reliance on such processes as working memory and selective attention. However, with maturation, there is increasing specialization, focalization, and integration of a few left hemisphere ventral prefrontal cortex brain regions (inferior frontal gyrus, insula, orbitofrontal gyrus) playing a more specialized role in response inhibition, giving rise to rapid response execution and improved task performance. These findings provide insight into the functional organization of the prefrontal cortex during development and suggest a dissociation of specific regions playing a role in response inhibition corresponding with age.

Limitations

The Go/NoGo task used in the current study involved experimental blocks comprised of both Go and NoGo trials. Thus, these findings may not solely reflect response inhibition but also changes in set, stimulus analysis, response preparation, and processing of conflict and error. Further developmental fMRI studies utilizing event-related paradigms will shed light on these issues. Our positive age-related findings are, however, in line with regions implicated in response inhibition by event-related studies using Go/NoGo tasks in typically developing adults (e.g., Liddle et al., 2001).

Clinical Implications

A potentially important implication is that conclusions regarding functional roles of the prefrontal cortex regions in adults may not be directly applicable to children. The majority of neuroimaging studies to date have investigated adult populations, and a prevailing assumption is that the findings will generalize to children. Studies indicating functional impairments in specific regions of the prefrontal cortex will need to carefully consider the effects of age and development in interpreting findings related to executive functioning. The results of the current study are also directly relevant to the understanding of psychiatric disorders known to have associated problems with response inhibition (e.g., Tourette's disorder, attention-deficit/hyperactivity disorder, and obsessive compulsive disorder). Although executive functioning difficulties associated with these disorders may result from discrete dysfunction in specific brain regions, these findings also suggest the possibility of a developmental dysmaturation as a contributing factor, at least for response inhibition. Additional developmental studies, as well as complementary longitudinal investigations, of other cognitive/executive functions in typically developing populations are needed in order to develop templates or growth curves to which children with atypical development, cognition, or behavior can be compared.

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