A Developmental Functional MRI Study of Prefrontal Activation during Performance of a Go-No-Go Task

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Abstract

This study examines important developmental differences in patterns of activation in the prefrontal cortex during performance of a Go-No-Go paradigm using functional magnetic resonance imaging (fMRI). Eighteen subjects (9 children and 9 adults) were scanned using gradient echo, echo planar imaging during performance of a response inhibition task. The results suggest four general findings. First, the location of activation in the prefrontal cortex was not different between children and adults, which is similar to our earlier pediatric fMRI results of prefrontal activation during a working memory task (Casey et al., 1995). Second, the volume of activation was significantly greater for children relative to adults. These differences in volume of activation were observed predominantly in the dorsal and lateral prefrontal cortices. Third, although inhibitory processes have typically been associated with more ventral or orbital frontal regions, the current study revealed activation that was distributed across both dorsolateral and orbitofrontal cortices. Finally, consistent with animal and human lesion studies, activity in orbital frontal and anterior cingulate cortices correlated with behavioral performance (i.e., number of false alarms). These results further demonstrate the utility of this methodology in studying pediatric populations.

INTRODUCTION

Recent advances in neuroimaging technology now make it possible to examine the developing brain in vivo (Kwong et al., 1992; Ogawa, et al., 1992). The implications of these advancements are profound and promise a whole new era in developmental research. The current study examines important developmental differences in patterns of activation in the prefrontal cortex. Maturational of the prefrontal cortex is assumed to correspond to the development of higher-level cognitive processes throughout childhood and adolescence (Luria, 1973; Golden, 1981; Case, 1985; Becker, Isaac, & Hynd, 1987; Welsh & Pennington, 1988). Disruption in the develop-
ment of this brain region has been suggested to underlie the behavioral symptomatology of a significant number of childhood psychiatric disorders (Chelune, Ferguson, Koon, & Dickey, 1986; Gorenstein, Mammato, & Sandy, 1989; Trommer, Hoeppner, & Zecker, 1991). By establishing normative developmental patterns of activation within the prefrontal cortex using this methodology, we hope to further our understanding and interpretation of prefrontal dysfunction in a number of developmental psychiatric and pathological populations.

Several general cognitive functions have been attributed to the frontal lobes including attention, problem solving, and executive functions (Shallice & Burgess, 1991; Stuss & Benson, 1986). Hypotheses concerning more specific cognitive processes have emerged. Two cognitive functions frequently ascribed to prefrontal cortex are working memory and response inhibition (Fuster, 1989; Goldman-Rakic, 1987; Mishkin, 1964; Petrides & Milner, 1982). Animal neurophysiological studies (Barone & Joseph, 1989; Fuster, 1989; Goldman-Rakic, 1987; Mishkin & Manning, 1978; Niki, 1974), human neurophysiological (Damasio, 1985; Petrides & Milner, 1982) and neuroimaging studies (Casey et al., 1995; Cohen et al., 1994; Grasby et al., 1993; Haxby et al., 1993; Jonides et al., 1993; Paulesu, Frith, & Frackowiak, 1972) provide strong support for the idea that certain areas of the prefrontal cortex are centrally involved in working memory. Dorsal and lateral regions of the prefrontal cortex have generally been associated with working memory, while more ventral and orbital frontal regions have generally been associated with behavioral inhibition (Fuster, 1989; Goldman-Rakic, 1987; Mishkin, 1964).

Evidence for the role of the prefrontal cortex, especially the orbital frontal cortex, in inhibitory mechanisms comes from a number of animal (Iversen & Mishkin, 1970; Sakurai & Sugimoto, 1985) and human studies (Grant & Berg, 1948, Malloy, Birnhr, & Duffy, 1993; Perret, 1964). These studies have shown that lesions to the prefrontal cortex produce deficits in performance of tasks that require inhibition of distracting prepotent response tendencies. Several developmental psychiatric disorders with assumed prefrontal abnormalities (e.g., obsessive compulsive disorder, or OCD, and attention deficit/hyperactivity disorder, or ADHD) have as part of their phenomenology the core problem of being unable to suppress or inhibit inappropriate responses or thoughts (George, 1991; George, Ketter, & Post, 1993; Insel, 1988; Trommer et al., 1991). Diamond and her colleagues (Diamond, 1990; Diamond & Doar, 1989; Diamond & Goldman-Rakic, 1989) have shown that both human and monkey infants fail to inhibit prepotent response tendencies in developmental tasks such as the A-not-B task until after frontal lobe development has accelerated and some suggest (e.g., Dempster, 1992) that the development of inhibitory mechanisms in the prefrontal cortex accounts for age-related differences in cognitive behaviors.

While our previous pediatric fMRI study of prefrontal activation examined working memory, the current study examines the involvement of the prefrontal cortex in response inhibition. One of the classic neuropsychological tasks that has been used extensively in the clinical setting as well as in animal research to assess frontal lobe functioning is the Go-No-Go paradigm (Mesulam, 1985). This task assesses the ability to inhibit a prepotent response. A recent paper by Malloy et al. (1993) reported deficits in performance of the Go-No-Go task in patients with lesions of the orbitofrontal cortex. This observation is consistent with the previously mentioned animal studies reporting perseverative interference in a behavioral set following ablations of the orbitofrontal cortex (Iversen & Mishkin, 1970) and with neuroimaging studies reporting hypermetabolism in the orbitofrontal cortex in OCD patients (Baxter et al., 1988; Swedo et al., 1989). More recently, this task has received considerable attention as a viable index of impulsivity within the ADHD literature (Trommer et al., 1991; Casey et al., 1997).

The current study examines important developmental differences in patterns of activation in the prefrontal cortex during response inhibition using a carefully modified version of the classic Go-No-Go paradigm. The task requires the subject to respond to any letter but an X with 75% of the trials being targets, or non-Xs, similar to Conners' (1995) reversed continuous performance task (CPT). In our version of the task, we have three conditions: (1) a Go condition with nontargets (i.e., Xs) and targets intermixed, (2) a Go condition consist-

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Conditions</th>
<th>Go5</th>
<th>No-Go</th>
<th>GoR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of stimuli</td>
<td></td>
<td>120</td>
<td>120</td>
<td>60</td>
</tr>
<tr>
<td>Interstimulus interval (ISI)</td>
<td></td>
<td>1500 msec</td>
<td>1500 msec</td>
<td>3500 msec</td>
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<tr>
<td>Number of responses</td>
<td></td>
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<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Interresponse interval (IRI)</td>
<td></td>
<td>1500 msec</td>
<td>3500 msec</td>
<td>3500 msec</td>
</tr>
</tbody>
</table>

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ing of all targets and controlling for stimulus parameters (number of stimuli and interstimulus interval), and (3) a GoR condition consisting of all targets and controlling for response parameters (number of responses and interresponse interval). Table 1 illustrates how the two control conditions of GoS and GoR uniquely control for stimulus and response parameters of the No-Go condition. Figure 1 illustrates the high frequency of targets maintained across the entire experiment by embedding the No-Go condition of 50% nontargets between the two control conditions (i.e., GoS and GoR). Thus, the percentage of targets is maintained at 75% across the entire experiment, which is necessary for building a compelling tendency to respond.

The current version of the task has two important characteristics. First, the same set of instructions applies to all task conditions; thus different strategies are not imposed upon the subject for the different conditions (i.e., the subject is simply to respond by pressing a button to any sequentially presented letter except X). Second, by including control tasks for both the number of stimuli and the number of responses, we may better isolate frontal circuitry involved in suppressing or inhibiting a compelling response from the frontal circuitry involved in stimulus encoding and response execution. More importantly for the purposes of this study, we can assess developmental differences in frontal circuitry in children during response inhibition.

**METHOD**

**Subjects**

Twenty subjects were recruited. The data from one male adult and one male child were excluded from the analyses due to significant head motion (1 mm in-plane). The remaining subjects were nine children (7 to 12 years, mean age = 9.92 years) and 9 young adults (21 to 24 years, mean age = 21.75 years) who were all right handed. Ten subjects were females and eight were males. All subjects were recruited from the Pittsburgh area and were paid $50 for their participation.

**Cognitive Task**

As described previously, the task consisted of the subject responding to any sequentially presented letter except X. The three conditions were: (1) a No-Go condition defined by the presence of 50% nontargets (i.e., Xs) and 50% targets (i.e., non-Xs) with stimulus duration of 500 msec and interstimulus interval of 1500 msec; (2) a GoS condition (i.e., control for number of stimuli) consisting of 100% targets (i.e., non-Xs) with the same number of stimuli and interstimulus durations as the No-Go condition; and (3) a GoR condition (i.e., control for number of responses) consisting of 100% targets with the same number of required motoric responses as the No-Go condition but with longer interstimulus intervals of 3500 msec to match the average interresponse interval during the No-Go condition. Stimulus duration was 500 msec for all three conditions and 60-sec blocks of each of the three conditions were repeated in an ABCCBA ordering twice (i.e., GoS No-Go GoR GoS No-Go GoS). There were a total of 120 trials each of the 2-sec No-Go and GoS trials, and 60 trials of the 4-sec GoR trials. This ordering of task conditions maintains a 75% target frequency across the entire task. Stimulus presentation was controlled by a Macintosh Quadra 660 AV computer using a rear projection screen and an InFocus projector system. A specially constructed hand-held fiber-optic response box, connected to a transducer via fiber-optic cables to
the Macintosh, was used to collect subject responses. Reaction times, false alarms, and misses were recorded.

**Scanning Procedures**

All subjects were screened carefully for any metal implants or contraindications for an MRI and then acclimated to the scanner environment (see Figure 2) in a simulator that mimics the scanner in appearance and sound. Images were acquired on a 1.5T GE scanner modified by Advanced NMR, Wilmington, MA. T1-weighted images were acquired using a spoiled gradient sequence (TR = 33, TE = 8, FOV = 24, and 256 × 192 matrix) to prescribe the functional slice locations. Eight coronal slices (5 mm skip 0) were prescribed, covering the entire prefrontal cortex from the genu of the corpus callosum to the frontal pole. T2*-weighted images were acquired using echo planar imaging (EPI) gradient echo sequence (TR = 6000, TE = 40, FOV = 20, Flip angle = 90 and 128 × 64 matrix). Structural T1-weighted coronal images were acquired in the same eight slice locations in order to localize activation. Ten repetitions of each slice location were acquired per 60-sec block of each condition in an ABCBRA sequence that was repeated twice (two runs). This ordering of conditions controls for systematic changes that may occur over time in the physiological measure (Bench et al., 1993). The total time in the scanner for each subject was approximately 1 h.

**Image Processing**

When using a method of neuroimaging that relies on hemodynamic changes to index neural activity, it is important to consider potential disparities between vascular and parenchymal sources of signal. The two most likely causes for signal changes in blood vessels are the blood oxygenation effect in veins draining an area of activation and the flow-related enhancement in both supply and draining vessels based on activity-related changes in flow. Both effects could potentially occur in vessels distal to the actual site of neural activity. We took two approaches to guard against vessel-related changes.

First, signal changes associated with vascular flow can be mitigated with an appropriate choice of pulse sequence parameters, similar to the way that imaging pulse sequences can be sensitized to flow. For example, a single-slice study using a short TR and moderate flip angle will be highly sensitized to flow-related changes (Dyyn, Moonen, DeBoer, Iperen, & Luyten, 1993; Frahm, Merboldt, & Hanicke, 1993), while longer TR pulse sequences (3 or more seconds) should have little flow sensitization. The pulse sequence parameters we used in this study (6-sec TR and 90° flip angle) have very little flow sensitivity. Secondly, we eliminated any significant regions of activation overlaying large vessels or activation of greater than 6% since they are associated with activation due to large vessels (Menon et al., 1993). The 6% criteria affected only the top 1% of values in the similar distributions of the percentage of change in signal for children and adults, thus the "less than 6%" criteria appears reasonable for pediatric populations within our age range of 7 to 12 years.

Because the typically observed change in MR signal as a result of experimental manipulation (for a 1.5 T scanner) is only 1 to 2% (Kwong et al., 1992), the variance in the MR signal attributed to experimental manipula-
ions is quite small, while the variance attributed to other factors (e.g., drifts in scanner sensitivity, systemic changes, etc.) may be quite large. Normalizing images under these conditions is assumed to be effective in reducing noise. When experimental manipulations result in large effect sizes that contribute significantly to the variance across images, the normalization process may dilute or reduce the size of the effect of interest. For the current study, image data were compensated for any drift in scanner sensitivity during the course of the experiment by normalizing the global signal intensity of each image to that of the first acquisition of that slice. Specifically, we determined the ratio of the mean signal intensity for each image (averaged across all voxels) to that of the first image acquired at that location and multiplied each voxel by this factor.

Following this mean compensation, each subject’s images were realigned in 2-D space using Woods’ automated image registration (AIR) algorithm (Woods, Cherry, & Mazziotta, 1992). Based on motion correction logfiles of the image registration software on our sample of 18 subjects, the in-plane movement in our pediatric and adult samples was almost identical, with mean movement in the x axis of 0.04 mm, in the y axis of 0.41 mm, and 0.05° in rotation for children and 0.44 mm, 0.59 mm, and 0.14° for the adults.

ANALYSIS
Image Analysis
A voxelwise multifactorial analysis of variance (ANOVA) was used in place of the standard t test subtraction to identify areas of significant task-related activation. The ANOVA can be used to control for the effects of nonspecific trends and spurious transients in the MR signal. Three analyses were performed using 2 (runs) × 2 (conditions) × ANOVAs. The three comparisons were (1) No-Go versus Go_r, (2) No-Go versus Go_l, and (3) Go_r versus Go_l. The first and second comparisons control for the number of stimuli and responses in the No-Go condition, respectively, while the third comparison distinguishes the two control conditions.

To maintain the probability of detecting a false positive constant across the experiment while avoiding the elimination of areas of activation that are roughly 48.83 mm³, which is our current voxel size (i.e., 3.125 × 3.125 × 5 mm), we used a combination of what is equivalent to a Bonferroni correction for small activation (48.83 mm³) and a cluster-size threshold analysis (Forman et al., 1995) for larger regions of activation. Single voxels of activation were included only if they passed a Bonferroni correction of p < 0.00001 (0.05/4096). Clusters of two or more contiguous voxels were included if they passed a p level of 0.001, which approximates a Bonferroni adjustment of p < 0.00001 (see Note 1). This procedure relies upon the assumption that areas of true neural activity will tend to stimulate signal changes over contiguous pixels and that the likelihood of observing significant contiguous pixels by chance is lower than observing significant single pixels scattered randomly across an image. Thus, with eighteen subjects and eight slices per subject, the probability of a type I error for the entire study was less than 0.001 (18 × 8 × 0.00001).

Regions of significant activation identified by these analyses were overlaid on corresponding structural MR images to permit anatomic localization. Assignment of regions of activation to five coarse prefrontal regions (the inferior frontal, middle frontal, orbital frontal, superior frontal, and anterior cingulate gyrus) was performed independently by two raters, using a standard brain atlas (Duvernoy, 1991). Regions of significant activation were weighted by the number of pixels comprising that specific active region to avoid biasing by single pixels in the calculation of the percentage of change in MR signal (see Note 2).

Activation in each of the five regions of interest was recorded separately for each hemisphere. We have collapsed these data in Tables 2, 3, and 4 since tests for laterality effects were limited due to our use of two 5-in surface coils to amplify the MR signal. No two coils are identical in sensitivity. Thus differences in activation in the two hemispheres were confounded by differences in coil sensitivity. Differences between the number of subjects showing activation in the five regions of interest and the number of data points upon which correlational analyses were based reflect data points for each hemisphere for each region.

RESULTS
Behavioral Results
Children and adults differed significantly (t_{16} = 3.08, p < 0.003) in the mean false alarm rate (27% and 8%, respectively) but did not differ significantly in mean reaction time or mean hit-rate during performance of the Go-No-Go task. Since the false alarm rate discriminated between the two age groups, correlational analyses were performed on both age and false alarm rate with magnitude and volume of activation for each region of interest.

Neuroimaging Results
Three comparisons (No-Go and Go_r, No-Go and Go_l, and Go_r and Go_l) were performed to assess group differences in location, volume, and magnitude of activation across task conditions and are reported below. To examine group differences in the volume and magnitude of activation by location, t scores were computed based on the volume and percentage of change in signal for each subject by group for each region of interest and across regions of interest. Means and standard errors for these measures for each comparison are provided in Tables 2
Table 2. The Number of Subjects with Reliable Activation in Each Region of Interest and Mean Magnitude and Volume of Activation Across These Subjects by Age Group for the No-Go versus Go, Comparison

<table>
<thead>
<tr>
<th>Regions of interest</th>
<th>Brodmann’s area</th>
<th>Number of subjects</th>
<th>Mean volume in mm³</th>
<th>Mean % change in MR signal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>24, 32</td>
<td>5</td>
<td>586 (290)²</td>
<td>1.86 (0.44)</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>45, 47</td>
<td>8</td>
<td>537 (220)</td>
<td>1.72 (0.28)</td>
</tr>
<tr>
<td>Middle frontal</td>
<td>9, 10, 46</td>
<td>7</td>
<td>537 (122)</td>
<td>1.44 (0.24)</td>
</tr>
<tr>
<td>Orbital frontal</td>
<td>11</td>
<td>6</td>
<td>459 (132)</td>
<td>1.95 (0.38)</td>
</tr>
<tr>
<td>Superior frontal</td>
<td>6, 8</td>
<td>3</td>
<td>342 (107)</td>
<td>1.72 (0.36)</td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>24, 32</td>
<td>5</td>
<td>244 (54)</td>
<td>1.54 (0.30)</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>45, 47</td>
<td>7</td>
<td>342 (93)</td>
<td>1.48 (0.12)</td>
</tr>
<tr>
<td>Middle frontal</td>
<td>9, 10, 46</td>
<td>5</td>
<td>244 (38)</td>
<td>1.53 (0.23)</td>
</tr>
<tr>
<td>Orbital frontal</td>
<td>11</td>
<td>6</td>
<td>195 (48)</td>
<td>1.47 (0.41)</td>
</tr>
<tr>
<td>Superior frontal</td>
<td>6, 8</td>
<td>3</td>
<td>195 (88)</td>
<td>1.10 (0.15)</td>
</tr>
</tbody>
</table>

² (1) standard error.

through 4. Each table reports statistics for areas of activation in the anterior cingulate, inferior frontal gyrus, middle frontal gyrus, orbital gyrus, and superior frontal gyrus. For each region of interest the following data are reported: the number of subjects showing activation in that structure; the corresponding Brodmann’s areas for each structure; the mean and standard error for volume of activation, computed first within subjects, and then calculated across subjects; and the mean and standard error for the percentage of difference in signal intensity averaged across subjects. Statistics and averages are across only those subjects showing activation in the corresponding structure. There were no significant differences between groups in number of subjects showing activation for the five regions of interest for any of the statistical comparisons reported below.

No-Go and Go, Contrast

The comparison of the No-Go and Go, conditions revealed bilateral activation in predominantly the inferior frontal, middle frontal, orbital frontal, and anterior cingulate gyri for both the children and adults (refer to Table 2). The volume (mm³) of activation within the entire prefrontal cortex was significantly correlated with age (r₁₈₄ = −0.30, p < 0.008) and statistically different between groups (t₁₈₀ = 2.54, p < 0.01) with larger mean volumes of activation in children (2440 mm³) relative to adults (1200 mm³). Correlations performed as a function of specific regions of interest revealed only a significant correlation between volume of activation and age for the middle frontal gyrus (r₁₂₀ = −0.47, p < 0.05). Developmental differences in prefrontal activation are depicted in Figures 3 and 4.

In order to determine whether the difference in volume of activation in children relative to adults was due to a difference in variance between the two age groups, variance maps were generated for each group across each condition. The variance between groups was not significantly different (t₁₄₂ = 0.68, p < 0.52) with average variances of 168 (SD = 111) and 147 (SD = 136) for children and adults, respectively.

While the magnitude (percentage of change in MR signal) of activation was not significantly different between children (1.7%) and adults (1.5%), it was correlated with behavioral performance (r₁₈₄ = 0.27, p < 0.01) for both children and adults. Poorer performance (i.e., greater number of false alarms) correlated with greater changes in signal; however, correlations by each region of interest revealed that this pattern only held true for the anterior cingulate (r₁₀ = 0.81, p < 0.0005, see Figure 5). Since children made 3 times as many false alarms as adults, partial correlations were performed to control for these variables. The correlation between age and volume of activation remained significant after controlling for behavioral performance (r₁₈₄ = −0.43, p < 0.0001) as did the correlation between performance and magnitude in activation after controlling for age (r₁₈₄ = 0.25, p < 0.02).
No-Go and GoR Contrast

The comparison of No-Go and GoR trials revealed reliable bilateral activation in the same five regions as the previous comparison, but greater volumes of activation were observed across all subjects (see Table 3). The volume of activation in the middle frontal gyri was significantly greater ($t_{27} = 2.28$, $p < 0.03$) for children ($1611 \text{ mm}^3$) than for adults ($684 \text{ mm}^3$). There was also a significant difference in the volume of activation in the superior frontal gyri ($t_{23} = 2.13$, $p < 0.05$) with children again showing more activation than adults ($677 \text{ mm}^3$ and $269 \text{ mm}^3$, respectively). These data are presented in Figure 6. Finally, there was a negative correlation ($r_{30} = -0.37$, $p < 0.05$) between the volume of orbital frontal activation and number of false alarms (see Figure 7). Thus, better performance (i.e., fewer false alarms or better response inhibition) was observed in those subjects with the greatest volumes of orbital frontal activation, regardless of age ($r_{30} = -0.41$, $p < 0.02$).

GoS and GoR Contrast

The comparison of GoS and GoR trials revealed bilateral activation in the same five regions of interest with similar patterns of activation for children and adults. There were no significant developmental differences and no significant correlations between volume and magnitude of activation with age or behavioral performance for any

Figure 4. Mean volume of activation in the prefrontal cortex for children and adults.
Figure 5. Percentage of change in MR signal intensity in the anterior cingulate gyrus as a function of number of false alarms.

Figure 6. Mean volume of activation in the middle (MFG) and superior frontal gyri (SFG) as a function of age group.

Table 3. The Number of Subjects with Reliable Activation in Each Region of Interest and Mean Magnitude and Volume of Activation Across These Subjects by Age Group for the No-Go versus GoR Comparison

<table>
<thead>
<tr>
<th>Regions of Interest</th>
<th>Brodmann's area</th>
<th>Number of subjects</th>
<th>Mean volume in mm³</th>
<th>Mean % change in MR signal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>24, 32</td>
<td>8</td>
<td>732 (137)³</td>
<td>1.80 (0.22)</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>45, 47</td>
<td>8</td>
<td>830 (186)</td>
<td>1.63 (0.21)</td>
</tr>
<tr>
<td>Middle frontal</td>
<td>9, 10, 46</td>
<td>7</td>
<td>1611 (332)²</td>
<td>1.72 (0.26)</td>
</tr>
<tr>
<td>Orbital frontal</td>
<td>11</td>
<td>9</td>
<td>655 (171)</td>
<td>1.86 (0.26)</td>
</tr>
<tr>
<td>Superior frontal</td>
<td>6, 8</td>
<td>7</td>
<td>677 (166)²</td>
<td>2.01 (0.32)</td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>24, 32</td>
<td>8</td>
<td>878 (230)</td>
<td>1.77 (0.25)</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>45, 47</td>
<td>9</td>
<td>1220 (386)</td>
<td>1.25 (0.11)</td>
</tr>
<tr>
<td>Middle frontal</td>
<td>9, 10, 46</td>
<td>8</td>
<td>684 (137)²</td>
<td>1.40 (0.16)</td>
</tr>
<tr>
<td>Orbital frontal</td>
<td>11</td>
<td>8</td>
<td>781 (200)</td>
<td>1.86 (0.20)</td>
</tr>
<tr>
<td>Superior frontal</td>
<td>6, 8</td>
<td>9</td>
<td>269 (93)²</td>
<td>1.64 (0.37)</td>
</tr>
</tbody>
</table>

³ (1) standard error.
² Significant group differences (p < 0.05).
Orbital Frontal Gyrus (No-Go – Go<sub>R</sub>)

\[ y = -0.01x + 13.88 \]
Linear \( R^2 = 0.25 \)
Quadratic \( R^2 = 0.29 \)

Figure 7. Number of false alarms plotted as a function of volume of activation in the orbital frontal gyri for each individual subject.

Finally, the percentage of change in MR signal (calculated as the difference between the signal value for a given time point from the mean signal value divided by the mean signal value) is plotted as a function of the experimental manipulation across regions of interests and subjects to show the reliability of changes in the MR signal (see Figure 8). These data are collapsed across both age groups and regions of interest. As is demonstrated, the change in the MR signal intensity corresponds nicely with the experimental manipulation across the eight blocks of ten images.

DISCUSSION

This study was an attempt to examine whether brain circuitry underlying inhibitory processes is the same in children and adults during performance of the Go-No-Go task. There were four general findings. First, the location of activation in the prefrontal cortex was not different between the age groups. This observation is similar to our results from our earlier pediatric (Casey et al., 1995; Cohen et al., 1994) fMRI studies of prefrontal activation during performance of a working memory task. Second, the volume of activation was significantly greater for children relative to the adults when performing the No-Go condition of the task. These differences in volume of activation were observed primarily within the dorsal and lateral prefrontal cortex. Third, although inhibitory

<table>
<thead>
<tr>
<th>Regions of interest</th>
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<th>Number of subjects</th>
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<th>Mean % change in MR signal</th>
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<tbody>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>24, 32</td>
<td>9</td>
<td>952 (195)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.79 (0.21)</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>45, 47</td>
<td>9</td>
<td>781 (146)</td>
<td>1.57 (0.20)</td>
</tr>
<tr>
<td>Middle frontal</td>
<td>9, 10, 46</td>
<td>8</td>
<td>1025 (190)</td>
<td>1.69 (0.24)</td>
</tr>
<tr>
<td>Orbital frontal</td>
<td>11</td>
<td>8</td>
<td>489 (83)</td>
<td>1.94 (0.36)</td>
</tr>
<tr>
<td>Superior frontal</td>
<td>6, 8</td>
<td>7</td>
<td>635 (132)</td>
<td>1.59 (0.27)</td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>24, 32</td>
<td>9</td>
<td>1050 (244)</td>
<td>1.57 (0.11)</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>45, 47</td>
<td>9</td>
<td>1123 (249)</td>
<td>1.49 (0.10)</td>
</tr>
<tr>
<td>Middle frontal</td>
<td>9, 10, 46</td>
<td>8</td>
<td>977 (239)</td>
<td>1.36 (0.09)</td>
</tr>
<tr>
<td>Orbital frontal</td>
<td>11</td>
<td>9</td>
<td>732 (171)</td>
<td>1.74 (0.26)</td>
</tr>
<tr>
<td>Superior frontal</td>
<td>6, 8</td>
<td>8</td>
<td>537 (195)</td>
<td>1.31 (0.08)</td>
</tr>
</tbody>
</table>

<sup>a</sup> (1) standard error.
processes have typically been associated with more ventral and orbital prefrontal regions (Fuster, 1989), the current study revealed activation that was distributed across both the dorsolateral and orbitofrontal cortices. Finally, consistent with the animal (Iversen & Mishkin, 1970; Sakurai & Sugimoto, 1985) and human literature (Grant & Berg, 1948; Malloy et al., 1993; Perret, 1964), only activity in the orbital frontal and anterior cingulate cortices correlated with behavioral performance (i.e., number of false alarms).

The greater volume of activity in the prefrontal cortex in children during performance of the Go-No-Go task relative to adults may be due to maturational factors including cerebral vessel size, synaptic density, blood flow, or oxygen utilization. However, since the observed differences were isolated to specific regions of interest (primarily dorsolateral prefrontal cortex) and the volumes of activation during control comparisons did not differ between the two age groups, these findings may be attributed to specific developmental differences in the level of task difficulty or cognitive processes required when performing the Go-No-Go task.

Both working memory and response inhibition may be required to perform this task given the observed activation in brain regions typically associated with these processes (i.e., dorsolateral and orbital frontal cortices, respectively). Alternatively, working memory and inhibition may reflect the same underlying mechanism, with the role of this mechanism being the support of task-relevant information against the effects of interference (Cohen et al., 1994). According to this view, the only difference between memory and inhibition is the source of interference. In memory tasks this comes from the cumulative effects of noise over a delay, while in inhibitory tasks, similar to the current one, it comes from specific competing sources of prepotent information. Support for this interpretation comes from behavioral results reported by Roberts, Hager, & Heron (1995) that increasing working memory load produced failures in inhibition on an antisaccade task. This result suggests that both working memory and behavioral inhibition may rely on a single, resource-limited mechanism.

According to this view, developmental differences specific to the dorsolateral prefrontal cortex may reflect children having to activate more of this brain region to maintain the representation of task-relevant information. By activating these representations, the tendency to respond even in the presence of Xs is suppressed. Of the nine children in this study, the four best performers (i.e., least number of false alarms) had the most middle frontal activation. Thus, the decrease in volume of activation in adults may correspond to an increase in neural selectivity as the child becomes more efficient at representing contextual information with age, especially within the context of conflicting information.

Alternatively, activation of the dorsal and lateral prefrontal cortices in children may serve as an index of how strong the tendency is to respond to a stimulus whether it is a target or a nontarget. Paus, Petrides, Evans, & Meyer (1993) have suggested that cognitive/motor commands from the prefrontal cortex are modulated by the anterior cingulate and funneled to the motor system. According to this view, one may predict that increases in activation of the prefrontal cortex should correspond to increases in activity in the anterior cingulate cortex and increases in number of false alarms. While activity in the anterior cingulate cortex was positively correlated with number of false alarms, as mentioned previously, children with the largest volumes of prefrontal activation had the fewest number of false alarms. Thus, this explanation does not appear to account for the greater volume of activity in dorsolateral prefrontal cortex in children.

While not predicted, it should be noted that similar volumes of prefrontal activation were observed for the No-Go and GoR comparison as for the GoS and GoR comparison (8317 and 8301 mm3, respectively) across all subjects. We believe these results are consistent with our previous interpretation of the role of the dorsolateral
prefrontal cortex in representing contextual information. The stimulus parameters including number of stimuli and interstimulus interval were identical for the No-Go and GoS conditions. Further, the instructions were identical and there were no discrete boundaries between these conditions, unlike the GoS condition where the stimuli were presented more slowly. Therefore, subjects did not know if a nontarget (i.e., an X) would be presented during the GoS condition.

However, the No-Go and GoS conditions differed in two important ways: 1) the task difficulty as indexed by behavioral performance (82.5 and 99.9% accuracy, respectively) and 2) the number of required responses (50 and 100%, respectively). Each of these factors could affect the overall volume of prefrontal activity in that one may expect greater activity as a function of increasing task difficulty or as a function of greater response frequency. Thus one interpretation for the similar volumes of activation across these conditions is that while the No-Go condition was more difficult and required greater mental effort or stronger representations of the task demands, it required fewer behavioral responses. On the other hand, the GoS condition was less difficult and required less mental effort to maintain the task demands but required the preparation and execution of twice as many motoric responses.

This interpretation may be consistent with the observed developmental differences as well. Clearly, the children had more difficulty with the No-Go condition than the adults (27 and 8% false alarm rate, respectively) and likewise made many more motoric responses (i.e., false alarms) than the adults during the No-Go condition. So if prefrontal activation in children is weighted by both task difficulty and response frequency during the No-Go condition, the children would be expected to show greater volumes of activation for the No-Go condition. Likewise, if prefrontal activation in adults is not significantly weighted by task difficulty (i.e., 92% accuracy) and response frequency (only 8% false alarms) during the No-Go condition, the adults may be expected to show greater prefrontal activation during the GoS condition, which is weighted by response frequency. In fact, the children had greater volumes of activation during the No-Go condition (4485 mm$^3$) than the GoS condition (3882 mm$^3$), while the adults showed greater activation for the GoS condition (4419 mm$^3$) than the No-Go condition (3832 mm$^3$). Although these differences did not reach significance, they may help explain why significantly greater volumes of prefrontal activity were observed overall for the children relative to the adults when comparing the No-Go and the GoS conditions directly.

Although across all subjects similar volumes of activation were observed for the No-Go and GoS conditions, correlations between the magnitude and volume of activation with behavioral performance were observed only for the anterior cingulate and orbital frontal gyri. These findings are consistent with both the clinical and animal literature of involvement of medial orbital circuitry (anterior cingulate and orbital frontal cortices) in response inhibition (Iversen & Mishkin, 1970; Malloy et al., 1993). Increased percentage of change in activation in the anterior cingulate gyrus corresponded to poorer performance (i.e., greater number of false alarms) across subjects in the No-Go versus GoS comparison. These data suggest that the cingulate may be more involved in driving responses than in inhibiting them. Thus, the greater the activity in the cingulate gyrus, the more likely it is that a motor response will be made. This interpretation of the data fits with the clinical literature reporting akinetic mutism and impaired motor initiation following infarcts and surgery of the anterior cingulate cortex (Devinsky, Morrell, & Vogt, 1995; Fesinmeir, Kuzniecky, & Garcia, 1990; Gugliotta & Silvestri, 1989; Nemeth & Hegedus, 1988).

The correlation between behavioral performance and volume of orbital frontal activation suggests that the greater the activation of the orbital frontal cortex, the fewer false alarms or greater the inhibition. Likewise, the less orbital activation there is, the less response inhibition is observed. This result is consistent with lesion studies whereby ablations of the orbitofrontal cortex result in perseverative interference in behavioral set (Iversen & Mishkin, 1970) and with neuroimaging studies of OCD patients who have demonstrated hypermetabolism in these regions (Baxter et al., 1988; Swedo et al, 1989). This disorder is characterized by an inability to control specific perseverative behaviors that is reminiscent of the deficits observed in animals with lesions to this region.

Finally, the lack of significant behavioral correlations with prefrontal activity during the control conditions may reflect asymptote performance during conditions without nontargets (99.9% accuracy overall). If performance were manipulated by increasing task difficulty (e.g., by presenting peripheral distractors or by degrading the target stimuli), one may expect prefrontal activity to correlate with behavioral performance for these conditions as well. Likewise, given the interpretation of the dorsolateral prefrontal cortex in supporting (i.e., representing) task-relevant information against interference and the possible inefficiency of children in this process, one may also expect similar developmental differences in prefrontal activity for these conditions as well.

In sum, these data suggest that both ventral and dorsal prefrontal circuitry is activated during performance of the Go-No-Go task and that the same underlying prefrontal circuitry is observed for both children and adults. However, children appear to be less efficient in inhibiting compelling responses when performing this task and activate more of the implicated prefrontal circuitry, especially more in the dorsal and lateral prefrontal regions. These results in conjunction with our previous reported findings (Casey et al., 1995) show promise for studying
biological mechanisms underlying both normal cognitive development and developmental psychiatric disorders characterized by prefrontal dysfunction.

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Notes

1. A complete description of the Monte Carlo simulations showing the distribution of different size clusters as a function of individual pixel alpha level and image dimensions is provided in Forman et al. (1995). While Forman’s tables for probability distributions of false positives for two or more pixels do not fall below 0.005, the probability of a false positive for the 0.001 alpha level was estimated using the same procedure which resulted in a probability of 1^-5 (i.e., 0.00001).

2. Single pixels of activation were scrutinized further by performing time series analysis to assess the extent that these data were well behaved (i.e., changes in MR signal corresponded with phasic experimental manipulations and not transients). Likewise as stated earlier, pixels with changes in MR signal of more than 6% were excluded.

REFERENCES


