Published in final edited form as:

J Am Acad Child Adolesc Psychiatry. 2008 October ; 47(10): 1141–1150. doi:10.1097/CHI.0b013e3181825b1f.

fMRI of Intrasubject Variability in ADHD: Anomalous Premotor Activity With Prefrontal Compensation

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Abstract

Objective—Children with attention-deficit/hyperactivity disorder (ADHD) consistently display increased intrasubject variability (ISV) in response time across varying tasks, signifying inefficiency of response preparation compared to typically developing (TD) children. Children with ADHD also demonstrate impaired response inhibition; inhibitory deficits correlate with ISV, suggesting that similar brain circuits may underlie both processes. To better understand the neural mechanisms underlying increased ISV and inhibitory deficits in children with ADHD, functional magnetic resonance imaging was used to examine the neural correlates of ISV during Go/No-go task performance.

Method—Event-related functional magnetic resonance imaging was used to study 25 children with ADHD and 25 TD children ages 8 to 13 years performing a simplified Go/No-go task. Brain-behavior correlations were examined between functional magnetic resonance imaging activation and ISV within and between groups.

Results—For TD children, increased rostral supplementary motor area (pre-supplementary motor area) activation during No-go events was associated with less ISV, whereas the reverse was true for children with ADHD for whom increased pre-supplementary motor area activation was associated with more ISV. In contrast, children with ADHD with less ISV showed greater prefrontal activation, whereas TD children with more prefrontal activation demonstrated more ISV.

Conclusions—These findings add to evidence that dysfunction of premotor systems may contribute to increased variability and impaired response inhibition in children with ADHD and that compensatory strategies eliciting increased cognitive control may improve function. However,

recruitment of prefrontal resources as a compensatory mechanism for motor task performance may preclude the use of those prefrontal resources for higher order, more novel executive functions with which children with ADHD often struggle.

Keywords

attention-deficit/hyperactivity disorder; intrasubject variability; response inhibition

Increased intrasubject variability (ISV) in response time is consistently reported in children with attention-deficit/hyperactivity disorder (ADHD) across various tasks.^{1–6} The consistency of this observation suggests that increased ISV may, in fact, be a defining feature of the syndrome ADHD.^{1,7} ISV has been described as a marker of response control,⁸ and during motor task performance, increased ISV appears to represent reduced efficiency of response preparation.^{9,10} The importance of examining ISV in children with ADHD is underscored by its correlation with deficits in response inhibition,^{1,4} with the latter also proposed to be a hallmark of ADHD.^{11,12}

Neural correlates of ISV during performance of a simplified Go/No-go task have been examined in typically developing (TD) children using functional magnetic resonance imaging (fMRI).¹³ In a group of 30 children, ages 8 to 13 years old, ISV was calculated using response times for Go events, and neural correlates of ISV were reported for both Go events (representing a task of habitual motor response) and No-go events (representing a task of response selection). For Go events, less ISV was associated with activation in the right anterior cerebellum (culmen), which is in circuit with premotor regions¹⁴ and important for motor response preparation.^{15,16} More ISV was associated with activation of the superior/middle frontal gyri and caudate (in circuit with prefrontal cortex). For No-go trials, less reaction time variability was associated with activation in the rostral supplementary motor area, or pre-SMA, a region important for response preparation and response selection (including selecting to inhibit a response)¹⁷ as evidenced by lesion, electrophysiological, and imaging studies.^{18–20} Increased ISV was again associated with activation of the superior/middle frontal gyri and caudate. In summary, less ISV was associated with activation in premotor circuits, and more ISV was associated with activation in prefrontal circuits, suggesting that in a simplified motor task, the use of premotor circuits is associated with more efficient task performance as compared to the use of prefrontal circuits associated with higher order cognitive control.

These findings are particularly relevant to children with ADHD, in whom anatomic and functional abnormalities of the pre-SMA have been identified.^{21–24} Similar to TD children with higher ISV, children with ADHD, who as a group demonstrate more ISV, may recruit prefrontal regions to compensate for less efficient use of premotor systems.

To understand the neural mechanisms underlying ISV during task performance in children with ADHD as compared to TD children, we examined the neural correlates of ISV during a simplified motor task of response inhibition. We used a Go/No-go task with a motor response that becomes entrained through frequent repetition at constant time intervals (Go events) and an infrequent demand to select not to respond (No-go events). A well-ingrained stimulus-response association (green = Go, red = No-go) was used to minimize extraneous cognitive demands (e.g., working memory). For several reasons, we chose to study groups of children with statistically equivalent task performance. First, this allows the investigation of mechanisms by which some children with ADHD are able to achieve equivalent task performance to that of TD children, despite decreased recruitment of the pre-SMA. In addition, the use of behaviorally matched groups minimizes confounds that result from differences in task difficulty including differences in task-related neural activation and

differences in statistical power due to unequal number of correct responses available for analysis.

We hypothesized that for both Go and No-go events, the relation between ISV and premotor activation would be the same in children with ADHD as in TD children, that within the group of children with ADHD, those exhibiting more activation within premotor systems would show less variability in performance. Given that children with ADHD with behavioral task performance equivalent to that of TD children demonstrate less pre-SMA activation than TD children during the response inhibition portion of this task (i.e., during No-go stimuli),²¹ we also hypothesized that for No-go events, the association of increased ISV with activation of regions within prefrontal circuits (prefrontal cortex and caudate nucleus) previously observed in TD children¹³ would be more robust within the ADHD group as compared to the TD children. Although disadvantageous in terms of automaticity, prefrontal circuit activation would suggest a compensatory mechanism for response inhibition by children with ADHD in the face of lesser activation of the pre-SMA.

METHOD

Participant Selection

Twenty-five children with ADHD and 25 sex-matched TD children (controls) participated in this study. Participants were recruited from outpatient clinics at the Kennedy Krieger Institute, from local area pediatricians, schools, social/service organizations (e.g., Boy/Girl Scouts), and chapters of Children and Adults with Attention-Deficit/Hyperactivity Disorder and from advertisements in the community (e.g., postings at libraries). Children were between the ages of 8 and 13 years and had Full Scale IQs ≥ 85 on the WISC-III²⁵ or WISC-IV.²⁶ No child had a history of speech-language disorder or reading disability; all of the children had standard scores of ≥ 85 on the Basic or Word Reading subtests of the Wechsler Individual Achievement Test²⁷ or Wechsler Individual Achievement Test II.²⁸

The structured parent interview, Diagnostic Interview for Children and Adolescents- fourth edition (DICA-IV)²⁹ and an ADHD-specific broad behavior rating scale (Conners Parent and Teacher Rating Scales-Revised, long form)³⁰ were used to confirm ADHD diagnosis. The Conners Parent Rating Scale-Revised and DICA-IV were also used to evaluate ADHD subtype. Seventeen children with ADHD met criteria for ADHD combined type, six met criteria for ADHD predominantly inattentive type, and two met criteria for ADHD predominantly hyperactive/impulsive type.

The DICA-IV was additionally used to examine for the presence of other psychiatric disorders in all of the children. Children who met criteria for comorbid conduct disorder, mood disorder, generalized anxiety disorder, separation anxiety disorder, or obsessive-compulsive disorder were excluded from this study. Children with ADHD and comorbid oppositional defiant disorder (ODD) or simple phobia were included; 11 subjects with ADHD met criteria for ODD, and five children with ADHD met criteria for simple phobia (including two of the children with ODD). No subject had a history of other neurological disorders, including Tourette syndrome. Twelve of the children with ADHD were being treated with stimulant medication, and their parents were requested to withhold the medication the day of and the day before testing. Withholding of medication as instructed was confirmed by parent report on the day of scanning. No children with ADHD were taking additional psychoactive medications.

Children were included in the TD control group only if they did not meet ADHD diagnostic criteria on any of the administered rating scales and questionnaires. None of the TD children

met criteria for a psychiatric disorder on the DICA-IV, except for one child with simple phobia. None of the control children were taking psychoactive medications.

This study was approved by the Johns Hopkins Medicine Institutional Review Board. After complete description of the study to the subjects, written informed consent was obtained from a parent or guardian, and assent was obtained from the participating child.

There is overlap between the subjects in this study and those cohorts in previous work examining response inhibition in children with ADHD²¹ and neural correlates of ISV in TD children.¹³ The present ADHD cohort is the same size of that previously reported²¹; however, group composition differs by two subjects. Two subjects from the original cohort were removed, one due to ISV 3 SDs greater than the ADHD group mean and the other to more closely match groups for performance. Two recently accrued subjects were added to the cohort. The current cohort of TD children differs by one subject from the group previously used for comparison with children with ADHD; the subject replaced did not have reaction time data due to technical malfunction. The current TD cohort ($n = 25$) shares 18 subjects with the larger cohort ($n = 30$) of children in which neural correlates of ISV have been previously reported.¹³

Analysis of Demographic and Behavioral Data

The behavioral data were analyzed using the JMP statistical package (version 5.1, SAS Institute, Inc., Cary, NC). Each participant's ISV was measured using the coefficient of variation (CV) calculated as $[(SD \text{ of Go reaction time})/(\text{mean Go reaction time})]$.³¹ Differences between groups were investigated using χ^2 tests (for nominal data) and two-tailed independent group t tests.

fMRI Go/No-go Paradigm

Children completed a simplified Go/No-go task previously described.²¹ Briefly, a well-ingrained stimulus-response association (green = Go, red = No-go) was used to minimize extraneous cognitive demands (e.g., working memory). Trials consisted of a green (Go) or red (No-go) spaceship presented for 300 ms, with sequential stimuli separated by an interstimulus interval of 1,500 ms. Children were instructed to use the right index finger to push a button as quickly as possible on the appearance of green but not red spaceships. The ratio of Go to No-go stimuli was 3:1. Between three and seven green spaceships appeared sequentially, whereas red spaceships occurred individually or two in a row; No-go stimuli were effectively jittered, with the interval between No-go stimuli varying depending on the number of preceding Go stimuli. Participants completed a short practice block followed by two full runs, each consisting of a total of 127 stimuli and lasting approximately 5 minutes. Rest periods in which a crosshair remained on the screen for 10 seconds occurred at the beginning and end of each run and four times at irregular intervals during each run. Stimulus presentation and response logging were completed using E-prime (Psychology Software Tools, Pittsburgh, PA).

Scanning Procedure and fMRI Data Preprocessing

Scanning Procedure—Scanning was completed in a 1.5-T ACS-NT Powertrack 6000 MRI scanner (Philips Medical Systems, Inc., Bothell, WA) using body coil transmission and quadrature end-capped head coil reception. T1-weighted high-resolution anatomic images were acquired for each participant and used in the creation of cost function masks. For the functional images, coronally oriented volumes were acquired every 2.5 seconds using single-shot echo planar imaging (EPI) 64×64 voxel matrix, $3.59 \times 3.59 \times 4.5$ -mm voxels, TE = 40 ms, and flip angle of 90° . Each volume was composed of forty-one 4-mm thick, interleaved slices (0.5-mm interslice gap). For a subset of participants (eight in the ADHD

group, five in the TD group), initial scanning parameters did not permit full coverage of the brain during EPI; for these subjects, each volume was composed of thirty-four 4.5-mm slices, and the posterior occipital lobe and a small region of the posterior aspect of the cerebellum were not captured.

Postacquisition Processing—Postacquisition image processing was carried out using MATLAB version 7.1 (Mathworks, Inc., Natick, MA) and SPM2 (Wellcome Department of Imaging Neuroscience, <http://www.fil.ion.ucl.ac.uk/spm/software/spm2>).

fMRI Data Preprocessing—Functional DICOM images were converted to Analyze format. Due to susceptibility artifacts present in EPI acquisition, cost function masking was used to optimize normalization to the EPI template.³² The functional volumes were time corrected to adjust for within-volume time of acquisition differences³³ and spatially realigned to the location of the first image in the time series. For each subject, a mean functional volume was created and coregistered to the subject's high-resolution anatomic image to permit optimal identification of susceptibility artifact. Masks were hand drawn using MRIcro (<http://www.sph.sc.edu/comd/rorden/mricro.html>). Functional images were normalized to the MNI EPI template using a 12-parameter affine transformation and 16 nonlinear deformations. The functional images were then smoothed³³ using a gaussian kernel of $6 \times 6 \times 6$ mm.

Head Motion Analysis—Head movement was measured using the translational (x , y , and z) and rotational (yaw, pitch, roll) realignment parameters for each subject as reported by SPM2 during spatial realignment. No subject demonstrated >3.5 mm of translational head movement in any direction, which is less than the size of one acquisition voxel ($3.59 \times 3.59 \times 4.5$ mm). The root mean square of translational movement was equivalent between the ADHD and TD groups ($t_{48} = 0.08$, $p = .93$), with the group root mean square mean and SD values as follows: ADHD, 0.28 ± 0.15 mm; control, 0.28 ± 0.17 mm. No subject demonstrated $>2^\circ$ of rotational head movement in any direction.

fMRI Data Analysis

SPM2 was used to fit general linear models³⁴ to the voxelwise time course data and to examine the quality and properties of the fitted models. Voxelwise t maps were constructed for each participant as a first-level analysis. Go or No-go associated activation in each voxel was contrasted with an implicit baseline of general task activation, including null time between trials and four 10-second rest breaks but excluding activation linked to five model regressors (Go, No-go, commission error, omission error, and anticipatory Go response <200 ms after stimulus presentation). The amplitude maps were then carried to a second-level analysis to test for significant group effects using gaussian random-field theory. The two-level strategy described is equivalent to a random-effects analysis in that it provides a representative activation for a given population that is dominated by intersubject rather than interscan variance.³⁵

Unless otherwise mentioned, all of the group analyses are reported at a voxel threshold of $p = .001$ and a cluster extent of 72 voxels, achieving a multiplicity-corrected statistical threshold of $p = .05$, determined by AlphaSim (<http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim>) after running 1,000 Monte Carlo simulations approximating random noise. The location of voxels significantly associated with each analysis was determined by summarizing local maxima separated by at least 8 mm and converting maxima from MNI to Talairach coordinate space using formulas provided by Matthew Brett (<http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml>). Coordinates were assigned

neuroanatomic and cytoarchitectonic labels using the Talairach Atlas36 and were reviewed by a neurologist (S.H.M.).

Single-group, whole-brain, random-effects analyses were accomplished in SPM2 by executing one-sample t tests on individual subjects' Go versus baseline and No-go versus baseline contrast images. Between-group two-sample t tests were performed with region of interest (ROI) analyses using the MarsBaR ROI toolbox (<http://marsbar.sourceforge.net>) to compare mean voxel values within the specified ROIs for the ADHD and TD groups. ROIs included all of the regions from the corrected TD or ADHD single-group maps for the corresponding contrast (Go or No-go); overlapping clusters in the TD and ADHD groups (e.g., primary motor cortex in Go contrasts) were combined into one ROI using the union of the clusters from the two groups. Bonferroni correction was made for the total number of ROIs examined across Go and No-go contrasts.

Brain-behavior correlations identifying regions of Go- or No-go-associated activation correlated with CV were completed for each group using linear regression models in SPM2; between-group differences in correlations between activation and CV were also identified in this manner. Clusters from thresholded group maps were selected as ROIs to further examine differences in correlation with CV between groups using analysis of covariance. To permit identification of areas of No-go-related brain activation correlating with ISV in children with ADHD and exploration of our a priori hypothesis regarding the role of prefrontal activation during response inhibition in children with ADHD, for this condition, prefrontal ROIs were identified from the ADHD group map at the lower threshold used in the previous examination of neural correlates of CV in TD children (uncorrected $p = .001$, 5 voxels).¹³ The clusters used to represent these prefrontal ROIs were acquired from the group map thresholded at uncorrected $p = .01$ in order to increase the validity of between-group comparisons within this ROI by examining differences over a larger number of voxels.

RESULTS

Behavioral Results

There was no significant difference between TD and ADHD groups for commission errors ($t_{48} = 0.32$, $p = .75$), omission errors ($t_{48} = -0.05$, $p = .96$), reaction time ($t_{48} = 0.78$, $p = .44$), and CV ($t_{48} = 1.01$, $p = .32$). See Table 1 for subject demographics and behavioral data. CV correlated with commission errors for the entire group (TD + ADHD) ($r_{48} = 0.45$, $p = .001$) and for the ADHD group ($r_{23} = .51$, $p = .01$). For the TD children, a strong trend toward correlation existed ($r_{23} = .37$, $p = .07$).

fMRI Results

Neural Correlates of the Go/No-go Task—Findings for within- and between-group analyses of activation associated with Go and No-go events were consistent with our findings previously reported from a cohort largely composed of the same subjects used in the current analyses.²¹ Briefly, no between-group differences were identified for Go-related activation. For No-go-related activation, ROI analyses revealed TD > ADHD activation in the pre-SMA (central voxel coordinates 0, 10, 47; cluster size = 1,495 voxels; $t_{48} = 2.99$, $p < .05$), right occipital cortex (BA19; central voxel coordinates 4, -55, -9; cluster size = 214 voxels; $t_{48} = 3.70$, $p = .004$), and superior medial cerebellum (central voxel coordinates 38, -70, -2; cluster size = 651 voxels; $t_{48} = 3.24$, $p < .05$).

Neural Correlates of RT Variability

Go within-group analyses: For the TD group, no regions of activation correlated with CV at the corrected threshold. For the ADHD group, CV positively correlated with Go-related activation in the right precentral gyrus (BA4/6), right inferior parietal lobule (BA40), and left postcentral gyrus (BA1/2; increased activation associated with more ISV); there were no regions with which CV was negatively correlated.

Go between-group analyses: In whole-brain analyses, there was a significant between-group difference in correlation between CV and Go-related activation in the left postcentral gyrus (BA1/2) extending to the inferior parietal lobule (BA40; Fig. 1, Table 2). For activity in this region, children with ADHD demonstrated a positive correlation with CV ($r_{23} = 0.55$, $p < .01$; increased activation associated with more ISV), whereas TD children demonstrated a negative correlation ($r_{23} = -0.74$, $p < .001$; increased activation associated with less ISV).

ROIs for further examining between-group differences in CV correlates of Go-associated activation included clusters of activation correlating with CV for the ADHD group (right precentral gyrus, right inferior parietal lobule, left postcentral gyrus). Significant between-group differences existed for each of these clusters after correction for multiple comparisons (Table 2). Differences in the left postcentral gyrus were demonstrated in whole-brain analysis. For activation in the right inferior parietal lobule (BA40), the ADHD group demonstrated a positive correlation with CV, and the TD group demonstrated no correlation (effect by diagnosis $t_{45} = 4.0$, $p < .001$). For right precentral gyrus (BA4/6) activation, again the ADHD group demonstrated a positive correlation with CV, and the TD group demonstrated no correlation (effect by diagnosis $t_{45} = 3.43$, $p < .01$).

No-go within-group analyses: For the TD group, No-go activation in the caudate was positively correlated with CV (increased activation associated with more variability). For the ADHD group, activation in the right inferior parietal lobule (BA40, extending anteriorly to BA6) positively correlated with CV. No regions in which No-go-associated activation negatively correlated with CV were identified for either group.

No-go between-group analyses: In whole-brain analyses, a significant between-group difference was identified in correlation of CV with No-go activation in the pre-SMA (Fig. 2, Table 2). The TD group demonstrated a negative correlation between CV and pre-SMA activation ($r_{23} = -0.79$, $p < .001$, increased activation associated with less ISV), whereas the ADHD group demonstrated a positive correlation ($r_{23} = 0.42$, $p < .05$, increased activation associated with more ISV).

ROIs for further examining between-group differences in correlation between CV and No-go-associated activation included regions identified in within-group analyses (caudate, right BA40). In addition, prefrontal ROIs in which CV negatively correlated with No-go activation in the ADHD group were identified, at the reduced threshold of $p < .001$ with cluster extent of 5 voxels, in the right and left superior frontal gyri (BA8 and BA9, respectively). Significant between-group differences in correlation between activation and CV existed for all four ROIs after correction for multiple comparisons. In the caudate, TD children showed a positive correlation between No-go activation and CV whereas the children with ADHD showed no correlation (effect by diagnosis $t_{45} = -4.05$, $p < .001$; Fig. 3A). In the right inferior parietal lobule, children with ADHD showed a positive correlation between No-go activation and CV, whereas the TD children showed no correlation (effect by diagnosis $t_{45} = 3.70$, $p < .001$). Within the right superior frontal gyrus (BA8), ADHD children showed a negative correlation between No-go activation and CV ($r_{23} = -0.67$, $p < .001$, increased activation associated with less ISV); for the TD children, activation was not

correlated with CV (effect by diagnosis $t_{45} = -3.63$, $p < .001$; Fig. 3B). For the left BA9 ROI, activation was not correlated with CV within the TD group. Negative correlation between activation and CV in the ADHD group was driven by an outlier; with the outlier removed, there was no longer correlation within the ADHD group nor a between-group difference. Table 2 summarizes regions of significant between-group differences in correlation of No-go-related activation and CV.

DISCUSSION

The differences in neural mechanisms underlying simple, overlearned response selection and inhibition in TD children and children with ADHD were studied by examining correlates of ISV in performance, as measured by the CV, during a simplified Go/No-go task. Consistent with previous reports, variability in performance was correlated with the rate of inhibitory failure within this cohort, supporting the notion that both reflect related aspects of response control. Dissociation was noted between TD children and children with ADHD with regard to amount of ISV associated with activation of motor and premotor systems for both simple motor responding (Go events) and response inhibition (No-go events). During response inhibition, an additional dissociation was noted in the amount of ISV associated with prefrontal activation.

During simple, overlearned motor responding, in TD children, increased activation of the left primary sensory cortex was associated with less ISV, whereas in children with ADHD, activation of this region was associated with more ISV. Children with ADHD additionally demonstrated more ISV in association with activation of the right inferior parietal lobule, a region important for visuomotor task performance,^{37,38} and right premotor/motor cortex. This suggests that TD children who rely on sensorimotor networks demonstrate less ISV during a simple motor task, whereas children with ADHD relying on these same networks demonstrate more ISV; this finding supports previously identified ADHD-associated anomalies in systems responsible for motor execution.^{39–41}

During response inhibition, activation of the pre-SMA by TD children was associated with less ISV. Contrary to our hypothesis, and in contrast to the findings for TD children, in children with ADHD increased pre-SMA activation was associated with more ISV. The pre-SMA plays an important role in response preparation and selection (including selecting not to respond),^{19,42,43} and in TD children, the relation between pre-SMA activation and CV is consistent with that found in previous studies demonstrating an association between ISV and pre-SMA function.^{13,31,44,45} We observed a second dissociation between groups with regard to activation of prefrontal-subcortical circuits and ISV; in children with ADHD, less ISV was associated with prefrontal (superior frontal gyrus) activation, whereas in TD children, ISV increased with increased activation of the caudate, which is in circuit with the prefrontal cortex.

Our finding in TD children that premotor/motor circuit activation is associated with more consistent motor performance than is prefrontal circuit activation can be appreciated in everyday life. For example, young baseball players are often instructed to “throw, don’t aim,” when learning to pitch. This adage is meant to teach pitchers to rely on more automatic movements, guided by rehearsed motor patterns (driven by pre-motor/motor circuits), rather than to overthink the movements necessary for each pitch, calling into play prefrontal systems. “Just throwing the ball” (reliance on premotor systems) is thought to lead to more consistent and accurate pitches, whereas too much aiming (use of higher order prefrontal systems) detracts from the learned motor pattern of pitching and results in more erratically delivered pitches. The current results support this notion that for TD children, “just throwing” (use of premotor systems) is associated with less variability in the

performance of a task in which the cognitive demands were minimized, thereby allowing for reliance on more automatic selection, whereas “aiming” (using higher order prefrontal systems) is associated with more variability in performance. For children with ADHD, however, these associations do not appear to hold true. In fact, the children with ADHD who performed with less variability demonstrated more “aiming” or use of higher order cognitive resources, whereas the children with ADHD who used the “just throwing” approach, with more activation of the pre-SMA, demonstrated more variation in task performance.

The current data suggest a functional anomaly of the pre-SMA in ADHD; those children with ADHD who activated the pre-SMA in association with response inhibition paradoxically had more variability in response. This adds to the growing evidence of abnormalities of the pre-SMA and other premotor regions in ADHD with regard to structure^{23,24} and function.^{21,22} In addition, our data suggest that when faced with a simplified motor task minimizing extraneous cognitive demands, the recruitment of prefrontal circuits associated with higher order cognitive control is a compensatory mechanism by which some children with ADHD are able to achieve more consistent performance despite abnormalities in pre-SMA activation. Based on data from TD children, in general, this strategy of “aiming,” or using prefrontal regions associated with higher order cognitive function, in the context of a task allowing for more automatic response selection/inhibition, is maladaptive in that it is associated with higher CV. The ADHD-associated anomalies of the pre-SMA and alternative reliance on other prefrontal resources, which typically represents a less automatic strategy, may explain the common finding of increased ISV among children with ADHD. In addition, use of prefrontal resources as a compensatory mechanism in this context may preclude the use of those prefrontal resources for higher order, more novel executive functions with which children with ADHD often struggle. Further examination of the neural correlates of response inhibition and their relation to CV during performance of tasks with additional cognitive/behavioral demands would be helpful in more fully characterizing neural activation patterns associated with response inhibition and ISV in ADHD. Likewise, examination of the neural correlates of ISV in children with ADHD with impaired response inhibition compared to their TD peers would be useful for understanding the applicability of these findings to all children with ADHD. In addition, given comorbidity of ODD in the current ADHD group but not the TD group, examination of larger groups of children with ADHD with and without ODD may further elucidate the contribution of ODD, if any, to the current findings. Last, as other authors have demonstrated delayed cortical maturation⁴⁶ and an association between cortical thickness and clinical outcomes in ADHD,²⁴ longitudinal examination of the neural correlates of response inhibition and ISV may add further information regarding the ADHD-associated functional anomalies reported here.

In conclusion, during simple, overlearned motor response selection/inhibition, recruitment of premotor/motor systems, including the pre-SMA, is associated with less variability in task performance in TD children, whereas recruitment of the same regions is associated with more variability in task performance in children with ADHD. In contrast, children with ADHD who recruit prefrontal brain regions associated with higher order cognitive processes demonstrate less variable performance, whereas TD children with similar recruitment patterns demonstrate more variable performance. These findings add to the increasing evidence that dysfunction of premotor/motor systems in children with ADHD may contribute to problems with motor and behavioral control, including increased variability and impaired response inhibition. Furthermore, these data suggest that those children with ADHD who are able to achieve performance equivalent to that of their TD peers rely on compensatory strategies eliciting increased cognitive control. Unlike TD children, some children with ADHD may improve their performance when they “aim” and don’t “just throw.”

Acknowledgments

This study was supported by the National Institute of Neurological Disorders and Stroke: K02NS04485 (S.M.), R01NS047781 (S.M.); the National Institute of Child Health and Human Development: K12HD001097 (S.S.), P30HD24061 (Mental Retardation and Developmental Disabilities Research Center); and Johns Hopkins General Clinical Research Center M01RR00052.

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Fig. 1.

Between-group differences in neural correlates of intrasubject variability (ISV) for Go-related activation. A, Sectional maps showing area in the left primary sensory cortex (BA1/2) in which correlation between the coefficient of variation (CV) and Go-associated activation was significantly different between typically developing (TD) and attention-deficit/hyperactivity disorder (ADHD) groups. Neurological convention is used (i.e., right = right hemisphere). B, Plot of the percentage of signal change in the region highlighted in (A) during Go-associated activation versus CV. Typically developing (TD) children demonstrate a negative correlation (increased activation associated with less ISV), whereas children with ADHD show a positive correlation (increased activation associated with more ISV). BA = Brodmann's area.

Fig. 2.

Between-group differences in neural correlates of intrasubject variability (ISV) for No-go-related activation. A, Sectional maps showing area in left pre-supplementary motor area (BA6) in which correlation between the coefficient of variation (CV) and No-go-associated activation was significantly different between typically developing (TD) and attention-deficit/hyperactivity disorder (ADHD) groups. Neurological convention is used (i.e., right = right hemisphere). B, Plot of the percentage of signal change in the region highlighted in (A) during No-go-associated activation versus CV. TD children demonstrate a negative correlation between activation and CV (increased activation associated with less ISV), whereas children with ADHD show a positive correlation (increased activation associated with more ISV).

Fig. 3.

Between-group differences in neural correlates of intrasubject variability (ISV) for No-go-related activation within subcortical and prefrontal regions of interest (ROIs). In the (A) caudate, TD children demonstrate a positive correlation between the coefficient of variation (CV) and No-go-associated activation (increased activation associated with more ISV), whereas children with ADHD show no correlation between CV and caudate activation. In the (B) right superior frontal gyrus (BA8), TD children demonstrate no correlation between CV and No-go-related activation, whereas children with ADHD demonstrate a negative correlation (increased activation associated with less ISV). For both ROIs, significant between-group difference exists, $p < .001$.

TABLE 1

Subject Characteristics and Performance Data

	ADHD (<i>n</i> = 25)	Control (<i>n</i> = 25)	<i>p</i>
Sex, males/females	15/10	14/11	.77
Handedness, right/left	21/4	23/2	.39
Age, y	10.7 ± 1.2	10.6 ± 1.4	.96
IQ	114.7 ± 12.6	112.7 ± 12.5	.58
% Commission errors	23.25 ± 14.2	22.06 ± 11.3	.75
% Omission errors	3.54 ± 3.9	3.60 ± 5.3	.96
Reaction time, ms	449.4 ± 117.2	424 ± 111.5	.44
Coefficient of variation	0.35 ± 0.08	0.32 ± 0.08	.32

Note: Data are provided as mean ± SD, unless otherwise specified.

TABLE 2
Regions of Significant Between-Group Differences in Correlation Between Activation and CV

Region	BA	x	y	z	Hem	T	Voxels	TD		ADHD		Dx by CV	
								r	t	r	t	p	p
Go													
Whole-brain analysis	Postcentral gyrus	1/2	-59	-25	45	L	4.83	158	-0.74***	0.55**	5.12	<.0001	<.0001
ROI analysis	Postcentral gyrus	1/2	-59	-25	45	L		89	-0.51**	0.63***	4.73	<.0001	<.0001
	Inferior parietal lobule	40	50	-30	53	R		105	0.06 (NS)	0.72***	4.00	<.001	<.001
	Precentral gyrus	4/6	63	-2	33	R		124	0.06 (NS)	0.65***	3.43	<.01	<.01
No-go													
Whole-brain analysis	Medial frontal wall	6	-12	5	66	L	4.72	95	-0.79***	0.42*	5.15	<.0001	<.0001
ROI analysis	Caudate		14	5	16	R		215	0.68***	0.10 (NS)	-4.05	<.001	<.001
	Inferior parietal lobule	40	59	-26	33	R		182	-0.06 (NS)	0.67***	3.7	<.001	<.001
	Superior frontal gyrus	8	18	26	45	R		182	0.26 (NS)	-0.67***	-3.63	<.001	<.001

Note: All coordinates are in Talairach space. BA = Brodmann's area; Hem = hemisphere; r = correlation coefficient (for activation within entire cluster); TD = Dx by CV = diagnosis by coefficient of variation effect; NS = not significant; ROI = region of interest.

*
p < .05

**
p < .01

p < .001.