

Atypical Motor and Sensory Cortex Activation in Attention-Deficit/Hyperactivity Disorder: A Functional Magnetic Resonance Imaging Study of Simple Sequential Finger Tapping

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Background: Attention-deficit/hyperactivity disorder (ADHD) has been shown to be associated with anomalous motor development, including excessive overflow movements. The neurological basis of these deficits has not been established. Functional magnetic resonance imaging (fMRI) was used to determine whether differences in brain activation during sequential finger tapping are present in children with ADHD compared with typically developing control subjects.

Methods: Twenty-two right-handed children between 8 and 12 years old, 11 with ADHD and 11 typically developing control subjects closely matched for age and gender, performed self-paced sequential finger tapping during fMRI acquisition.

Results: There were no significant between-group differences in speed of sequential finger tapping. The between-group whole-brain comparison showed greater magnitude of activation for control subjects than children with ADHD in the right superior parietal lobe during both right-handed and left-handed finger tapping. The region-of-interest analysis within Brodmann Area 4 revealed that children with ADHD showed a significantly smaller extent of fMRI activation in the primary motor cortex contralateral to the finger-sequencing hand.

Conclusions: Despite similar speed of sequential finger tapping, children with ADHD showed decreased contralateral motor cortex and right parietal cortex activation during both right-handed finger sequencing (RHFS) and left-handed finger sequencing (LHFS). The fMRI findings suggest that children with ADHD have anomalous development of cortical systems necessary for execution of patterned movements.

Key Words: Attention-deficit/hyperactivity disorder, fMRI, motor, children, frontal, parietal

Children with symptoms of attention-deficit/hyperactivity disorder (ADHD) consistently demonstrate subtle abnormalities on motor examination (Denckla and Rudel 1978; Kadesjo and Gillberg 1998; Mostofsky et al 2003; Piek et al 1999; Szatmari and Taylor 1984). Compared with age-matched typically developing peers, they perform more slowly on timed motor tasks (Denckla and Rudel 1978) with greater variability in speed (Rubia et al 1999b) and greater degree of motor overflow movements (Denckla and Rudel 1978; Mostofsky et al 2003; Szatmari and Taylor 1984). Motor overflow findings in ADHD include excessive mirror movements, which are unintentional movements that mimic the intentional movement being executed on the opposite side of the body.

The subtle motor exam abnormalities in children with ADHD appear to be developmental in nature. Overflow movement during performance of a timed simple motor task is a normal examination finding in a healthy young child. By early school age, motor overflow associated with repetitive motor tasks is markedly decreased in typically developing children (Cohen et al 1967; Denckla and Rudel 1978; Largo et al 2001). However, in

children with ADHD, motor overflow on repetitive motor tasks frequently persists beyond age 9 years, and this finding can help clinicians distinguish children with ADHD from control subjects (Denckla and Rudel 1978). Compared with simple repetitive motor tasks, motor overflow during sequential tasks typically persists longer and with greater interindividual variability; some mirror overflow during sequential finger tapping is still a normal finding up to age 13 years (Denckla 1985).

Motor overflow in children with ADHD suggests impaired or immature automatic inhibition of unintentional movement. Coincidentally, intentional motor control, including response inhibition, is also impaired in ADHD (Mostofsky et al 2001; Ross et al 2000; Rubia et al 1998). We have reported that measures of motor overflow correlate with measures of conscious, effortful response inhibition (Mostofsky et al 2003), which suggests that these two motor control findings in children with ADHD may both represent manifestations of a generalized impairment in the ability to inhibit unwanted movement. Many authors propose that impaired response inhibition contributes to the cognitive and behavioral abnormalities associated with ADHD (Barkley 1997; Denckla and Rudel 1978). Thus, atypical motor development in children with ADHD may be a biomarker for the disorder, appearing to run in parallel with and be closely associated with the behavioral deficits of the disorder. This underscores the value of further investigating the anomalous motor findings in children with ADHD.

The neural correlates of motor overflow in children with ADHD, as investigated using transcranial magnetic stimulation (TMS), include significantly reduced transcallosal (interhemispheric) inhibition in children with ADHD compared with control subjects (Moll et al 2000). Since deficient interhemispheric inhibition is the suspected mechanism for age-appropriate mirror overflow (Cincotta et al 2002; Danek et al 1992; Mayston et al 1999), the TMS data suggest a common physiological/matura-

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tional basis for mirror overflow in young typically developing children and in children with ADHD.

Functional neuroimaging has been used to investigate the neural correlates of motor control in children with ADHD. Thus far, functional magnetic resonance imaging (fMRI) of ADHD has primarily been applied to investigations of behavioral and cognitive tasks related to motor response preparation—in particular, measures of response inhibition such as Go/No-Go and Stop-Signal tasks (Durston et al 2003; Rubia et al 1999a; Vaidya et al 1998). Differences in fMRI activation associated with motor execution between subjects with and without ADHD have also been reported, but the relatively complex tasks used in these studies required subjects to integrate visual or auditory cues to maintain an experimenter-defined pace or to modify the timing or force of finger movements (Ben-Pazi et al 2003; Pitcher et al 2002; Rubia et al 1999b).

To our knowledge, fMRI has not been used to examine motor cortex activation in children with ADHD during self-paced sequential finger tapping. Self-paced sequential finger tapping has been used with fMRI to examine the neural correlates of motor execution in healthy adults (Allison et al 2000; Baraldi et al 1999) and in children. Findings in children with unilateral brain lesions reveal greater bilateral motor cortex activation compared with typically developing children (Cioni et al 2001; Vandermeeren et al 2003). Therefore, this approach appears to be well suited to investigating the neural correlates of subtle motor abnormalities observed in children with ADHD.

We hypothesize that mirror overflow and other subtle motor abnormalities in children with ADHD are manifestations of atypical neuronal activity, particularly in the primary motor cortex. To test this hypothesis, we compared fMRI activation during self-paced sequential finger tapping in children with ADHD and age- and gender-matched control subjects. Group differences in activation were measured using whole-brain analysis and a region-of-interest (ROI) analysis within Brodmann area (BA) 4 to test the hypothesis that children with ADHD would show different activation profiles in primary motor cortex.

Methods and Materials

Participant Selection

Fourteen children with ADHD and 13 age- and gender-matched typically developing children met criteria for this study. Three ADHD subjects and two control subjects had excessive motion during scanning, so that 11 children with ADHD (mean age = 10.4 years, SD = 1.2) and 11 control subjects (mean age = 10.4 years, SD = 1.4) were included in the analyses. Each group consisted of eight boys and three girls. All subjects were right-handed based on the Physical and Neurological Exam for Subtle Signs (Denckla 1985).

Participants were recruited from several sources, including outpatient clinics at the Kennedy Krieger Institute, advertisements placed with community-wide service groups, volunteer organizations, local schools and medical institutions, and by word of mouth. Potential subjects were initially screened using rating scales and questionnaires completed by each child's parents and a selected teacher. Parents completed the ADHD Rating Scale IV-Parent Version (DuPaul et al 1998) and the Conners' Parent Rating Scale-Revised (Conners et al 1998); teachers completed the Teacher Version of the same two scales.

Subjects were considered to screen positive for ADHD if they met criteria on at least one parent and one teacher rating scale. The diagnosis of ADHD was confirmed by a child neurologist (S.H.M.). A structured parent interview, the Diagnostic Interview for Children

and Adolescents (DICA-IV) (Reich 2000), was administered by at least a master's level psychologist used to confirm the diagnostic subtype of ADHD and to rule out any comorbid psychiatric diagnoses. Two participants met criteria for ADHD, predominantly inattentive type; nine participants met criteria for ADHD, combined type.

Potential subjects were excluded if they met criteria for conduct disorder, mood disorder, generalized anxiety disorder, separation anxiety disorder, or obsessive-compulsive disorder. One subject with combined-type ADHD met criteria for oppositional defiant disorder. Children were also excluded from this study for full-scale intelligence quotient (IQ) less than 85 on the Wechsler Intelligence Scale for Children, Third Edition (WISC-III) (Wechsler 1991) or for suspected comorbid reading disability, based on either parent report or discrepancy between full-scale IQ on the WISC-III and the reading composite from the Wechsler Individual Achievement Test (WIAT) (Psychological Corporation 1992). None of the subjects with ADHD had any history of other neurological disorders, including Tourette syndrome. Eight of the children with ADHD were being treated with stimulant medication (five with methylphenidate and three with dextroamphetamine), and their parents were requested to withhold the medication the day of and the day prior to testing. Children with ADHD were not included in the study if they were taking any other psychoactive medications for ADHD or any other neuropsychiatric disorder.

Children were included in the control group only if they did not meet ADHD diagnostic criteria on any of the administered rating scales and questionnaires. None of the control subjects had any history of neurological or psychiatric disorders as determined using the DICA-IV. None of the control subjects were taking any psychoactive medications.

This study was approved by the Johns Hopkins Medical Institutional Review Board. For all subjects, written consent was obtained from a parent/guardian and assent was obtained from the participating child.

Motor Assessment

The Physical and Neurological Examination for Soft Signs (PANESS) (Denckla 1985) was used to assess motor function outside of the scanner. Although the examiner was not specifically blinded to the participant's diagnosis, the use of this structured, scripted assessment tool requires objective identification of motor findings. An examiner documented the presence or absence of motor overflow and the time to complete different categories of motor tasks, including stressed gaits, balancing tasks, repetitive timed movements, and patterned timed movements, to produce a composite total PANESS score. The information most pertinent to this analysis was timed sequential finger tapping by successive finger opposition, i.e., tapping each finger on a hand to the thumb in a fixed sequence (index-middle-ring-little). The time to complete 20 taps (i.e., five complete sequences) for each hand was recorded using a stopwatch. The examiner also recorded presence or absence of motor overflow during this timed task.

fMRI Finger-Sequencing Paradigm

Subjects performed a sequential finger-tapping task during scanning. For both right-handed finger sequencing (RHFS) and left-handed finger sequencing (LHFS), subjects were asked to successively tap each finger on a hand to the thumb in a fixed sequence (index-middle-ring-little) and to repeat the sequence until they received their next visual instruction. Right-handed

finger sequencing and LHFS alternated with periods during which subjects were instructed to rest. The rest contrast was included so as to allow comprehensive examination of brain activation associated with self-paced sequential finger tapping.

Immediately prior to entering the scanner, subjects were instructed how to perform the finger-sequencing task. The proper sequence of movements was demonstrated for the participant, who then demonstrated that he/she understood the instructions by executing the correct movements with each hand. Care was taken not to count the finger taps or name the fingers aloud during the training. Just before the acquisition of images, the subjects engaged in a short practice session in which they were shown the same screens that would be presented during the actual task (“Tap your Right Hand,” “Tap your Left Hand,” and “Rest”). During this practice session, they received verbal feedback and encouragement to do the correct sequence of movements with the correct hand and to continue repeating the sequence until the screen changed.

The fMRI task consisted of a 30-second block of rest followed by four identical 90-second cycles of 30 seconds of one hand tapping followed by 30 seconds of the other hand tapping and 30 seconds of rest for a total scan time of 390 seconds. The starting hand was counterbalanced across subjects. Paradigm programming and display were done using E-Prime (Psychology Software Tools Inc., Pittsburgh, Pennsylvania) running on a Windows operating system (Microsoft, Redmond, Washington). During the scan, the computer-controlled instructions were projected on a screen at the head of the scanner and viewed by the subjects via a 45°-angled mirror affixed to the magnetic resonance imaging (MRI) head coil. Subjects were prompted with the visual instructions (“Tap your Right Hand,” “Tap your Left Hand,” and “Rest”) that remained on the screen throughout each 30-second time period. During scanning, finger movements were video recorded and the videotapes later reviewed to determine the total number of finger taps for each hand.

Scanning Procedure

Scanning was carried out in a 1.5 Tesla ACS-NT Powertrack 6000 MRI scanner (Philips Medical Systems, Inc., Andover, Massachusetts) using body coil transmission and quadrature end-capped head coil reception. Axially oriented volumes were acquired every 3 seconds using single-shot echo planar imaging 64 × 64 voxel matrix, 3.59 × 3.59 × 5.5 mm voxels, echo time (TE) 64 milliseconds, and flip angle 70°. Each volume was composed of 5-mm slices (.5-mm interslice gap) with full-brain coverage for five ADHD subjects and seven control subjects. For the other subjects, scans did not provide whole-brain coverage but were angled to include the cerebellum, lacking only the most anterior/ventral portion of the frontal poles.

fMRI Data Analysis

All postacquisition image processing was carried out using MATLAB (The Mathworks, Inc., Natick, Massachusetts) and SPM99 (Wellcome Department of Imaging Neuroscience, London, England; <http://www.fil.ion.ucl.ac.uk/spm/spm99.html>). Digital Imaging and Communications in Medicine (DICOM) images were converted to Analyze format and then time corrected to adjust for within-volume time of acquisition differences (Calhoun et al 2000), spatially realigned to the location of the mean image, and then smoothed (Friston et al 1996) using a Gaussian kernel that was half the resolution of the acquisition matrix (7 × 7 × 11 mm³). The whole-brain data were spatially normalized to Montreal Neurological Institute (MNI)-labeled space (Evans 1993) using a full-brain template; the partial-brain data were spatially normalized to a

modified MNI-labeled template to account for the absence of data in the most anterior ventral portion of the frontal poles. All of the data was resampled into voxels of 2 mm³.

SPM99 was used to construct and test the fit of the image data to a general linear model (Friston et al 1995) that specifically tested for and created statistical maps corresponding to the time course of RHFS in contrast to rest and LHFS in contrast to rest. Voxelwise *t* maps were constructed for each subject as a first level analysis; 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 variance rather than interscan variance (Holmes and Friston 1998). The locations of voxels significantly associated with RHFS (right-rest contrast) and with LHFS (left-rest contrast) were determined for each subject. They were summarized by their local maxima separated by at least 8 mm and the maxima converted from MNI to Talairach coordinate space (Medical Research Council-Cognition and Brain Sciences Unit, Cambridge, England; <http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml>). These coordinates were assigned neuroanatomic and cytoarchitectonic labels using the Talairach Daemon (Research Imaging Center, University of Texas Health Science Center at San Antonio, Texas; <http://ric.uthscsa.edu/resources/body.html>) and were reviewed by a neurologist (S.H.M.).

Head Motion Analysis

Head movement was measured by computing the root mean square of the x, y, and z realignment parameters for each subject. These parameters are reported by SPM99 during spatial realignment. Analysis of variance (ANOVA) was used to compare the average root mean square of displacements between ADHD and control groups.

Analysis of subject head motion during scanning showed no significant difference in average displacement between the ADHD and control groups (ADHD mean = .25 ± .2, control mean = .33 ± .6, *p* = .67). None of the subjects demonstrated greater than 3.5 mm of head movement in any direction, which is less than the size of one acquisition voxel (3.59 × 3.59 × 5.5 mm).

Whole-Brain Random Effects Analysis

Whole-brain random effects analyses were accomplished in SPM99 by executing one- and two-sample *t* tests on the individual subject's right-rest and left-rest contrast images. The single group contrasts for ADHD and control subjects are reported at uncorrected *p* < .001 with an extent threshold of 84 voxels, which is equivalent to a false-positive rate of .05 over the whole brain (i.e., corrected *p* < .05) based on Monte Carlo simulations run using AlphaSim (National Institute of Mental Health, Bethesda, Maryland, http://afni.nimh.nih.gov/afni/about/afni_summary/view?searchterm=alphasim). The same threshold was applied to the between-group contrast images with results reported for the “control greater than ADHD” activation. The contrast image for “ADHD greater than control” activation did not reveal any clusters at the threshold of corrected *p* < .05.

Due to the nature of the between-group contrasts, potential differences that appear to be associated with “control greater than ADHD” activation during tapping could actually be due to differences in activation during the baseline “rest” in the opposite direction (“ADHD greater than control”). To determine the most appropriate interpretation of the results of the between-group contrasts, a mask of those results was made and applied to the

within-group contrast images for both tapping compared with rest (right-rest and left-rest) and rest compared with tapping (rest-right and rest-left). The number of active voxels present in the masked region at the same threshold used during whole-brain analysis ($p < .001$) was determined to see whether the tapping or rest condition was associated with the active voxels.

Region-of-Interest Analysis

Regions-of-interest corresponding to BA 4 and putamen were defined using the Wake Forest University PickAtlas (Wake Forest University School of Medicine, Winston Salem, North Carolina; http://www.fmri.wfubmc.edu/downloads/WFU_PickAtlas_User_Manual.pdf). The voxel count for each ROI was defined as the number of voxels within the ROI that were at or above a height of activation determined by a corrected threshold of $p < .05$: this will be referred to as the extent of activation. The voxel counts for each individual were recorded from their own right-rest and the left-rest contrast images. The individual voxel counts were then analyzed using a Mann-Whitney test to determine whether there were any between-group differences. A nonparametric test was chosen for these comparisons because the findings were not normally distributed.

To quantify the magnitude of activation for each individual during both LHFS and RHFS, we summed the area under the curve for the fitted, epoch-related response at the peak voxel of activation in the contralateral motor cortex. The area under the curve was determined by summing positive values of the fitted response for the appropriate hand on the interval from 0 to 60 seconds. We then used a two-sample t test to determine whether there were any between-group differences.

To ensure that there was no systematic difference in the localization of motor cortex activation between groups, we compared the location of foci within the motor cortex to Talairach coordinates for both left and right hand primary motor cortex locations that have been previously reported (Stippich et al 2002). For each individual, we calculated the vector distance from the peak focus of activation to that reported by Stippich et al (2002). We performed between-group two-sample t tests for right hand (ADHD mean distance = 11 ± 4 mm, control mean distance = 9 ± 4 mm, $p = .4$) and left hand (ADHD mean distance = 9 ± 4 mm, control mean distance = 11 ± 4 mm, $p = .1$) to confirm that there was no significant difference between how close each group's peak motor cortex activation during tapping was to a standard for location of hand motor cortex. We also performed a two-sample t test between participants with

full-brain coverage ($n = 12$, 7 control subjects, 5 ADHD subjects) and partial-brain coverage ($n = 10$, 4 control subjects, 6 ADHD subjects) to confirm that this was not associated with a difference in localization of the hand motor cortex. There were no significant differences in localization of hand motor cortex for either right hand (full-brain coverage mean distance = 10 ± 4 mm, partial-brain coverage mean distance = 10 ± 4 mm, $p = .8$) or left hand (full-brain coverage mean distance = 9 ± 3 mm, partial-brain coverage mean distance = 11 ± 4 mm, $p = .08$).

Results

Task Performance

On motor assessment performed outside the scanner, children with ADHD had significantly higher total PANESS scores, indicating a poorer performance on this composite measure of subtle motor abnormalities (ADHD mean score = 21 ± 8 , control mean score = 14 ± 6 ; $p = .03$). A comparison of the presence of motor overflow during sequential finger tapping performed outside the scanner revealed a between-group difference that was not statistically significant. During right-handed finger sequencing, 3 out of 11 children with ADHD showed mirror overflow compared with only 1 out of 11 control subjects (chi-square = 1.2, $p = .3$). During left-handed finger sequencing, there was no difference between groups: 1 child with ADHD and 1 control subject demonstrated mirror overflow (overlapping with those demonstrating overflow during RHFS). There were also no significant between-group differences in time to complete five finger-tapping sequences during either RHFS (ADHD mean = 8.9 seconds \pm 3.0, control mean = 9.1 seconds \pm 3.5; $p = .8$) or LHFS (ADHD mean = 9.6 seconds \pm 3.1, control mean = 9.3 seconds \pm 2.8; $p = .97$).

For analysis of performance during scanning, videotape recordings for 18 (8 control subjects; 10 ADHD subjects) of the 22 study subjects were available for a visual count of the number of individual finger-to-thumb taps. There was no significant difference between the ADHD and control groups either during RHFS (ADHD mean = 60 ± 7 individual taps in each 30-second block, control mean = 63 ± 9 individual taps in each 30-second block; $p = .5$) or LHFS (ADHD mean = 60 ± 11 individual taps in each 30-second block, control mean = 61 ± 9 individual taps in each 30-second block; $p = .9$).

Whole-Brain Within-Group Analyses

As a first step, separate random effects analyses were computed with the individual right-rest (RHFS) and left-rest (LHFS)

Table 1. Control Group

	Right Hand		Left Hand	
	Cluster Size	Coordinates	Cluster Size	Coordinates
	Voxels	x, y, z	Voxels	x, y, z
Primary Sensorimotor Cortex				
Right	560	46, -32, 50	3435	38, -34, 57
Left	2435	-42, -24, 58	341	-48, -34, 53
Cerebellum				
Right	2235	20, -50, 26	91	24, -58, -28
Left	—	—	808	-26, -70, -25
Medial Prefrontal Cortex (BA 32/6)	—	—	131	10, 8, 42

Size and location of suprathreshold clusters; activation at uncorrected $p < .001$ with an extent threshold of 84 voxels, which is equivalent to corrected $p < .05$ (see Methods and Materials for details). Coordinates are in Talairach space. BA, Brodmann area.

Table 2. ADHD Group

	Right Hand		Left Hand	
	Cluster Size	Coordinates	Cluster Size	Coordinates
	Voxels	x, y, z	Voxels	x, y, z
Primary Sensorimotor Cortex				
Right	—	—	957	46, -19, 56
Left	1271	-50, -21, 53	103	-53, -6, 41
Cerebellum				
Right	1369	10, -76, -10	326	16, -91, -4
Left	223	-16, -80, -13	526	-22, -56, -22
			315	-16, -80, -13
Medial Prefrontal Cortex (BA 6)	236	6, 7, 53	209	6, 2, 46

Size and location of suprathreshold clusters; activation at uncorrected $p < .001$ with an extent threshold of 84 voxels, which is equivalent to corrected $p < .05$ (see Methods and Materials for details). Coordinates are in Talairach space. BA, Brodmann area.

contrasts for each diagnostic group (i.e., ADHD and control groups). During RHFS and LHFS, both groups of children demonstrated the expected finding of predominant activation in the contralateral primary sensorimotor cortex and the ipsilateral cerebellum. Additionally, both groups showed supplementary motor area [(SMA)/medial BA 6] activation. The suprathreshold clusters and their locations in Talairach coordinates are listed in Table 1 for control subjects and Table 2 for the children with ADHD. Figure 1 shows the RHFS and LHFS images for each group.

Whole-Brain Between-Group Analysis

Between-group differences were assessed using whole-brain analysis. The control group showed greater magnitude of activation in superior regions of the right parietal lobe during both RHFS and LHFS. Results for the “control greater than ADHD” contrast are reported in Figure 2 and Table 3. There were no suprathreshold activations on the “ADHD greater than control” contrast.

Due to the nature of this between-group contrast, the finding

could reflect either greater activation during tapping in the control group or greater activation during rest in the ADHD group. To determine which interpretation of the results was more appropriate, we compared the number of active voxels on the within-group images in the parietal lobe region of interest that was functionally determined by the “control greater than ADHD” contrasts. For RHFS, the ADHD rest-right image contained 0 voxels versus the control right-rest image, which contained 108 voxels. For LHFS, the ADHD rest-left image contained 6 voxels, while the control left-rest image contained 148 voxels. The findings are therefore more likely to reflect greater activation during tapping in the control group.

Region-of-Interest Analysis

The ROI analysis in BA 4 was then used to test our hypothesis of between-group differences in primary motor cortex activation. During both RHFS and LHFS, the group with ADHD showed a significantly smaller extent of activation in the contralateral

(A) Control Group

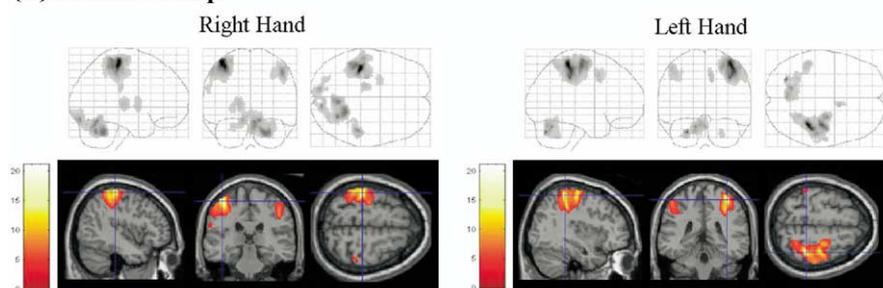
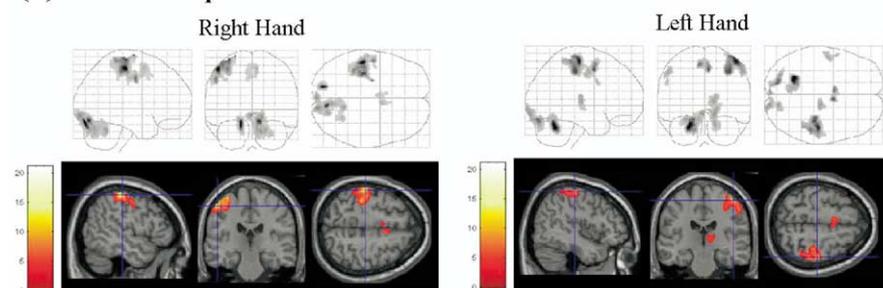


Figure 1. Areas of activation during sequential finger tapping within the (A) control group ($n = 11$) and the (B) ADHD group ($n = 11$) at a threshold equivalent to corrected $p < .05$ (see Methods and Materials, fMRI Data Analysis for details). Color images depict peak sensorimotor cortex activation. ADHD, attention-deficit/hyperactivity disorder; fMRI, functional magnetic resonance imaging.

(B) ADHD Group



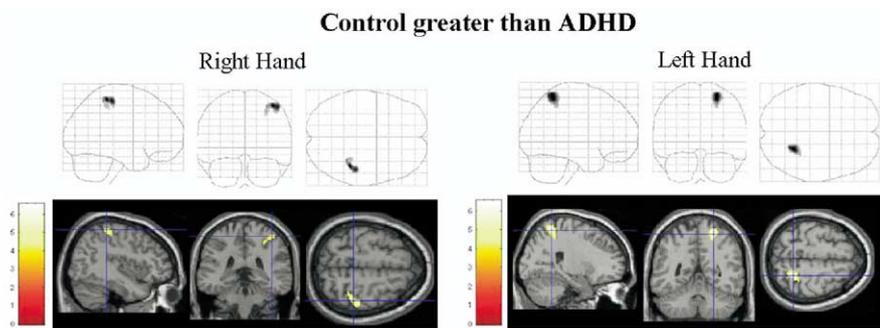


Figure 2. Areas of greater activation among the control group ($n = 11$) compared with the group of children with ADHD ($n = 11$) during sequential finger tapping at a threshold equivalent to corrected $p < .05$ (see Methods and Materials, fMRI Data Analysis for details). Color images depict peak parietal lobe activation. ADHD, attention-deficit/hyperactivity disorder; fMRI, functional magnetic resonance imaging.

primary motor cortex than the control children (see Table 4). These comparisons are graphically depicted in Figure 3. No statistically significant group differences were seen in the ipsilateral motor cortex.

To examine specificity of the BA 4 ROI findings, we repeated the analysis in the putamen. There were no statistically significant between-group differences in extent of activation during RHFS in the ipsilateral putamen ($p = .4$) and contralateral putamen ($p = .1$) nor were there any differences during LHFS in the ipsilateral putamen ($p = .3$) or contralateral putamen ($p = .2$).

To confirm that the between-group differences on the ROI analysis were related to extent rather than magnitude of activation, we quantified the magnitude of activation by summing the area under the curve (AUC) for the fitted, epoch-related response at the peak voxel of activation in the contralateral motor cortex (see Methods and Materials). There were no between-group differences in magnitude of activation for either RHFS (ADHD mean AUC = 397 ± 227 , control mean AUC = 344 ± 127 , $p = .5$) or LHFS (ADHD mean AUC = 393 ± 172 , control mean AUC = 307 ± 155 , $p = .2$).

Discussion

This study found several areas of differential fMRI activation between children with ADHD and control subjects. Findings of anomalous motor development have been consistently reported in children with ADHD (Denckla and Rudel 1978; Kadesjo and Gillberg 1998; Mostofsky et al 2003; Piek et al 1999; Szatmari and Taylor 1984) and we hypothesized that children with ADHD would show differences in fMRI activation of primary motor cortex during performance of a self-paced sequential motor task. The results of the ROI analysis in primary motor cortex (BA 4) support our hypothesis; we found a smaller extent of activation in children with ADHD in the contralateral primary motor cortex for both right- and left-handed finger sequencing. Use of whole-brain analysis to broaden our perspective on between-group differences in neural activation during this simple motor task did not replicate the primary motor cortex findings but instead revealed a decreased magnitude of activation in right superior

parietal cortex in children with ADHD compared with control subjects.

The finding of greater extent of activation in the contralateral primary motor cortex in control subjects compared with children with ADHD is consistently observed during both right-handed and left-handed sequential finger tapping. We interpret this to be a true difference in extent of activation, since our measure of magnitude of activation in this region (the area under the average epoch time course curve) was not significantly different between groups. To make sure that control subjects were not activating with greater extent over all brain regions, the ROI analysis was completed in a subcortical, motor-related region, the putamen; there were no between-group differences in either the right or left putamen during LHFS and RHFS.

The greater extent of activation in the contralateral motor cortex among control subjects suggests that the children with ADHD are utilizing less of the primary motor cortex than control subjects to perform this simple motor task. In the face of equivalent speed of tapping, the smaller extent of activation in the children with ADHD could be interpreted as indicating greater efficiency of motor cortex activity in ADHD, i.e., that they are able to use fewer neurons than control subjects to accomplish the task. However, this interpretation is not consistent with the typically slower, less rhythmical and therefore less efficient motor performance observed in studies of children with ADHD (Denckla and Rudel 1978; Mostofsky et al 2003; Szatmari and Taylor 1984) nor the fact that our group of children with ADHD showed poorer performance on a standardized motor examination than did the group of control subjects.

Alternatively, this finding might help to explain why children with ADHD generally demonstrate greater mirror overflow movements than do their typically developing peers (Denckla and Rudel 1978; Mostofsky et al 2003; Szatmari and Taylor 1984). Transcranial magnetic stimulation evidence suggests impaired interhemispheric inhibition in children with ADHD compared with control subjects (Moll et al 2000). Therefore, one possible explanation for finding a smaller extent of activation in the contralateral primary motor cortex in ADHD is that it represents

Table 3. Control > ADHD

	Right Hand		Left Hand	
	Cluster Size	Coordinates	Cluster Size	Coordinates
	Voxels	x, y, z	Voxels	x, y, z
Right Parietal Lobe	175	42, -32, 57 (BA 40) 32, -32, 50 (BA 3)	312	24, -46, 58 (BA 7)

Size and location of suprathreshold clusters; activation at uncorrected $p < .001$ with an extent threshold of 84 voxels, which is equivalent to corrected $p < .05$ (see Methods and Materials for details). Coordinates are in Talairach space. ADHD, attention-deficit/hyperactivity disorder; BA, Brodmann area.

Table 4. fMRI Region-of-Interest Analysis

	ADHD	Control	Mann-Whitney
Contralateral			
Left Motor Cortex During Right Finger-Sequencing	130 (94)	223 (98)	$p = .03^a$
Right Motor Cortex During Left Finger-Sequencing	165 (95)	306 (76)	$p = .0007^a$
Ipsilateral			
Right Motor Cortex During Right Finger-Sequencing	18 (21)	31 (41)	$p = .4$
Left Motor Cortex During Left Finger-Sequencing	25 (31)	60 (58)	$p = .2$

Values in the columns labeled ADHD and Control are the average number of active voxels in either the right or left BA 4, as indicated, with the standard deviation in parentheses.

fMRI, functional magnetic resonance imaging; ADHD, attention-deficit/hyperactivity disorder.

^aIndicates significant differences in activation between the two groups.

insufficient recruitment of neuronal activity necessary to mobilize transcallosal interhemispheric inhibition. Group differences were not found in ROI analyses of the ipsilateral motor cortex. While more frequent occurrence of mirror movements in ADHD might be expected to be associated with increased neuronal activity in the ipsilateral motor cortex, it could also be associated with insufficient inhibitory capacity from the contralateral motor cortex resulting in relatively greater activation in the ipsilateral motor neurons than expected. The two effects may mitigate each other, making group differences in ipsilateral motor cortex activation difficult to interpret. While a correlation between our fMRI findings with a behavioral measure of motor overflow might allow us to explore this possibility, we were unable to accurately assess mirror movements during scanning using videotape recording of the scan sessions. Augmenting fMRI data with other techniques, such as electromyography (EMG) that could precisely record both intentional and overflow movements that may be imperceptible or simply unobserved by the human eye, will facilitate further exploration of the complexities of anomalous interhemispheric motor inhibition in ADHD (Cohen et al 1967; Denckla and Rudel 1978; Kadesjo and Gillberg 1998; Mostofsky et al 2003; Piek et al 1999; Szatmari and Taylor 1984).

Whole-brain contrasts revealed decreased magnitude of activation in children with ADHD in BA 7 and BA 40 of the right superior posterior parietal cortex compared with control subjects during both RHFS and LHFS. Due to the nature of this contrast, this finding could reflect either greater activation during tapping in the control group or greater activation during rest in the ADHD group. Our interpretation that the result reflects greater activation during tapping in the control group is supported by the presence of this area of activation on the control group contrast images for

both RHFS (right-rest) and LHFS (left-rest) and not on the rest-right or rest-left images for the group of children with ADHD. The right parietal cortex appears to be particularly important for somatotopic imagery and “spatial attention to external locations,” both of which facilitate selection of appropriate new attentional foci (Posner and Petersen 1990). In more general terms, the posterior parietal cortex functions to integrate visual and somatosensory information and has also been implicated in retrieval of motor movement representations (Danckert et al 2002; Heilman et al 1982; Seitz et al 1997) and generating kinetic strategies (Mesulam 1999). Thus, our data suggest that the control group may be better able to engage posterior parietal systems important for mapping of movements in personal space, which may facilitate performance of the correct sequence of finger movements.

Previous functional imaging studies of motor control in children with ADHD, including those incorporating simple finger tapping, have used tasks with greater cognitive/behavioral demands than the task used in this study. One study involved visually paced finger tapping in two alternating conditions, i.e., in response to either frequent or infrequent visual cues. The fMRI analysis comparing children with ADHD with a control group performing this task revealed less prefrontal (anterior cingulate gyrus, BA 32) and medial parietal (posterior cingulate gyrus, BA 31) activation among the ADHD subjects (Rubia et al 1999a). Given the behavioral task demands, the findings may reflect differences in a frontoparietal network thought to be important for vigilance and shifting attention (Posner 1997). A second study used a simpler version of this task that removed the requirement to switch between frequent and infrequent cues; under these conditions, no differences in prefrontal or medial parietal brain activation were observed between the ADHD and control groups (Rubia et al 2001). Similarly, our findings in the current study did not reveal any statistically significant differences in prefrontal or medial parietal activation. Rather, we found differences in the contralateral primary motor cortex and right superior posterior parietal cortex during both right- and left-handed simple, self-paced finger sequencing, suggesting that children with ADHD also show differences in cortical systems important for execution of patterned movements.

Strengths, Limitations, and Potential Confounds

Movement artifact on fMRI images of subjects with ADHD is a potential confound, but it is unlikely to be a source of systematic error in this study, since no significant between-group differences in average head displacement were found.

It has been demonstrated that frequency of tapping can impact functional brain imaging results (Kawashima et al 1999). A strength of our study is that the two groups did not differ in

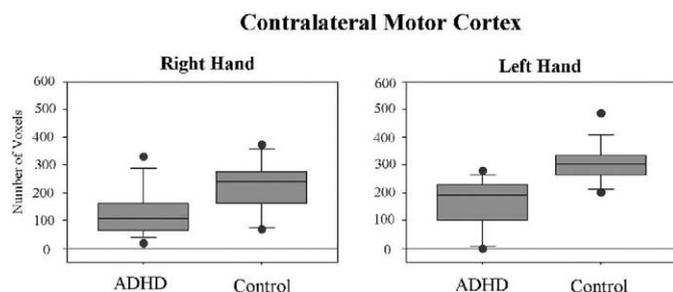


Figure 3. Boxplots illustrating the significant ($*p = .04$, $**p = .0007$) between-group differences in mean extent of fMRI activation within contralateral Brodmann area 4 during right hand and left hand finger-tapping sequences. Gray areas indicate the range of data within the 25th to 75th percentile and error bars indicate 10th and 90th percentiles. Circles indicate data points beyond the 10th or 90th percentiles. The horizontal dark lines within gray areas are medians. fMRI, functional magnetic resonance imaging.

speed of tapping either during scanning or during motor assessment outside of the scanner; our findings of between-group differences in neural activation are therefore less likely to represent differences in speed of tapping and are more likely to reflect an effect of diagnosis, i.e., whether or not the subjects have ADHD. While our sample of children with ADHD did not show a statistically significant difference from control subjects specifically in speed of tapping during scanning, they did show subtle motor impairments compared with control subjects based on overall performance on a standardized examination for subtle motor signs (PANESS) conducted outside the scanner. Our sample of children with ADHD is, therefore, likely to be representative of the general population of children with ADHD for whom subtle motor impairment is a commonly reported finding.

A further limitation is that our methodology did not allow us to account for potential between-group differences in variability of reaction time that have been previously reported (Rubia et al 1999b), which could manifest as differences in cadence and rhythm during tapping. Another potential confound is between-group differences in the force of finger tapping, which has been documented to correlate to regional cerebral blood flow in the motor cortex (Dettmers et al 1995). A possible modification to the task that could incorporate measures of force and cadence of tapping would require subjects to tap on a force plate or button box. However, we specifically elected to use finger apposition rather than a button press, as it has been our clinical experience that finger apposition is more likely to elicit motor overflow.

Our interpretation of our findings was also limited by the fact that we were not able to measure motor overflow during scanning. Since the video record was incomplete and difficult to score on overflow, it was not possible to accomplish a between-group comparison of overflow during scanning, nor was a meaningful correlation with fMRI measures possible. Assessment of overflow outside the scanner using a categorical measure (presence or absence) revealed a greater number of ADHD subjects showed overflow movement than did control subjects; however, this difference was not statistically significant. It is interesting to note that the three children with ADHD who demonstrated motor overflow were older (10.5 years, 10.7 years, and 12.4 years) than the one control subject (9.3 years). This could suggest that the motor overflow demonstrated by the control participant, as compared with that displayed by the three children with ADHD, is more likely to be attributable to his young age. We must also consider the possibility that data collected using the PANESS may have been confounded by the examiner not being specifically blinded to the participant's diagnosis, although the expected effect of this bias would be to increase the between-group differences in motor overflow. An improvement would be to use EMG and/or accelerometry to provide objective, quantitative measurements of both intentional and overflow movements and to add substantial behavioral data for correlation to the fMRI findings. It could also provide insight into subclinical motor overflow that has been noted in previous EMG studies (Bodwell et al 2003) and may allow for examination of more subtle gradations in the amount of overflow across age groups.

The number of subjects included in this investigation is similar to other fMRI studies, but a larger number of subjects might have provided increased power to detect differences suggested by trends in the data. The small sample size also precluded detailed examination of effects on the fMRI activation patterns due to differences in age, gender, and ADHD subtype, which have all

been demonstrated to influence motor performance (Mostofsky et al 2003).

Our findings of between-group differences may have also been impacted by the fact that 8 of the 11 children with ADHD were being treated with stimulant medication, although in all cases the medication was discontinued at least 36 hours prior to both clinical testing and imaging. Chronic administration (4 to 5 weeks) of methylphenidate to children with ADHD has been associated with normalization of regional cerebral blood flow (Lee et al 2005), and we cannot rule out the possibility of confound due to medication status.

Finally, the choice of rest as a baseline condition, although used for many previous studies (Allison et al 2000; Baraldi et al 1999; Parks et al 2003; Rivkin et al 2003), could be modified for future investigations. The information obtained from fMRI is a measure of changes in activation between one behavioral state and another. In this study, the behavioral state of rest was chosen as the baseline for comparison with the sequential finger-tapping task to capture the motor cortex activation associated with this simple motor behavior. In future studies, the choice of repetitive finger tapping as a baseline might be used to isolate activation related to overflow, since the former tends not to elicit overflow, whereas sequential finger tapping does.

Summary

The general consensus in the literature is that children with ADHD demonstrate less motor maturity than their typically developing peers when performing timed sequential motor tasks. Functional magnetic resonance imaging was employed to test the hypothesis that children with ADHD would activate primary motor cortex differently than their typically developing peers during a self-paced sequential finger-tapping task. Our ROI analysis, designed to test the hypothesis, revealed that children with ADHD recruit a smaller extent of contralateral primary motor cortex than do control subjects. This may be a clue to understanding the impairments of motor inhibition observed in ADHD, including excessive overflow movements that may be interpreted as relatively decreased interhemispheric inhibition. On whole-brain fMRI analysis, the children with ADHD showed relatively decreased activation in the right superior parietal cortex. This finding suggests that children with ADHD are less able to recruit posterior parietal systems important for motor imagery necessary to guide the correct sequence of finger movements. Further studies are planned with concurrent collection of fMRI and EMG data during the performance of motor tasks to refine the correlation of motor behavior to cortical activation.

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Allison JD, Meador KJ, Loring DW, Figueroa RE, Wright JC (2000): Functional MRI cerebral activation and deactivation during finger movement. *Neurology* 54:135–142.

Baraldi P, Porro CA, Serafini M, Pagnoni G, Murari C, Corazza R, et al (1999): Bilateral representation of sequential finger movements in human cortical areas. *Neurosci Lett* 269:95–98.

- Barkley RA (1997): Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychol Bull* 121: 65–94.
- Ben-Pazi H, Gross-Tsur V, Bergman H, Shalev RS (2003): Abnormal rhythmic motor response in children with attention-deficit-hyperactivity disorder. *Dev Med Child Neurol* 45:743–745.
- Bodwell JA, Mahurin RK, Waddle S, Price R, Cramer SC (2003): Age and features of movement influence motor overflow. *J Am Geriatr Soc* 51: 1735–1739.
- Calhoun V, Adali T, Kraut M, Pearlson G (2000): A weighted least-squares algorithm for estimation and visualization of relative latencies in event-related functional MRI. *Magn Reson Med* 44:947–954.
- Cincotta M, Borgheresi A, Boffi P, Vigliano P, Ragazzoni A, Zaccara G, et al (2002): Bilateral motor cortex output with intended unimanual contraction in congenital mirror movements. *Neurology* 58:1290–1293.
- Cioni G, Montanaro D, Tosetti M, Canapicchi R, Ghelarducci B (2001): Reorganisation of the sensorimotor cortex after early focal brain lesion: A functional MRI study in monozygotic twins. *Neuroreport* 12:1335–1340.
- Cohen HJ, Taft LT, Mahadeviah MS, Birch HG (1967): Developmental changes in overflow in normal and aberrantly functioning children. *J Pediatr* 71:39–47.
- Conners CK, Sitarenios G, Parker JD, Epstein JN (1998): Revision and restandardization of the Conners Teacher Rating Scale (CTRS-R): Factor structure, reliability, and criterion validity. *J Abnorm Child Psychol* 26:279–291.
- Danckert J, Ferber S, Doherty T, Steinmetz H, Nicolle D, Goodale MA (2002): Selective, non-lateralized impairment of motor imagery following right parietal damage. *Neurocase* 8:194–204.
- Danek A, Heye B, Schroedter R (1992): Cortically evoked motor responses in patients with Xp22.3-linked Kallmann's syndrome and in female gene carriers. *Ann Neurol* 31:299–304.
- Denckla MB (1985): Revised neurological examination for subtle signs. *Psychopharmacol Bull* 21:773–800.
- Denckla MB, Rudel RG (1978): Anomalies of motor development in hyperactive boys. *Ann Neurol* 3:231–233.
- Dettmers C, Fink GR, Lemon RN, Stephan KM, Passingham RE, Silbersweig D, et al (1995): Relation between cerebral activity and force in the motor areas of the human brain. *J Neurophysiol* 74:802–815.
- DuPaul GJ, Power TJ, Anastopoulos AD, Reid R (1998): *ADHD Rating Scale-IV*. New York: Guilford.
- Durston S, Tottenham NT, Thomas KM, Davidson MC, Eigsti IM, Yang Y, et al (2003): Differential patterns of striatal activation in young children with and without ADHD. *Biol Psychiatry* 53:871–878.
- Evans A (1993): 3D statistical neuroanatomical models from 305 MRI volumes. *IEEE Nucl Sci Symp Med Imaging* 1813–1817.
- Friston KJ, Holmes A, Poline JB, Price CJ, Frith CD (1996): Detecting activations in PET and fMRI: Levels of inference and power. *Neuroimage* 4:223–235.
- Friston KJ, Holmes AP, Worsley KJ, Poline JB, Frith CD, Frackowiak RSJ (1995): Statistical parametric maps in functional imaging: A general linear approach. *Hum Brain Mapp* 2:189–210.
- Heilman KM, Rothi LJ, Valenstein E (1982): Two forms of ideomotor apraxia. *Neurology* 32:342–346.
- Holmes AP, Friston KJ (1998): Generalisability, random effects and population inference. *Neuroimage* 7:5754.
- Kadesjo B, Gillberg C (1998): Attention deficits and clumsiness in Swedish 7-year-old children. *Dev Med Child Neurol* 40:796–804.
- Kawashima R, Inoue K, Sugiura M, Okada K, Ogawa A, Fukuda H (1999): A positron emission tomography study of self-paced finger movements at different frequencies. *Neuroscience* 92:107–112.
- Largo RH, Caflich JA, Hug F, Muggli K, Molnar AA, Molinari L (2001): Neuro-motor development from 5 to 18 years. Part 2: Associated movements. *Dev Med Child Neurol* 43:444–453.
- Lee JS, Kim BN, Kang E, Lee DS, Kim YK, Chung JK, et al (2005): Regional cerebral blood flow in children with attention deficit hyperactivity disorder: Comparison before and after methylphenidate treatment. *Hum Brain Mapp* 24:157–164.
- Mayston MJ, Harrison LM, Stephens JA (1999): A neurophysiological study of mirror movements in adults and children. *Ann Neurol* 45:583–594.
- Mesulam MM (1999): Spatial attention and neglect: Parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. *Philos Trans R Soc Lond B Biol Sci* 354:1325–1346.
- Moll GH, Heinrich H, Trott G, Wirth S, Rothenberger A (2000): Deficient intracortical inhibition in drug-naive children with attention-deficit hyperactivity disorder is enhanced by methylphenidate. *Neurosci Lett* 284: 121–125.
- Mostofsky SH, Lasker AG, Cutting LE, Denckla MB, Zee DS (2001): Oculomotor abnormalities in attention deficit hyperactivity disorder: A preliminary study. *Neurology* 57:423–430.
- Mostofsky SH, Newschaffer CJ, Denckla MB (2003): Overflow movements predict impaired response inhibition in children with ADHD. *Percept Mot Skills* 97:1315–1331.
- Parks MH, Morgan VL, Pickens DR, Price RR, Dietrich MS, Nickel MK, et al (2003): Brain fMRI activation associated with self-paced finger tapping in chronic alcohol-dependent patients. *Alcohol Clin Exp Res* 27:704–711.
- Piek JP, Pitcher TM, Hay DA (1999): Motor coordination and kinaesthesia in boys with attention deficit-hyperactivity disorder. *Dev Med Child Neurol* 41:159–165.
- Pitcher TM, Piek JP, Barrett NC (2002): Timing and force control in boys with attention deficit hyperactivity disorder: Subtype differences and the effect of comorbid developmental coordination disorder. *Hum Mov Sci* 21:919–945.
- Posner MI (1997): *Images of Mind*. New York, NY: Scientific American Library.
- Posner MI, Petersen SE (1990): The attention system of the human brain. *Annu Rev Neurosci* 13:25–42.
- Reich W (2000): Diagnostic interview for children and adolescents (DICA). *J Am Acad Child Adolesc Psychiatry* 39:59–66.
- Rivkin MJ, Vajapeyam S, Hutton C, Weiler ML, Hall EK, Wolraich DA, et al (2003): A functional magnetic resonance imaging study of paced finger tapping in children. *Pediatr Neurol* 28:89–95.
- Ross RG, Harris JG, Olincy A, Radant A (2000): Eye movement task measures inhibition and spatial working memory in adults with schizophrenia, ADHD, and a normal comparison group. *Psychiatry Res* 95:35–42.
- Rubia K, Oosterlaan J, Sergeant JA, Brandeis D, v Leeuwen T (1998): Inhibitory dysfunction in hyperactive boys. *Behav Brain Res* 94:25–32.
- Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SC, Simmons A, et al (1999a): Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: A study with functional MRI. *Am J Psychiatry* 156:891–896.
- Rubia K, Taylor A, Taylor E, Sergeant JA (1999b): Synchronization, anticipation, and consistency in motor timing of children with dimensionally defined attention deficit hyperactivity behaviour. *Percept Mot Skills* 89: 1237–1258.
- Rubia K, Taylor E, Smith AB, Oksanen H, Overmeyer S, Newman S, et al (2001): Neurophysiological analyses of impulsiveness in childhood hyperactivity. *Br J Psychiatry* 179:138–143.
- Seitz RJ, Canavan AG, Yaguez L, Herzog H, Tellmann L, Knorr U, et al (1997): Representations of graphomotor trajectories in the human parietal cortex: Evidence for controlled processing and automatic performance. *Eur J Neurosci* 9:378–389.
- Stippich C, Ochmann H, Sartor K (2002): Somatotopic mapping of the human primary sensorimotor cortex during motor imagery and motor execution by functional magnetic resonance imaging. *Neurosci Lett* 331: 50–54.
- Szatmari P, Taylor DC (1984): Overflow movements and behavior problems: Scoring and using a modification of Fogs' test. *Dev Med Child Neurol* 26:297–310.
- Vaidya CJ, Austin G, Kirkorian G, Ridlehuber HW, Desmond JE, Glover GH, et al (1998): Selective effects of methylphenidate in attention deficit hyperactivity disorder: A functional magnetic resonance study. *Proc Natl Acad Sci U S A* 95:14494–14499.
- Vandermeeren Y, Sebire G, Grandin CB, Thonnard JL, Schlogel X, De Volder AG (2003): Functional reorganization of brain in children affected with congenital hemiplegia: fMRI study. *Neuroimage* 20:289–301.
- Wechsler D (1991): Wechsler Intelligence Scale for Children—III. San Antonio, TX: The Psychological Corporation.
- Wechsler DL (1992): Wechsler Individual Achievement Test. San Antonio, TX: The Psychological Corporation.