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Interhemispheric asymmetry of regional cerebral blood flow in prepubescent boys with attention deficit hyperactivity disorder

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Summary

The prefrontal cortex is asymmetric in both structure and function. In normal subjects, the right prefrontal cortex is activated more than the left during response inhibition. Patients with attention deficit hyperactivity disorder (ADHD) have impaired response inhibition and altered structural interhemispheric asymmetry. This study was conducted to examine the functional interhemispheric asymmetry during response inhibition in children with ADHD. Subjects were divided into three groups according to the level of motor hyperactivity. Blood flow tracer ^{99m}Tc-ethyl cysteinate dimer was injected while subjects were performing a response inhibition task (RIT), followed by single photon emission computerized tomography (SPECT). After three-dimensional reconstruction, filtering and smoothing, individual scans were morphed to a template. Three average group images were created from individual scans. Each average group image was subtracted voxel-by-voxel from its mirror image to compare the regional cerebral blood flow (rCBF) in the right and left cerebral hemispheres, yielding images of significant interhemispheric rCBF asymmetry. The severe hyperactivity group exhibited most prefrontal left > right rCBF asymmetry and left > right occipitoparietal asymmetry. Reversal of functional prefrontal asymmetry in boys with severe motor hyperactivity supports the hypothesis of right prefrontal cortex dysfunction in ADHD. (© 2001 Lippincott Williams & Wilkins)

Keywords: ADHD, SPECT, interhemispheric asymmetry, hyperactivity, response inhibition.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a heterogeneous syndrome of inattention, impulsivity and motor hyperactivity. Lack of known biological markers complicates the diagnosis of ADHD [1]. There have been several functional brain imaging studies of adults and adolescents with ADHD, but only a few have focused on prepubescent boys, the population with the highest ADHD incidence [2]. Hyperactivity is a common symptom of the 'combined' and the 'predominantly hyperactive' types of ADHD; it often decreases in adolescence and is less common in girls with ADHD, in whom the 'predominantly inattentive' type of ADHD is more prevalent. The 'combined' and the 'predominantly hyperactive' types of ADHD may be biologically distinct from the 'predominantly inattentive' type [3–6]. A functional imaging study focused on prepubescent boys with ADHD could yield useful information about the functional biological markers of hyperactivity. A decreased ability to delay response, leading to impulsivity and inattention, may be the fundamental abnormality in ADHD [7]. This function is mediated by a distributed neural network that includes parts of the frontal, occipitoparietal and superior temporal cortices, as well as the subcortical structures [8, 9]. Functional magnetic

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resonance imaging (fMRI) and single photon emission computerized tomography (SPECT) studies of response inhibition reported asymmetric activation of the right prefrontal cortex in normal subjects [10–13]. Structural interhemispheric asymmetry in normal children and adults has also been demonstrated [14–16]. In children with ADHD, this right > left structural asymmetry is lost or reversed [17–20]. This study tests the hypothesis that, due to functional right hypofrontality, the prefrontal asymmetry of the regional cerebral blood flow (rCBF) in predominantly hyperactive prepubescent boys with ADHD will be absent or reversed during response inhibition tasks (RITs), and that this pattern of neuronal activity will be detectable by SPECT imaging with a blood flow tracer.

Methods

Subjects

Following institutional review board approval, subjects in clinical treatment for ADHD were recruited from pediatric, child psychiatry and family practices in the San Francisco Bay area. Subjects were screened using DSM IV-based parent and teacher questionnaires, which rated the DSM IV criteria for inattention and hyperactivity on a scale of 0 to 3 [21, 22]. Exclusion criteria were as follows: a failure to meet the DSM IV criteria for ADHD; female sex; Tanner stage >2; history of head trauma; IQ <85; known chronic medical or neurological illness; conduct, mood or psychotic disorder; left-handedness; treatment with medications other than methylphenidate (MPH). Sixty-one children met the initial entry criteria and were evaluated in three office visits by a multidisciplinary team consisting of a clinical psychologist, child psychiatrist and pediatrician. Children were also assessed with the Wechsler Intelligence Schedule – Children (WISC), Gordon Diagnostic System 'observed hyperactivity checklist', Levine parent and teacher questionnaires, Barkley's hyperactivity and co-morbidity items and a clinical hyperactivity rating scale (Table 1) [23–26]. Twenty boys with ADHD and four normal controls, 8–12 years of age (average age, 10.2 years; median age, 10 years), completed the study. Eighteen met DSM IV criteria for the combined type and two for the predominantly inattentive type of ADHD. Subjects were assigned to the severe (n=7), moderate (n=6) or low (n=7) hyperactivity groups according to their average clinical hyperactivity score and the consensus of the multidisciplinary team. This method is closest to the current standard of practice in the clinical evaluation of ADHD [27, 28]. All ADHD subjects were treated with an MPH dose of 10–30 mg per day for an average of 6 months (range, 3–12 months) and demonstrated a clinical improvement. The use of a consensus opinion of an experienced team was felt to be closest to the diagnostic process in clinical practice. No statistically significant difference in DSM IV inattention scores ($P>0.4$, paired t-tests assuming unequal sample size) was demonstrated among the severe, moderate and low hyperactivity groups. The groups differed significantly in the observed hyperactivity checklist score (Table 1) and DSM IV hyperactivity ratings ($P<0.05$). The four age- and sex-matched (average age, 10 years; median age, 10 years), right-handed normal controls had a full psychological, psychiatric and medical evaluation prior to inclusion in the study (Table 2). An attempt to recruit additional normal subjects was unsuccessful. The control group was too small for a valid comparison with subject groups and was not included in the final analysis.

Table 1. Clinical ADHD hyperactivity symptoms checklist: maximum score 25, minimum score 0.

Restless	0	1	2	3	4	5
Fidgets	0	1	2	3	4	5
Foot tapping	0	1	2	3	4	5
Hands moving	0	1	2	3	4	5
Unable to sit still	0	1	2	3	4	5

Image acquisition and activation task

Image acquisition and analysis were performed by a team that was blind to the clinical data acquired by the clinical team, including the assignment of the subjects to the ADHD severity and subtype groups. MPH was withheld for 24 h before the scan. After an intravenous line placement for tracer injection and a 5 min RIT practice session, subjects began the RIT on a computer. The task has been described by Vaidya *et al*. [29]. Briefly, it consisted of six alternating 'go' or 'no go' blocks lasting 25 s each. A 'block' is a 25 s interval that begins with task instructions requiring action or inaction in response to a consonant letter displayed on the screen ('press mouse for all letters' for the 'go' blocks; 'do not press mouse for X' for the 'no go' blocks), followed by a consonant letter in each trial. 'X' was not presented and 'C' occurred in 50% of the 'go' trials. 'X' occurred in 50% of the trials in the 'no go' block. Other letters were not repeated in either block. The radiopharmaceutical was injected 2.5 min after starting a 5 min CPT. Patients were imaged 20–30 min after the RIT.

Radiopharmaceutical and instrumentation

An age-adjusted dose (average, 13 mCi; 480 MBq) of ^{99m}Tc-ethyl cysteinate dimer (Dupont, Billerica, MA,

USA) was administered, and the subject continued to perform the RIT for an additional 2.5 min. Images were recorded with a Siemens 'MultiSpect 3 (Des Planes, IL, USA) triple-head scanner, with 8 mm full width at half-maximum (FWHM) resolution, using high-resolution parallel-hole collimators and a photopeak centred at 140 keV with a 15% window, for 22 s per frame with 3° increments (40 frames per detector, total of 120 frames, using a 128×128 matrix). Data were recorded in a dedicated computer system (Siemens ICON) and reconstructed using filtered backprojection with a low pass cosine filter at 0.55 cycle·scm^{-1}.

Image analysis

Automated image analysis was performed as follows. Following filtered backprojection reconstruction of the data, the volume data set was segmented using a Canny-Deriche edge detector to define three-dimensional edges [30, 31]. Utilizing the edges, individual SPECT data were matched to a single template by morphing using a modified iterative closest point method [32–34]. This process rendered the individual volume images morphologically identical, while preserving relative densities of tracer uptake at various points of the image. The morphed images were normalized to the voxel of maximum activity within the brain. The morphed individual images were combined in average group images representing all ADHD subjects together (ALL) and severe (severe), moderate (moderate) and low (low) hyperactivity groups separately. Interhemispheric rCBF asymmetry was evaluated by morphing each case to its mirror image, generating average group images for the original and matched mirror image for each group (ALL, severe, moderate, low) and subtracting each average group image from its mirror image. We defined significant differences between average image sets as follows. A threshold of significance for differences in voxel values was set so that no differences would be found between two randomly mixed average groups composed of all subjects (n=24). The random groups were formed by averaging images of half of the cases with the mirror images of the other half. No differences are expected between such groups. This threshold was then applied in all comparisons in the study (severe, moderate, low and ALL vs. their mirror image). Significant differences in perfusion were displayed in a three-dimensional (3-D) format as a volume of colour superimposed on a shaded outline of the head. Colours were used only to separate contiguous volumes of difference and do not indicate any other parameter of perfusion differences. Anatomic location was determined by visual correlation of the findings displayed in the 3-D viewer with triangulation capability with stereotactic and anatomic atlases of the brain [35, 36].

Results (Table 3)

(1) Prefrontal interhemispheric left > right asymmetry was present in the severe and moderate groups, implying a decrease in the right prefrontal rCBF relative to the left. In the severe group, the volume of asymmetry as a percentage of the total brain volume was greater than that in the moderate group (0.1%

Table 3. Location and size of interhemispheric asymmetry (see Fig. 1).

	ADHD Group		
Asymmetry	*Severe*	*Moderate*	*Low*
Left > right	Prefrontal 0.1 BA 9; 44; 46	Prefrontal† BA 44; 46	No
Left > right	Temporal 0.2*	Temporal†	No
Left > right	Parietal 0.1* BA 19; 39	Parietal† BA 19; 39	No
Right > left	Parietal 0.1* BA 39; 40	Parietal† BA 39; 40	Parietal† BA 39; 40
Right > left	Occipital 0.2*	Occipital†	Occipital†
Total group % of asymmetric brain volume	0.7*	0.11*	0.07*

*Volume of difference as percentage of the total brain volume. 0.2% of the brain volume is equivalent to approximately 15 000 neurons [37]. †Less than 0.05% of total brain volume.

Table 2. Subject characteristics.

Overall hyperactivity score	*n*	*Average age*	*Full IQ*	*Clinical hyperactivity score**	*Gordon hyperactivity score†*	*DSM IV hyperactivity score*	*DSM IV inattention score*
Severe	7	9.7	106	22.1	22	21.7	23
Moderate	6	9.7	118	17	16	16.6	20.2
Low	7	11	113	3.6	10.4	10.42	10.24
Normal	4	10.9	121	0.5	10.4	5.3	7.8

*See Table 1. †Gordon observational score [25].

vs. 0.03%). In the severe group, the asymmetry was in the superior and middle frontal gyri, corresponding to Brodmann areas (BA) 9 and 46; in the moderate group, it was located closer to the middle frontal gyrus (BA 44 and 46).

(2) Other regions of interhemispheric asymmetry unique to the severe group were the left > right asymmetry in the superior temporal gyrus and the inferior part of the supramarginal gyrus (BA 40 and 42) and the right > left in the occipitoparietal cortex (BA 19 and 39).

(3) The total volume of asymmetric rCBF in the severe group was approximately seven times the volume of asymmetry in the other groups (0.7% vs. 0.1% vs. 0.07%).

(4) Parietal right > left asymmetry in the region of the supramarginal and angular gyri (BA 39/40, the somatosensory association area) was present in all subject groups.

(5) Occipital right > left asymmetry (BA 18/19 in severe, moderate, low; BA 17 in severe) was seen in all ADHD groups (Fig. 1). The volume of occipital asymmetry was greater in the severe than in the moderate or low groups (0.2% vs. less than 0.05%).

(6) Occipital right > left asymmetry in the occipital pole (BA 17; primary visual cortex) was present in the severe group only.

(7) The ALL group was created by averaging low, moderate and severe group data; the pattern of asymmetry was almost identical to that of the low group, because averaging diminished the significance of asymmetries most prominent in the severe group below the threshold of statistical significance.

Discussion

Our results indicate abnormal functional interhemispheric asymmetry of a functionally significant cortical volume in ADHD [37]. Studies of baseline (resting) brain activity in ADHD have not shown a consistent pattern of interhemispheric asymmetry [38–40]. Creating an externally uniform (e.g. sound, lighting, eyes closed or open) and internally uniform (e.g. mood and cognition) environment is difficult, especially in children. Focusing attention on a task may reduce the variability in the conditions around the time of tracer distribution in the brain [41]. Recent fMRI and electroencephalographic (EEG) studies have shown a failure of right prefrontal cortex activation during response inhibition paradigms in boys with ADHD vs. normal controls [29, 42–44]. Loss or reversal of the normal functional prefrontal asymmetry may be absent in females with ADHD. A large ^{18}F-fluorodeoxyglucose (^{18}FDG) positron emission tomography (PET) study did not show right hypofrontality in adolescent girls with ADHD [45]. In another large (n=117) study, boys with ADHD exhibited a loss of right dominance of prefrontal EEG activity, while girls showed an enhancement of the normal right dominant pattern [46].

The hypothesis of functional right hypofrontality in ADHD is further supported by the fact that brain regions activated by RITs are also affected by the loss or reversal of normal structural asymmetry in ADHD [18]. Studies in normal children and adults [10, 11] suggest the presence of right > left functional asymmetry during response inhibition. In our subjects, this asymmetry was reversed in the severe, but only absent in the moderate or low groups, indicating a lesser degree of functional right hypofrontality in the low and moderate ADHD groups. Unlike in the severe group, it was only sufficient to abolish, but not reverse, the normal right > left asymmetry. This illustrates how approaching ADHD as a discrete and homogeneous disorder could create false negative results in imaging and other studies.

One of the advantages of an automated whole-brain method of analysis over methods based on region of interest (ROI) analysis is that areas of significant asymmetry may be found in brain regions that were not part of the original hypothesis. All ADHD groups showed a right > left asymmetry in the left occipital cortex. A SPECT study performed in ADHD subjects with their eyes open found higher than normal activation of bilateral primary visual cortex (BA 17) and visual association areas in ADHD [47]. Activation of the occipital cortex supports its proposed supplementary role in attention, but could also be related to an increasing difficulty in maintaining visual focus on the screen in severely hyperactive children [48–51]. A study using an auditory rather than visual attention task would help to distinguish between these possibilities [52].

Parietal left > right asymmetry in BA 19 and 39 was present only in the severe group, suggesting that this could be an additional area of functional abnormality in hyperactive ADHD. It is remarkable that, while parietal asymmetry has not been reported in boys with ADHD, functional right > left parietal asymmetry has been reported in girls [45].

PET, MRI, electrophysiological and neuropsychological data point to striatal as well as frontal dysfunction during response inhibition in ADHD [17, 29, 42–44, 53–55]. We did not find an asymmetry of rCBF in the subcortical structures. A dopamine transporter (DAT) binding ligand (TRODAT) SPECT study showed a low density of DAT in the bilateral basal ganglia in untreated ADHD adults, and an increase in DAT density after MPH treatment. This indicates that the basal ganglia dysfunction in ADHD could be either symmetric or not be evident as a perfusion abnormality [56].

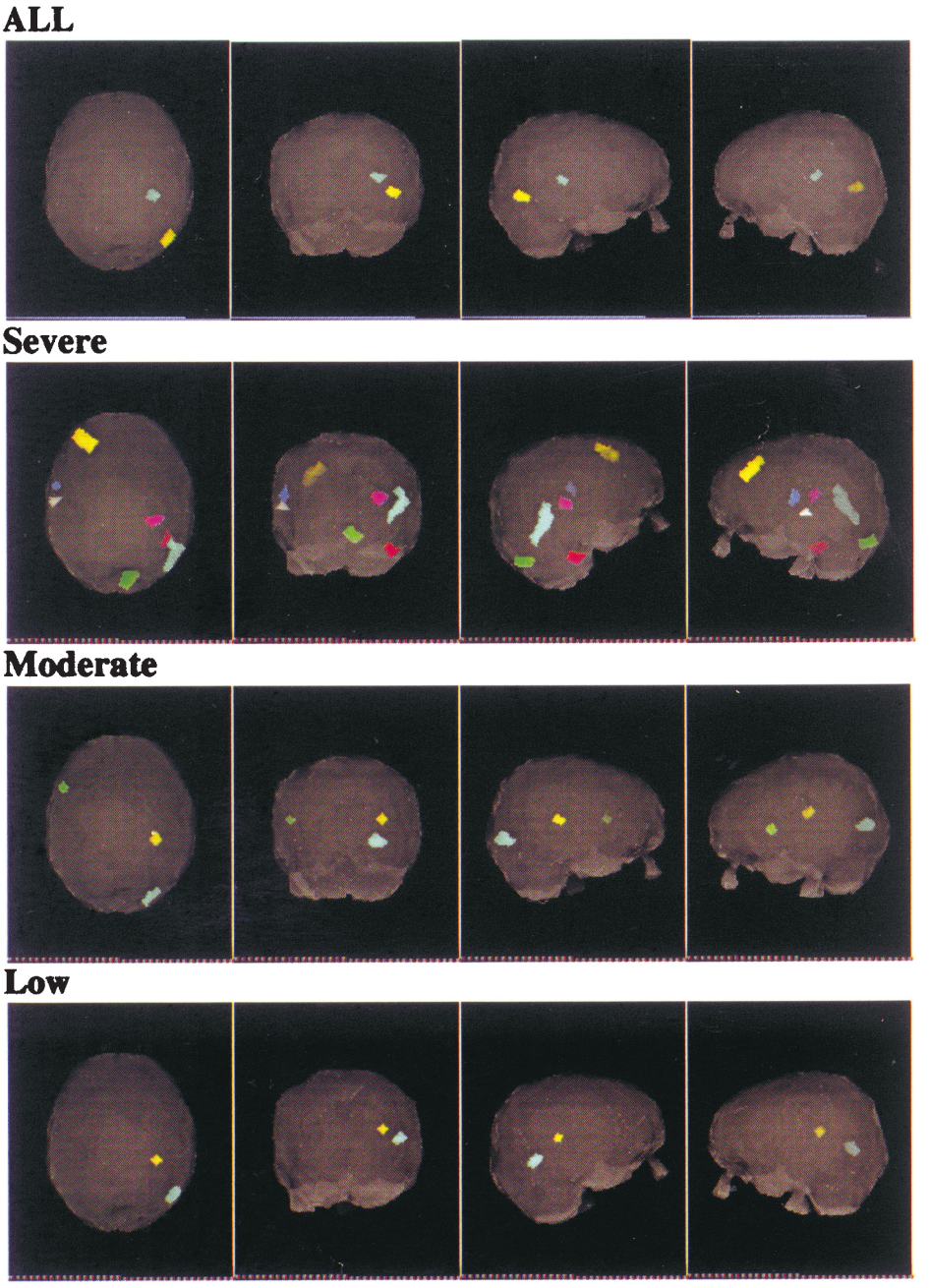

Fig. 1. Regions of significant interhemispheric asymmetry of rCBF in all subjects (ALL) and in the severe, moderate and low hyperactivity ADHD groups. Superior, posterior, right and left lateral projections. The left side of the image is on the left side of the reader. Each colour indicates a contiguous volume of significant asymmetry (but not its magnitude). The severe hyperactivity group has a larger volume of asymmetry than the other groups in the prefrontal (left > right) and occipitoparietal (right > left) cortex.

Difficulties in recruiting adequate control groups in pediatric studies involving exposure to levels of ionizing radiation considered to be safe have meant that no recent ADHD studies have included a normal control group [57]. In a prospective study, it is hard to anticipate recruitment difficulties and impossible to anticipate the results. Until recently, the lack of normal controls in PET and SPECT studies of pre-adolescent ADHD patients has been addressed either by cross-study comparisons with data from normal adults or by using a control group with

non-ADHD psychiatric and neurological disorders [45, 47]. Both approaches have limitations. Pre-pubescent children have the highest prevalence of ADHD and there is evidence that both normal and abnormal brain functions in this age group are different from those in older patients, limiting the value of cross-study comparison with normal but older subjects [58]. Alterations of functional and structural interhemispheric asymmetry have been reported in dyslexia, oppositional defiant disorder, depression, obsessive–compulsive disorder, schizophrenia and other disorders, some of which are highly co-morbid with ADHD and may have a characteristic activation pattern during RIT that could overlap with ADHD [59–62].

Our approach to the problem of an inadequate normal group was to use a within-subject, voxel-by-voxel whole-brain interhemispheric comparison, making a single voxel rather than a brain region a unit of comparison and using each subject as his or her own control. With increasing access to fast computing, automated template-based methods of image analysis are likely to become as popular among researchers and clinicians for brain applications as they already have for cardiac studies [30] (http://www.segamicorp.com). While group results do not guarantee that right hypofrontality has diagnostic value in individuals, they add to a growing body of evidence for right prefrontal dysfunction in ADHD, making it a potentially clinically valuable diagnostic marker. Further studies of larger samples using standardized automated methods of image analysis and correlation with MRI would help to determine whether decreased right prefrontal or left occipitoparietal perfusion during RIT have clinical diagnostic value.

We studied male subjects only. In the general population, the male to female ratio of ADHD incidence ranges between 4 : 1 for the 'combined' type to 2 : 1 for the 'predominantly inattentive' type. Among children referred for treatment, this ratio is considerably higher, because boys with ADHD have a higher prevalence of motor hyperactivity and a higher incidence of co-morbid oppositional defiant disorder and other disorders with disruptive behavioural manifestations that prompt referral [1, 63]. There is evidence of significant gender differences in both normal and abnormal functional brain anatomy [64]. Specifically, compared to males, females have decreased lateralization of the spatial functions to the right hemisphere and the verbal and fine motor functions to the left hemisphere, indicating that our findings cannot be extrapolated to girls without further study [65]. This confluence of practical and theoretical issues makes single gender studies the prevailing approach in functional imaging of ADHD, with studies in adults and boys often preceding studies of similar design in girls [42–44, 47, 53, 54].

Conclusions

Our study has demonstrated abnormal functional asymmetry of the prefrontal and occipitoparietal rCBF in hyperactive boys with ADHD using a voxel-based automated whole-brain method of SPECT image analysis. This result is consistent with previous reports of decreased right prefrontal function in ADHD during response inhibition. Further research is necessary to establish the diagnostic value of functional right hypofrontality in ADHD.

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