A neural basis for the development of inhibitory control

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Abstract

The present study explores the neural basis of the development of inhibitory control by combining functional neuroimaging with a parametric manipulation of a go-nogo paradigm. We demonstrate how the maturation of ventral fronto-striatal circuitry underlies the development of this ability. We used event-related fMRI to examine the effect of interference on neural processes involved in inhibitory control in children and adults. Nogo trials were preceded by either 1, 3 or 5 go trials and then compared to one another. Both children and adults showed an increase in errors with increasing interference. Successful response inhibition was associated with stronger activation of prefrontal and parietal regions for children than for adults. In adults, activation in ventral prefrontal regions increased with increasing interference from go trials. Unlike adults, the circuitry appeared to be maximally activated in children when suppressing a behavioral response regardless of the number of preceding responses. Furthermore, activation in ventral fronto-striatal regions correlated with both age and performance. These findings suggest that immature cognition is more susceptible to interference and this is paralleled by maturational differences in underlying fronto-striatal circuitry.

Clearly, the ability to suppress irrelevant information and actions becomes more efficient with age. A number of classic developmental studies have demonstrated that these cognitive abilities develop throughout childhood (Case, 1972; Diamond & Doar, 1989; Flavell, Beach & Chinsky, 1966; Keating & Bobbitt, 1978; Pascual-Leone, 1970). More recently, developmental theories have been extended to emphasize inhibitory processes in their account of cognitive development (Harnishfeger & Bjorklund, 1994) such that immature cognition is characterized by susceptibility to interference in overriding an attentional or behavioral response (e.g. Brainerd & Reyna, 1993; Dempster, 1992; Munakata, 1998). For example, performance on Stroop, flanker and go-nogo tasks continues to develop over childhood and does not reach full maturity until roughly 12 years or later (Bunge, Dudukovic, Thomason, Vaidya & Gabrieli, 2002; Carver, Livesey & Charles, 2001; Casey, Trainor, Orendi, Schubert, Nystrom, Giedd et al., 1997; Casey, Forman, Franzen, Berkowitz, Braver, Nystrom et al., 2001; Diamond, 1990; Diamond, Cruttenend & Nederman, 1994; Diamond & Taylor, 1996; Enns & Akhtar, 1989; Enns & Cameron, 1987; Enns, Brodeur & Trick, 1998; Gerstadt, Hong & Diamond, 1994; Luria, 1961; Jones, Rothbart & Posner, in press; Passler, Isaac & Hynd, 1985; Ridderinkhof & Van der Molen, 1997; Ridderinkhof, Van der Molen & Band, 1997; Rubia, Overmeyer, Taylor, Brammer, Williams, Simmons et al., 2000; Tipper, Bourque, Anderson & Brehaut, 1989; Van der Meer & Stemerdink, 1999). These studies show a developmental trend in the ability to suppress information and actions over the ages of 4 to 12 years as indexed by mean reaction times and accuracy rates. Age-related differences in accuracy are not observed on these tasks in the absence of interfering information (e.g. Enns et al., 1998). In sum, the developmental literature suggests refined development of cognitive control in terms of both overriding behavioral and attentional responses during mid- to late childhood.

In order to address the question of how maturational changes in the brain coincide with this significant behavioral development, we used event-related fMRI with a variation of a go-nogo task in children and adults. Bunge et al. (2002) recently demonstrated that children aged 8 to 12 rely on an immature network of regions when performing such tasks, with ventral prefrontal regions not activating as in adults. However, children do not
perform these tasks as well as adults, indicating that task demands may be quite different for both groups. We chose to manipulate task difficulty by parametrically varying the number of go trials preceding a nogo trial (see Figure 1). Such manipulations allow for comparisons between groups on trials of similar performance. More importantly, this manipulation allows one to test the extent to which immature cognition is characterized by susceptibility to interference by varying the salience of the interfering information. In other words, if children’s performance is more susceptible to interference, then the tendency to make an inappropriate response (i.e. respond on a nogo trial) would be expected to increase as a function of the number of preceding responses (i.e. 1, 3 or 5 go trials) and decrease as a function of age.

In a previous study with adults, we showed that errors increased on nogo trials as a function of the number of preceding go trials, and activity in ventral prefrontal cortex, cingulate cortex and parietal cortex paralleled this response (Durston, Thomas, Worden, Yang & Casey, 2002). Thus, we observed a main effect of preceding context both behaviorally and physiologically in adults. In the current study we address both the behavioral and physiological response of the preceding context manipulation in children. We hypothesize that children will show more susceptibility to interference as the number of go trials preceding a nogo trial increases. At the neural level, they may recruit the same circuitry as adults, yet less efficiently, by activating these regions to a higher level or by showing a more diffuse pattern of activation. Alternatively, children may rely on the recruitment of other areas to perform the task. These hypotheses are not mutually exclusive as children may recruit the same brain regions as adults, but in a less efficient or focal way, in addition to recruiting others (Bunge et al., 2002; Casey et al., 1997; Casey, Thomas, Welsh, Badgaiyan, Eccard, Jennings & Crone, 2000; Gaillard, Hertz-Pannier, Mott, Barnett, LeBihan & Theodore, 2000; Klingberg, Forssberg & Westerberg, 2002; Luna, Thulborn, Munoz, Merriam, Garver, Minshew et al., 2001; Thomas, King, Franzen, Welsh, Berkowitz, Noll et al., 1999).

Methods

Paradigm

The subject’s task was to press a button in response to visually presented stimuli, but to avoid responding to a rare nontarget. The task consisted of 5 runs, which lasted 3 minutes and 56 seconds each. Each run contained a total of 57 trials, with 75% go trials, resulting in a total of 70 nogo trials, including 20 of each type (with 1, 3 or 5 preceding go trials) per subject. The order of presentation of the different types of nogo trials was pseudorandomized. In order to make the task more interesting for children, characters from the Pokemon cartoon series were used as stimuli. Stimulus duration was 500 ms and the inter-stimulus interval was 3500 ms (total trial length = 4000 ms).

Subjects

Twenty healthy right-handed subjects completed the study with less than 1 voxel of movement. These subjects included ten adults (mean age = 28.0 years, 5 male) and ten children (mean age = 8.7 years, range 6.2–10.3; 5 male). Subjects were screened for any contraindications for MRI. Prior to scanning, we obtained written consent or assent from all subjects, and from a parent or legal guardian for the children, according to the declaration of Helsinki. The procedure was approved by the institutional review board at Weill Medical College of Cornell University.
total of 12 children were excluded from the study after having participated in a scanning session, due to excessive motion in the scanner or not performing the task.

**Scan acquisition**

EPI BOLD images were acquired in 24 axial slices on a 1.5 T GE Signa scanner, covering most of the brain (TR = 2000, TE = 40, 64 × 64, 4 mm slice thickness, 3.125 × 3.125 mm in-plane resolution). Anatomical Spin Echo images were also collected (TR = 500, TE = min, 256 × 256, FOV = 20, 4 mm slice thickness) in the same locations as the functional slices. Stimuli were presented using the integrated functional imaging system (IFIS) (MR Devices) that uses a LCD video display in the bore of the MR scanner and a fiberoptic response collection device. Scanning sessions lasted no longer than one hour. The functional images were collected in 20–25 minutes, while the anatomical images were collected within a similar timeframe. The participants were shown cartoons during the anatomical scans to prevent boredom and restlessness.

**Analysis**

AIR (Automated Image Registration) version 3.08 (Woods, Cherry & Mazziotta, 1992) was used for motion correction, image smoothing (2 mm), and cross registration of data. Cross registration was checked by visual inspection of an overlay of each subject’s brain with the brain chosen as the standard. There were no differences in variance between groups in the MR signal thus a voxelwise, multifactorial ANOVA was performed pooling data into a 20 (subjects) × 2 (group) × 4 (trial type; go trials and nogo trials preceded by 1, 3 or 5 go trials) design, averaging across all 5 runs. In order to increase power, post hoc analyses were performed comparing go to nogo trials as in a traditional go-nogo task, both for the group as a whole, and then for each group separately. For each trial type, two 2-second scans were included in the analyses taken at the peak of the hemodynamic response (4 and 6 s after stimulus presentation) yielding 40 data points per trial type per subject. Regions of three or more contiguous voxels (p < 0.01) were identified (Forman, Cohen, Fitzgerald, Eddy, Mintun & Noll, 1995). In order to separate regions of interest (ROIs) that had more than one maximum with contiguous voxels, analyses were also performed at more conservative p-values, ranging from p < 0.0001 to p < 0.005 to examine whether these regions were behaving in the same way. If not, they were treated as separate ROIs. Images were warped into stereotaxic space using AFNI (Cox, 1996) to localize regions of activity, based on the coordinate system of the Talairach atlas (Talairach & Tournoux, 1988). Only correct trials were analyzed. A post hoc scan-by-scan analysis similar to one used by Casey et al. (2000) was performed on brain regions identified as having significant MR signal change by the omnibus ANOVA to test for a differential response in children and adults on the three different types of nogo trials. Finally, Pearson’s correlations between MR signal change and behavioral measures were calculated for these same ROIs.

**Results**

**Behavioral results**

Overall, adults were both faster and more accurate than children on the task (559 versus 691 ms, T = 2.50, p = 0.02; 95.5% versus 90.3%, T = 2.08, p = 0.05). The number of errors on the nogo trials increased with number of preceding go trials for both adults and children (2.5%, 5%, 6%, p < 0.05 and 8%, 12.5%, 14.5%, p < 0.05, respectively). Both reaction time on the go trials and overall accuracy (including both misses and false alarms) correlated with age (r = −0.58, p < 0.009 and r = 0.66, p < 0.002, respectively).

**FMRI results**

**Effects of condition (go trials versus nogo trials)**

The 20 (subjects) × 2 (condition) ANOVA showed a main effect of condition on MR signal change. Regions in bilateral ventral prefrontal cortex (BA 44/47; max F = 9.99, p < 0.01 on right; max F = 9.05, p < 0.01 on left), right dorsolateral prefrontal cortex (BA 9/46; max F = 12.08, p < 0.01), and the right parietal lobe (BA 40, max F = 36.60, p < 0.0001) showed an increase in MR signal for nogo trials compared to go trials in both children and adults. However, the increase in signal was larger for children than adults in all three regions. Left primary motor cortex (BA 4) showed a decrease in activation for the nogo trials (no motor response) compared to go trials (motor response) for both adults and children (max F = 64.00, p < 0.0001; see Table 1 and Figure 2).

**Effects of context**

The 20 (subjects) × 4 (context) ANOVA showed no significant main effect of preceding context. Follow-up ANOVAs on each group independently showed a context effect for adults in the inferior frontal gyrus (BA 9/44; max F = 7.51, p < 0.005 on right; max F = 13.37, p < 0.005 on left), cingulate gyrus (right anterior, BA 32; max F = 9.01, p < 0.05; and bilateral posterior, BA 23/31;
max $F = 10.07, p < 0.005$ on right and max $F = 7.30, p < 0.005$ on left) and left superior parietal cortex (BA 7; max $F = 7.02, p < 0.005$), but no effect of context for children (see Table 1).

Effects of group by condition

The 20 (subjects) $\times$ 2 (group) $\times$ 2 (condition) ANOVA showed regions in bilateral inferior frontal gyrus (BA 44; max $F = 29.64, p < 0.0001$ on right; max $F = 19.43, p < 0.0001$ on left), left anterior cingulate gyrus (BA 24/32; max $F = 36.13, p < 0.0001$) and in the left caudate nucleus (max $F = 19.96, p < 0.0001$) that showed an increase in MR signal for nogo trials in adults but not consistently in children.

Post hoc comparisons

$T$-tests comparing percent signal change for each type of nogo trial in regions from the group $\times$ condition interaction revealed that the difference in signal change for children and adults was only significant for the nogo after 1 go trial type ($T = 2.16, p = 0.04$ for nogo trials after 1 preceding go trial; $T = 1.61, p = 0.12$ for nogo trials after 3 preceding go trials; $T = 1.16, p = 0.26$ for nogo trials after 5 preceding go trials) (see Figure 3). Pearson’s correlations with overall accuracy on this task were also calculated for these regions. MR signal in bilateral inferior frontal cortex (BA 44), the left caudate nucleus and left anterior cingulate gyrus (BA 32) correlated with overall accuracy ($r = 0.55, p < 0.011$; $r = 0.71, p < 0.0001$; $r = 0.66, p < 0.001$, respectively; see Figure 4).

Discussion

In this study we examined the maturation of neural circuitry involved in the development of inhibitory control. We manipulated the salience of a behavioral response (button press) by parametrically varying the number of go trials preceding a nogo trial. Both children and adults showed an increase in errors on nogo trials as a function of the salience of the response, with children making significantly more errors overall. Both children and adults activated regions associated with response inhibition for nogo trials. However, the magnitude of the MR signal change was larger for children. Adults showed increases in MR signal to nogo trials, as a function of increasing number of preceding go trials. Children did not show this context effect, as the MR signal was high

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Regardless of number of preceding go trials. MR signal changes in the striatum and ventral frontal cortex correlated with accuracy on the go-nogo task, providing further support for a role of ventral fronto-striatal circuitry and its maturation in inhibitory or cognitive control.

It is well documented that the ability to override a salient response develops with age (Carver et al., 2001; Casey et al., 1997, 2001; Diamond, 1990; Diamond et al., 1994; Diamond & Taylor, 1996; Enns & Akhtar, 1989; Enns & Cameron, 1987; Enns et al., 1998; Gerstadt et al., 1994; Luria, 1961; Jones et al., in press; Passler et al., 1985; Ridderinkhof & Van der Molen, 1997; Ridderinkhof et al., 1997; Rubia et al., 2000; Tipper et al., 1989; Van der Meere & Stemerding, 1999). We showed that children had poorer performance than adults, as evidenced by both reaction time and accuracy. Furthermore, performance correlated with age, demonstrating a decrease in susceptibility to interference with age.

Activity in bilateral ventral prefrontal cortex, the right parietal lobe, and right dorsolateral prefrontal cortex increased during performance of nogo trials. This is consistent with evidence from many other studies that have demonstrated that these regions are involved in response inhibition (Bunge et al., 2002; Casey et al., 1997, 2001; Durston et al., 2002; Garavan, Ross & Stein, 1999; Konishi, Nakajima, Uchida, Sekihara & Miyashita, 1998;}

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Konishi, Nakajima, Uchida, Kikyo, Kameyama & Miyashita, 1999; Luna, Thulborn, Munoz, Merriam, Garver, Minshew et al., 2001; Rubia et al., 2000; Vaidya, Austin, Kirkorian, Ridlehuber, Desmond, Glover et al., 1998). The increase in activation in these regions was much larger for children than adults. However, the change in MR signal in left primary motor cortex for the comparison of go versus nogo trials was the same for both groups, suggesting a differential response in sensorimotor versus association cortex across these age groups for this task (see Figure 2). Whereas activation of the sensorimotor cortex in children is comparable to adult levels, the activation of association cortex is much greater, suggesting different developmental trajectories for these regions in the context of the current task.

As reported previously, adults showed an effect of preceding context in both behavior (mean accuracy) and in MR signal change in regions in prefrontal and parietal cortex (Durston et al., 2002). This effect, while observed in the behavioral data of the children, was not present in their pattern of brain activity. This suggests that children are more susceptible to interference regardless of the preceding context. As such, they show no context effect as the MR signal change is already high and remains high regardless of the number of preceding go trials (see Figure 3). This is consistent with the behavioral data as accuracy for children on nogo trials following a single go trial was comparable to adult accuracy on nogo trials following 5 go trials. Moreover, this interpretation is consistent with the imaging results as the MR signal across these regions was greater for children than adults on nogo trials.

MR signal was shown to correlate with behavioral performance in several regions, including inferior frontal gyrus, cingulate gyrus, and the caudate nucleus. These regions have been implicated in inhibitory control tasks by several others (Bunge et al., 2002; Casey et al., 1997, 2001; Garavan et al., 1999; Konishi et al., 1998, 1999; Rubia et al., 2000; Vaidya et al., 1998), including a report by Casey et al. (1997) of a correlation between MR signal in ventral prefrontal cortex and performance. Some of these same regions that correlated with behavioral performance showed a context effect in adults (inferior frontal gyrus and cingulate gyrus). Furthermore, the older children in this study tended to display the more ‘adult’ pattern of activation in these regions, supporting continued maturation of this circuitry.

The reported negative correlation between activation of the anterior cingulate gyrus and performance in this study appears contradictory to a previous report of a positive correlation between anterior cingulate activity and errors on a go-nogo task (Casey et al., 1997). However, performance in that study was defined as the number of false alarm errors on the nogo trials, whereas the accuracy measure in the present paper includes both false alarms and misses on the go trials. Clearly if the subjects were failing to respond on go trials, the effect on later nogo trials would be different.

Overall, our findings support the view that immature cognition is characterized by greater susceptibility to interference. This conclusion is supported by both the behavioral and the imaging data. Children had more difficulty inhibiting a response to nogo trials, regardless of the number of go trials preceding them. Likewise, patterns of brain activity (change in MR signal) in children and adults differed with children activating prefrontal (BA 46/47) and parietal regions (BA 40) significantly more than adults. Moreover, activation of fronto-striatal circuitry approximated the adult pattern as a function of increasing age and improved performance. In sum, our findings confirm the continued maturation of ventral fronto-striatal circuitry underlying the development of inhibitory control across the ages of 6 to 10 years.

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