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Functional Magnetic Resonance Imaging Investigation of the Effects of Neurofeedback Training on the Neural Bases of Selective Attention and Response Inhibition in Children with Attention-Deficit/Hyperactivity Disorder

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Two functional magnetic resonance imaging (fMRI) experiments were undertaken to measure the effect of neurofeedback training (NFT), in AD/HD children, on the neural substrates of selective attention and response inhibition. Twenty unmedicated AD/HD children participated to these experiments. Fifteen children were randomly assigned to the Experimental (EXP) group whereas the other five children were randomly assigned to the Control (CON) group. Only subjects in the EXP group underwent NFT. EXP subjects were trained to enhance the amplitude of the SMR (12–15 Hz) and beta 1 activity (15–18 Hz), and decrease the amplitude of theta activity (4–7 Hz). Subjects from both groups were scanned one week before the beginning of NFT (Time 1) and 1 week after the end of NFT (Time 2), while they performed a "Counting Stroop" task (Experiment 1) and a Go/No-Go task (Experiment 2). At Time 1, in both groups, the Counting Stroop task was associated with significant activation in the left superior parietal lobule. For the Go/No-Go task, no significant activity was detected in the EXP and CON groups. At Time 2, in both groups, the Counting Stroop task was associated with significant activation of the left superior parietal lobule. This time, however, there were significant loci of activation, in the EXP group, in the right ACC, left caudate nucleus, and left substantia nigra. No such activation loci were seen in CON subjects. For the Go/No-Go task, significant loci of activation were noted, in the EXP group, in the right ventrolateral prefrontal cortex, right ACcd, left thalamus, left caudate nucleus, and left substantia nigra. No significant activation of these brain regions was measured in CON subjects. These results suggest that NFT has the capacity to functionally normalize the brain systems mediating selective attention and response inhibition in AD/HD children.

KEY WORDS: selective attention; response inhibition; AD/HD children; neurofeedback; functional magnetic resonance imaging; prefrontal cortex; anterior cingulate; striatum.

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INTRODUCTION

Attention Deficit Hyperactivity Disorder (AD/HD), a frequent developmental disorder of childhood, affects 3–7% of children and frequently continues into adulthood (Barkley, 1996). AD/HD in childhood negatively affects academic performance and leads to increased risk for antisocial disorders and drug abuse in adulthood (Mannuzza, Klein, Bessler, Malloy, & Hynes, 1997). This syndrome is mainly characterized by deficits in selective attention and response inhibition (Barkley, 1997). These symptoms reflect impairments in cognitive executive functions. These functions refer to the dynamic regulatory capacities for the initiation and maintenance of efficient attainment of goals (Lezak, 1990), as well as the inhibition of behavioral responses that are inappropriate in the current context (Shallice, 1988). This type of behavioral regulation is essential to successfully adapt one's behavior to changing environmental demands.

Cognitive executive functions are closely related with prefrontal and striatal brain systems (Godefroy, Lhullier, & Rousseaux, 1996; Leimkuhler & Mesulam, 1985; Smith & Jonides, 1999). In line with this, a number of structural magnetic resonance imaging (MRI) studies have found significant volumetric reduction of prefrontal cortical areas (Aylward et al., 1996; Castellanos et al., 1994, 1996, 2001, 2002; Durston et al., 2004; Filipek et al., 1997; Hill et al., 2003; Garavan, Ross, Murphy, Roche, & Stein, 1993; Kates et al., 2002; Mataro, Garcia-Sanchez, Junque, Estevez-Gonzalez, & Pujol, 1997; Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002; Overmeyer et al., 2001; Sowell et al., 2003) and caudate nucleus (Castellanos et al., 1994, 1996, 2001, 2002; Filipek et al., 1997; Hynd et al., 1993; Mataro et al., 1997) in children and adolescents with AD/HD.

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) studies carried out in AD/HD children, adolescents, or adults have shown decreased metabolism in the striatum and diverse prefrontal regions during resting state (Amen & Carmichael, 1997; Kim, Lee, Shin, Cho, & Lee, 2002; Lou, Henriksen, Bruhn, Borner, & Nielsen, 1989; Sieg, Gaffney, Preston, & Hellings, 1995; Zametkin et al., 1990). Moreover, SPECT studies have demonstrated decreased perfusion in prefrontal areas involved in the control of attentional processes in AD/HD individuals (Amen & Carmichael, 1997; Kim et al., 2002), and a functional MRI (fMRI) study reported no activation of the anterior cingulate cortex (ACC) in adults with AD/HD while they performed a Counting Stroop task (Bush et al., 1999) (a variant of the Stroop task-Stroop, 1935). This task, which implicates selective attention and response inhibition, exploits the conflict between a well-learned behavior (i.e., reading) and a decision rule that requires this behavior to be inhibited. Converging evidence from PET and fMRI indicate that the dorsal division of the ACC (or ACcd, Brodmann area-BA-24b′-c′ and 32′) plays a key role in the various cognitive processes involved in the Stroop task (e.g., interference, allocation of attentional resources, response selection) (Bush et al., 1998; Bush, Luu, & Posner, 2000).

The capacity to inhibit behaviors or responses that are inappropriate in the current context can be studied using Go/No-Go tasks, in which the participant is required to refrain from responding to designated items within a series of stimuli. Several studies (Castellanos et al., 2000; Hartung, Milich, Lynam, & Martin, 2002; Iaboni, Douglas, & Baker, 1995; Itami & Uno, 2002; Vaidya et al., 1998) have shown that AD/HD subjects

exhibit more errors on Go/No-Go tasks. Furthermore, the results of a number of fMRI studies during Go/No-Go tasks indicate that several prefrontal regions (ACC, dorsolateral prefrontal cortex, orbitofrontal cortex, ventrolateral prefrontal cortex) (Casey, Durston, & Fossella, 2001; Garavan, Ross, & Stein, 1999; Garavan et al., 2002; Kiehl, Liddle, & Hopfinger, 2000; Konishi, Nakajima, Uchida, Sekihara, & Miyashita, 1998; Liddle, Kiehl, & Smith, 2001; Menon, Adleman, White, Glover, & Reiss, 2001; Rubia, Smith, Brammer, & Taylor, 2003) and the striatum (Menon et al., 2001) are crucially involved in response inhibition. Underactivation of the striatum (Booth et al., 2005; Durston et al., 2003; Rubia et al., 1999; Teicher et al., 2000; Vaidya et al., 1998) and prefrontal regions (Booth et al., 2005; Rubia et al., 1999; Tamm, Menon, Ringel, & Reiss, 2004; Vaidya et al., 1998) has been observed in children and adolescent with AD/HD during Go/No-Go tasks.

The results of several clinical studies carried out during the last thirty years suggest that neurofeedback may be efficacious in treating children with AD/HD (Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003; Kropotov et al., 2005; Linden, Habib, & Radojevic, 1996; Lubar & Shouse, 1976; Lubar & Lubar, 1984; Lubar, Swartwood, Swartwood, & O'Donnell, 1995; Monastra, Monastra, & George, 2002; Rossiter & LaVaque, 1995; Rossiter, 2004; Shouse & Lubar, 1979; Tansey, 1984, 1985; Thompson & Thompson, 1998). In many of these studies, the operant enhancement of sensorimotor rhythm (SMR) (12–15 Hz) and/or beta 1 (15–20 Hz) EEG activity from the regions overlying the Rolandic area, was trained concomitantly with suppression of theta (4–7 Hz) activity. The basic assumption guiding this approach is that SMR enhancement reduces problems of hyperactivity, whereas increasing beta 1 activity and suppressing theta activity diminishes attention deficits (Lubar & Shouse, 1976). In keeping with this assumption, these studies demonstrated that neurofeedback training (NFT) can significantly reduce attention deficits and hyperactivity in children with AD/HD.

In this context, the main objective of this work was to measure the effects of NFT, in AD/HD children, on the neural substrates of selective attention and response inhibition. FMRI experiments were conducted during a Counting Stroop task (Experiment 1) and a Go/No-Go task (Experiment 2). Behavioraly, we predicted that NFT would significantly improve performance on both tasks. Neurally, we predicted that NFT would significantly increase ACcd activity during the Counting Stroop task, and prefrontal as well as striatal activity during the Go/No-Go task.

MATERIALS AND METHODS

Subjects

The study sample was composed of 20 AD/HD children. These AD/HD children were randomly assigned to either an Experimental (EXP) group or a control (CON) group. Fifteen AD/HD children comprised the EXP group (4 girls and 11 boys, mean age: 10.2, *SD*: 1.3, range: 8–12) and five ADHD children comprised the CON group (5 boys, mean age: 10.2, *SD*: 0.8, range: 9–11). The EXP group received NFT whereas the CON group received no treatment (the CON group served specifically to measure the effect of passage of time). The parents of the subjects gave written informed consent and the study was approved

by the ethics research committees of the Centre hospitalier de l'Université de Montréal (CHUM), Hôpital Notre-Dame, and Hôpital Ste-Justine (a pediatric hospital affiliated with Université de Montréal). Inclusion criteria for all subjects were: (1) age 8 to 12 years; (2) right-handedness (Edinburgh Handedness Inventory, Oldfield, 1971); (3) $IQ > 85$ (based on the *Wechsler Intelligence Scale for Children*-Revised—WISC-R); and (4) a diagnosis of AD/HD based on the DSM-IV criteria (DSM-IV, 1994). All were native French speakers. Exclusion criteria for all subjects were the presence of: (1) any current Axis I psychiatric diagnosis other than AD/HD; (2) a learning disability (e.g., dyslexia, dyscalculia); (3) a neurologic disorder (e.g., epilepsia); (4) a neuropsychiatric disorder (e.g., Major Depressive Disorder, Obsessive-Compulsive Disorder).

No subjects were taking psychostimulant drugs during the study (subjects in both EXP and CON groups were treated with methylphenidate before the beginning of the study-none of the subjects did undergo cognitive training before this study). Clinical and neuropsychological assessments were performed at the Hôpital Ste-Justine's AD/HD Clinic. Clinical assessment included: (1) psychiatric, medical, and neurologic evaluations by a board certified child psychiatrist; (2) structured diagnostic interview with the Structured Clinical Interview (Spitzer, Williams, Gibbon, & First, 1992) and an AD/HD symptom checklist from DSM-IV (1994). Neuropsychological testing included the Digit Span subtest of the Wechsler Intelligence Scale for Children—Revised (WISC-R) (Wechsler, 1981) to assess attention span and the Integrated Visual and Auditory Continuous Performance Test (IVA, version 4.3) to evaluate visual and auditory attention (Tinius, 2003). The Conners Parent Rating Scale–Revised (CPRS-R) (Full Scale Attention Quotient and Full Scale Response Control Quotient) was also used to obtain parental reports of subjects's behavioral problems regarding specifically inattention and hyperactivity (Conners et al., 1997). Scaled scores were used for data analysis.

The Digit Span, the IVA, and the CPRS-R were administered at Time 1 (1 week before the beginning of the NFT) and Time 2 (1 week after the end of the NFT). At Time 1 the EXP and CON groups did not differ cognitively and behaviorally (Table I). Within- and between-groups comparisons were performed using two-tailed *t*-tests.

NFT

NFT was based on a protocol previously developed by Lubar and Lubar (1984). It was conducted over a period of 13 weeks and a half (40 sessions, three training sessions per-week). The training was divided in two phases (20 sessions in each phase): in the first phase, subjects in the EXP group were trained to enhance the amplitude of the SMR (12–15 Hz) and decrease the amplitude of theta activity (4–7 Hz); in the second phase, EXP subjects learned to inhibit the amplitude of their theta waves (4–7 Hz) and increase the amplitude of their beta 1 waves (15–18 Hz). NFT was provided using the Lexicor NRS-24 Biolex program (version 2.40) (Lexicor, Boulder, CO) and the Procomp + Biograph program (version 2.1) (Thought Technology Ltd, Montreal, Canada). For each subject, these systems were used in an alternating manner. Each session lasted 60 min. EEG was recorded from CZ, with reference placed on the left earlobe and ground electrode on the right earlobe. A sampling rate of 128 Hz with 2 s epochs was used. Skin impedance was less than 5 KΩ. The pertinent frequencies were extracted from EEG recordings and feed back using an audio-visual online feedback loop in the form of a video game. Each session

Table I. Neuropsychological Data

	Time 1		Time 2	
	CON	EXP	CON	EXP
Digit span				
Mean	7.6	9.8	8.8	11.6*
SD	1.9	2.9	3.4	3.7
IVA				
Mean	78.2	77.5	78.4	85***
SD	24	22	33.4	18
CPRS-R				
Inattention				
Mean	73.4	71.6	71.2	58.9****
SD	9.9	8.4	12.1	7.2
Hyperactivity				
Mean	75.8	79.4	73.8	64.3*
SD	9.9	10.8	9.3	18.9

Note. CON: Control; EXP: Experimental; IVA: Integrated Visual and Auditory Continuous Performance Test; CPRS-R: Conners Parent Rating Scale—Revised.
*$p < 0.05$; ***$p < 0.005$;****$p < 0.001$.

was subdivided in 2 min periods (that were gradually increased up to 10 min). During these periods, subjects were either attempting to maintain a state of relaxation, solve mathematical problems or read texts.

EXPERIMENT 1

Behavioral Protocol

The behavioral protocol used was based on the protocol conceived by Bush and colleagues (1998) with respect to the Counting Stroop task. Subjects were instructed that they would see sets of one to four identical words appear on the screen. They were told also to report, through button-press, the number of words in each set, regardless of what the words were. During ''Neutral'' blocks, the words consisted of names of common animals (dog, cat, bird, or mouse) whereas during ''Interference'' blocks, the stimuli were the number words ''one,'' ''two,'' ''three,'' or ''four'' (words were presented in French). Subjects were told that the keypad buttons represented one, two, three, and four from left to right, and subjects utilized the index and middle fingers of the right hand to respond. Subjects were instructed that the sets would change every 1.5 s. In addition, they were told to answer as quickly and accurately as possible. Immediately prior to entering the scanner, subjects completed a 1-min computerized practice version of the task (20 Neutral trials followed by 20 Interference trials). During the functional scan, which started with 9 s of fixation on a cross, six 30 s blocks of the Neutral words alternated with six Interference blocks. Subjects completed 20 trials during each (Neutral/Interference) block, i.e., 120 total trials of each type during the functional scan session. The order of presentation of the blocks was counterbalanced across subjects. Accuracy (percent correct) and reaction times were monitored during the scan (due to space limitations, the reaction time data will be presented and discussed in a separate article).

Using the E-Prime software (version 1.1, Psychology Software Tools, Inc., Pittsburgh, PA), stimuli were produced on an IBM Aptiva P3 600 MHz and projected, via a Plus U4136 color LCD projector (Tokyo, Japan), through a collimating lens onto a rear-projection screen that was fastened vertically in the magnet bore at neck level. Subjects viewed the stimuli on a tilted mirror placed in front of their head. Individual words subtended about 1°of the visual angle vertically, and sets of four words subtended a visual angle of about 6° vertically.

Image Acquisition

Echoplanar images (EPI) were acquired on a 1.5 Tesla system (Sonata, Siemens Electric, Erlangen, Germany). Twenty-eight slices (4 mm thick) were acquired every 2.65 sec in an inclined axial plane, aligned with the AC-PC axis. These T2*. weighted functional images were acquired using an EPI pulse sequence (echo-spacing time = 0.8 ms, TE = 54 ms, Flip = 90°, FOV = 215 mm, voxel size = 3.36 mm × 3.36 mm × 4 mm, matrix = 64 × 64). Following functional scanning, high-resolution data were acquired via a Tl-weighted three-dimensional volume acquisition obtained using a gradient echo pulse sequence (TR = 9.7 ms, TE = 4 ms, flip = 12°, FOV = 250 mm, matrix = 256 × 256).

FMRI Data Analysis

Data were analyzed using Statistical Parametric Mapping software (SPM2, Wellcome Department of Cognitive Neurology, London, UK). Images for all subjects were realigned to correct for artifacts due to small head movements. The images for all subjects were then spatially normalized into an MRI stereotactic space, and convolved in space with a three-dimensional isotropic Gaussian kernel (12 mm FWHM) to improve the signal-to-noise ratio and to accommodate for residual variations in functional neuroanatomy that usually persist between subjects after spatial normalization. Even if the subjects were children, the Talairach and Tournoux (1988) template was used since Burgund et al. (2002) have recently shown that even if there are some small anatomical differences between the brain' structures and sulci of adults (age range: 18–30) and those of children (age range: 7–8), those differences do not compromise the usefulness of an adult stereotactic space for children's functional images, assuming a functional resolution of 5 m in images averaged across children.

For the statistical analysis, the time series of the images were convolved with the hemodynamic response function which approximates the activation patterns. Effects at each and every voxel were estimated using the general linear model. Voxel values for the contrasts of interest yielded a statistical parametric map of the *t* statistic (SPM *t*), subsequently transformed to the unit normal distribution, (SPM Z). To identify the brain regions associated with the Counting Stroop task a random-effects model was implemented to compare the brain activity associated with the Interference trials and that associated with the Neutral trials (Interference minus Neutral). This procedure allows one to make inferences on the population of which participants are deemed representative (Friston & Frackowiak, 1997). At Time 1 and Time 2 this model was implemented to produce the Interference minus Neutral contrasts for both EXP and CON groups (within-group

statistical comparison). This model was implemented using a multistage approach. First, each subject's data were summarized with an appropriate single image per condition. These single scan per condition per subject images were then entered into a group analysis, i.e., a model at the between subject level using a one-sample *t*-test. The variance of these single images from subject to subject consisted of contributions from both the between and within subject components of variance, in the correct proportions. In addition, for the Interference minus Neutral contrast, a two-sample *t*-test was carried out to compare the mean blood oxygenation level-dependent (BOLD) response within each group at Time 2 v. Time 1. Height threshold was set at $p < 0.001$ ($z = 3.09$), uncorrected for multiple comparisons. Only clusters showing a spatial extent of at least five contiguous voxels were kept for image analysis.

EXPERIMENT 2

Behavioral Protocol

The event-related Go/No-Go task consisted of a 3250 ms rest epoch at the beginning and a 3250 ms second rest epoch at the end of the task, during which subjects passively viewed the plus sign. The letters "O" (66.7% of trials) and "V" (33.3% of trials) were presented in random order every 3500 ms for 250 ms. Subjects were instructed to respond with a key press to the letter "O" (Go trials) and to withhold the response to letter "V" (No-Go trials). A higher percentage of "O" stimuli allowed for the build-up of a prepotent response. All subjects responded using the forefinger of the right hand. In total, subjects completed 120 trials (80 Go trials and 40 No-Go trials). Accuracy (percent correct) and reaction times were recorded during the scan (the reaction time data will be discussed in a separate report). Stimuli were presented as in Experiment 1.

Image Acquisition

FMRI data were acquired using the same scanning parameters as in Experiment 1. The task was programmed using the E-Prime software (version 1.1, Psychology Software Tools, Inc., Pittsburgh, PA) on an IBM Aptiva P3 600 MHz. Initiation of the scan and task was synchronized using a TTL pulse delivered to the scanner timing microprocessor board from a button box connected to the IBM.

FMRI Data Analysis

Data were analyzed using SPM2. Image preprocessing was identical to that in Experiment 1. General linear modeling was carried out for the functional scans from each subject by modeling the measured event-related BOLD signals and regressors to determinate the relationship between the experimental parameters and the hemodynamic response. Event-related analyses were performed by using the default statistical parametric mapping basis function, a synthetic hemodynamic response function consisting of two gamma functions and its derivative. Regressors were generated by convolving a train of delta functions (repre-

senting the sequence of individual trials) with the base function. The linear combination of all the regressors was used to model the hemodynamic response to two conditions: No-Go and Go trials. The six realignment parameters produced during motion correction served as covariates. The images for each participant were concatenated into a single image for each of the two conditions. The specific effects of response inhibition were tested by applying appropriate linear contrasts to the parameter estimates for the No-Go minus correct Go contrast, resulting in a contrast map for each participant. The contrast images of all participants were entered into second-level group analyses conducted with a random-effects statistical model.

RESULTS

Neuropsychological Data

At Time 1, there was no significant difference between CON and EXP subjects with regard to the average scores on the Digit Span, the IVA, and the CPRS-R (Table I). This suggests that before EXP subjects started the NFT, inattention and hyperactivity were equivalent in both groups. At Time 2, the scores of the CON subjects on the three tests were not significantly different than those at Time 1 (Table I). For the EXP group, however, the scores on the Digit Span and the IVA significantly increased at Time 2, compared to Time 1 (Digit Span: $p < 0.05$; IVA: $p < 0.005$) (Table I). Furthermore, at Time 2 the scores on the Inattention and Hyperactivity components of the CPRS-R significantly decreased, relative to Time 1 (Inattention: $p < 0.001$; Hyperactivity: $p < 0.05$) (Table I).

EXPERIMENT 1

Behavioral Data

For the Neutral trials at Time 1, the average accuracy scores (percentage of correct responses) were not statistically different between the CON (58.4%, $SD = 24$) and EXP (48.1%, $SD = 25.5$) groups (Table II). At Time 2, the average accuracy score of the CON subjects (59.6%, $SD = 24.3$) was comparable to that of Time 1. For the EXP group, this score was significantly higher ($P < 0.05$) at Time 2 (67%, $SD = 18.3$) than Time 1 (Table II).

Table II. Counting Stroop Task (Percentage of Correct Responses)

	Time 1		Time 2	
	CON	EXP	CON	EXP
Neutral trials				
Mean	58.4	48.1	59.6	67*
SD	24	25.5	24.3	18.3
Interference trials				
Mean	55.8	48.2	56.8	68*
SD	24.1	23.8	24.3	13.9

Note. CON: Control; EXP: Experimental.
*$p < 0.05$.

For the Interference trials, the pattern was very similar, that is, at Time 1 the average accuracy scores of the CON (55.8%, $SD = 24.1$) and EXP (48.2%, $SD = 23.8$) groups were comparable (Table II). At Time 2, the average accuracy score of the CON subjects (56.8%, $SD = 24.3$) was not different than that of Time 1. For the EXP group, this score was significantly greater ($p < 0.05$) at Time 2 (68%, $SD = 13.9$) than Time 1 (Table II).

Functional MRI Data

CON Group

At Time 1, the Interference minus Neutral contrast generated a significant locus of activation in the left superior parietal lobule (BA 7) (Table III, Fig. 1). At Time 2, this contrast was associated with another locus of activation in the left superior parietal lobule (BA 7) (Table III, Fig. 1). The two-sample *t*-test performed to compare BOLD responses at Time 1 and Time 2 did not reveal anything significant.

EXP Group

At Time 1, the Interference minus Neutral contrast produced a significant locus of activation in the left superior parietal lobule (BA 7) (Table III, Fig. 1). At Time 2, this contrast was associated with another locus of activation in the left superior parietal lobule (BA 7) (Table III, Fig. 1). Significant loci of activation were also detected in the right ACcd (BA 32), left caudate nucleus and left substantia nigra (Table III, Fig. 1). Moreover, a two-sample *t*-test revealed that BOLD activation in the right

Table III. Interference Minus Neutral Contrast at Time 1 and Time 2

Group	Region	Brodmann area	Talairach coordinates (mm)			Z-statistic
			x	*y*	*z*	
TIME 1						
EXP	L Superior parietal lobule	7	− 36	− 46	50	3.83
CON	L Superior parietal lobule	7	− 16	− 80	37	3.44
TIME 2						
EXP	R ACcd	32	3	27	35	4.54
	L Caudate nucleus		− 12	12	14	4.34
	L Superior parietal lobule	7	− 23	− 60	30	3.60
	L Substantia nigra		− 12	− 19	− 5	3.02
CON	L Superior parietal lobule	7	− 12	− 56	41	3.93

Note. Stereotaxic coordinates are derived from the human atlas of Talairach and Tournoux (1988) and refer to medial-lateral position (*x*) relative to medline (positive = right), anterior-posterior position (*y*) relative to the anterior commissure (positive = anterior), and superior–inferior position (*z*) relative to the commissural line (positive = superior). Designation of Brodmann areas for cortical areas are also based on this atlas. CON: Control; EXP: Experimental; L: Left; R: Right.

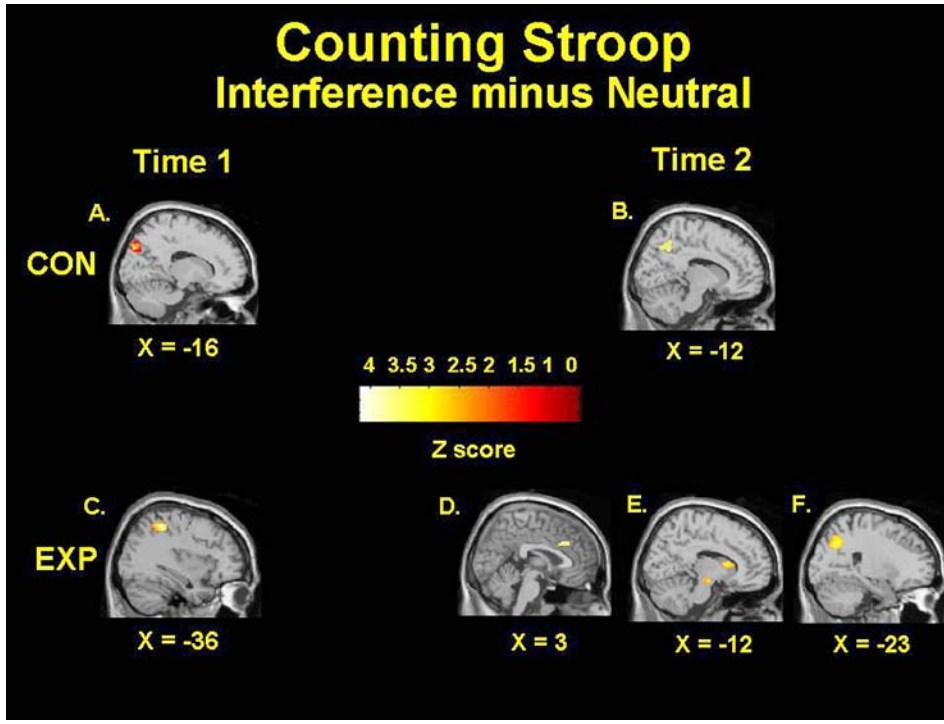

Fig. 1. Statistical activation maps at Time 1 and Time 2 produced by the Interference minus Neutral contrast. Images are sagittal sections for the data averaged across subjects. At Time 1, significant loci of activation were detected in the left superior parietal lobule for both the CON (A) and EXP (C) groups. At Time 2, activations were also noted in this cortical region for the CON (B) and EXP (F) groups. In addition, for the EXP group only, significant loci of activation were measured in the right ACcd (D), as well as the left caudate nucleus and left substantia nigra (E).

ACcd (BA 32) and left caudate nucleus was significantly greater at Time 2 than Time 1 (Table IV).

EXPERIMENT 2

Behavioral Data

For the Go trials at Time 1, the average accuracy scores (percentage of correct responses) were not statistically different between CON (92.4%, $SD = 20$) and EXP (88%, $SD = 15$) subjects (Table V). At Time 2, the average accuracy score of the CON subjects (84%, $SD = 15$) was comparable to that of Time 1. For the EXP group, this score was significantly greater ($p < 0.05$) at Time 2 (95%, $SD = 4.9$) than Time 1 (Table V).

For the No-Go trials at Time 1, the average accuracy scores of the CON (74%, $SD = 11.3$) and EXP (78%, $SD = 13.8$) groups were comparable (Table V). At Time 2, the average accuracy score of the CON subjects (84%, $SD = 11.5$) was not different than that of Time 1. For the EXP group, this score was significantly higher ($p < 0.0005$) at Time 2 (94%, SD 4.8) than Time 1 (Table V).

Table IV. EXP Group: Time 1 v. Time 2 (Interference Minus Neutral Contrast)

Group	Region	Brodmann area	Talairach coordinates (mm)			*Z*-statistic
			x	*y*	*z*	
EXP	R ACcd	32	3	30	27	3.42
	L Caudate nucleus		− 12	17	8	3.16

Note. Stereotaxic coordinates are derived from the human atlas of Talairach and Tournoux (1988) and refer to medial–lateral position (*x*) relative to medline (positive = right), anterior–posterior position (*y*) relative to the anterior commissure (positive = anterior), and superior–inferior position (*z*) relative to the commissural line (positive = superior). Designation of Brodmann areas for cortical areas are also based on this atlas. CON: Control; EXP: Experimental; L: Left; R: Right.

Functional MRI Data

CON Group

At both Time 1 and Time 2, the No-Go minus Go contrast did not produce any significant locus of activation. The two-sample *t*-test performed to compare BOLD responses at Time 1 and Time 2 did not reveal anything significant.

EXP Group

The No-Go minus Go contrast did not produce any significant locus of activation at Time 1. At Time 2, significant loci of activation were noted in the right ACcd (BA 24/32), right ventrolateral prefrontal cortex (BA 47), left thalamus, left caudate nucleus, and left substantia nigra (Table VI, Fig. 2). A two-sample *t*-test confirmed that BOLD signal in these brain regions was significantly greater at Time 2 relative to Time 1.

DISCUSSION

The Time 2 v. Time 1 comparison of the average scores on the Digit Span, the IVA, and the CPRS-R reveals that the neurofeedback protocol used here led to a significant decrease

Table V. Go/No-Go task (Percentage of Correct Responses)

	Time 1		Time 2	
	CON	EXP	CON	EXP
Go trials				
Mean	92.4	88	84	95*
SD	20	15	15	4.9
No-Go trials				
Mean	74	78	84	94*
SD	11.3	13.8	11.5	4.8

Note. CON: Control; EXP: Experimental.
*$p < 0.05$; **$p < 0.0005$.

Table VI. Go/No-Go No-Go Minus Go Contrast at Time 2

Group	Region	Brodmann area	Talairach coordinates (mm)			Z-statistic
			x	*y*	*z*	
EXP	L Thalamus		− 3	− 17	− 1	5.12
	L Substantia nigra		− 3	− 12	− 9	4.27
	R ACcd	24/32	3	44	3	4.01
	L Caudate nucleus		− 18	− 16	26	3.73
	R Ventrolateral prefrontal cortex	47	36	17	− 6	3.97

Note. Stereotaxic coordinates are derived from the human atlas of Talairach and Tournoux (1988) and refer to medial–lateral position (*x*) relative to medline (positive = right), anterior–posterior position (*y*) relative to the anterior commissure (positive = anterior), and superior–inferior position (*z*) relative to the commissural line (positive = superior). Designation of Brodmann areas for cortical areas are also based on this atlas. CON: Control; EXP: Experimental; L: Left; R: Right.

of inattention and hyperactivity, which are primary symptoms of AD/HD. Indeed, the EXP group showed marked improvement in attention and behavioral inhibition following NFT. This improvement was associated with a better performance on the Counting Stroop task (for both Neutral and Interference trials) and the Go/No-Go task (for both Go and No-Go

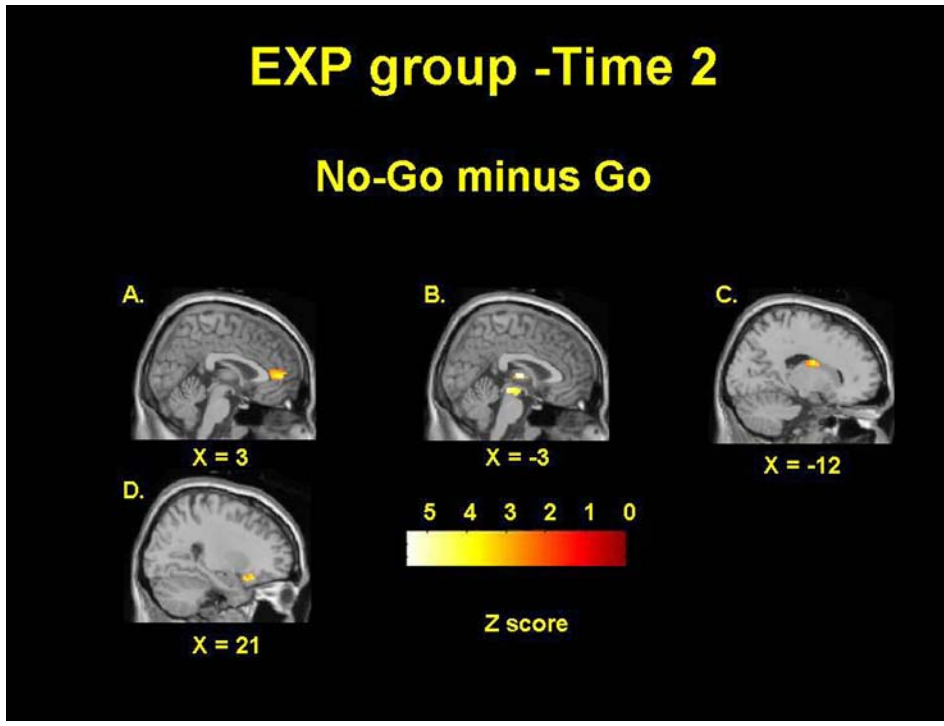

Fig. 2. Statistical activation maps measured at Time 2 in the EXP group (No-Go minus Go contrast). Significant loci of activation were measured in the right ACcd (A), left thalamus and left substantia nigra (B), left caudate nucleus (C), and right ventrolateral prefrontal cortex (D).

trials).With respect to the CON group, no such change was noted at Time 2 relative to Time 1. These neuropsychological and behavioral findings accord with those of previous studies showing that NFT can significantly improve attention and response inhibition in AD/HD children (Fuchs et al., 2003; Kropotov et al., 2005; Linden et al., 1996; Lubar & Shouse, 1976; Lubar & Lubar, 1984; Lubar et al., 1995; Monastra et al., 2002; Rossiter & LaVaque, 1995; Rossiter, 2004; Shouse & Lubar, 1979; Tansey, 1984, 1985; Thompson & Thompson, 1998). Our neuropsychological and behavioral findings provide further empirical support to the view that neurofeedback can be considered an effective treatment for children with AD/HD.

At Time 1 and Time 2, for EXP and CON groups the performance on the Counting Stroop task (Interference minus Neutral contrast) was associated with significant loci of activation in the left superior parietal lobule (BA 7). Functional neuroimaging studies have associated activity in superior parietal lobule—a component of the posterior attentional system-with visual vigilance (Pardo, Fox, & Raichle, 1991; Vandenberghe et al., 1996), and shifts of visual spatial attention (Corbetta, Miezin, Shulman, & Petersen, 1993; Vandenberghe, Gitelman, Parrish, & Mesulam, 2001). The left superior parietal lobule activations seen here for both groups of subjects may be related to such attentional processes.

No activation of the ACcd was detected at Time 1 for both groups of subjects. This is consistent with the results of an fMRI study recently carried by Bush et al. (1999). In this study, adults with AD/HD did not activate the ACcd while they performed a Counting Stroop task. For the EXP group at Time 2, significant loci of activation were seen in the right ACcd (BA 32), left caudate, and left substantia nigra. For the CON group, no activation was detected in these cerebral structures. As for the ACcd, a large corpus of functional brain imaging data reveals that this brain region exerts a pivotal role in the cognitive processes involved in the Stroop task (Bush et al., 1998; Bush et al., 2000), being critically implicated in selective attention, the selection of an appropriate response, and the suppression of inappropriate behavioral responses (Carter et al., 1998; Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1991; Pardo, Pardo, Janer, & Raichle, 1990; Paus, Petrides, Evans, & Meyer, 1993; Peterson et al., 1999). Given this, we posit that the better performance of the EXP subjects at Time 2 v. Time 1 was related to the normalization, following NFT, of neural activity in the ACcd, a central component of the anterior attentional system.

For both groups at Time 1, the No-Go minus Go contrast did not produce any significant locus of activation. This findings is in line with the results of previous fMRI studies having demonstrated an underactivation of the striatum (Booth et al., 2005; Durston et al., 2003; Rubia et al., 1999; Teicher et al., 2000; Vaidya et al., 1998) and diverse prefrontal areas (Booth et al., 2005; Rubia et al., 1999; Tamm et al., 2004; Vaidya et al., 1998) in children and adolescent with AD/HD during Go/No-Go tasks. For the EXP group at Time 2, however, significant loci of activation were detected in the right ACcd (BA 24/32), right ventrolateral prefrontal cortex (BA 47), left thalamus, left caudate nucleus, and left substantia nigra. These findings agree with the results of functional neuroimaging studies showing that the ACcd (Liddle et al., 2001; Menon et al., 2001), the ventrolateral prefrontal cortex (Garavan et al., 1999; Liddle et al., 2001; Menon et al., 2001), and the caudate nucleus (Booth et al., 2005; Menon et al., 2001) are implicated in the various cognitive processes underlying behavioral inhibition. Thus, the ACcd would be involved in decision formation and monitoring, whereas the ventrolateral prefrontal cortex would be specifically implicated in response inhibition (Liddle et al., 2001). Regarding the caudate nucleus, there

is some evidence that this brain region is involved in the motor inhibition of inappropriate behaviors (Casey et al., 2001). The caudate nucleus receives extensive anatomic projections from the frontal cortex and sends input back via the globus pallidus and then thalamus (Goldman-Rakic, 1987). This fronto-striatal network modulates neural computations in the supplementary motor area, which plays a pivotal role in motor planning, initiation, and timing (Deiber, Honda, Ibanez, Sadato, & Hallett, 1999). The involvement of the thalamus in this network may explain the thalamic activation noted here during the No-Go trials.

The significant activations of the left caudate and left substantia nigra noted in the EXP group at Time 2, for both the Counting Stroop task and the Go/No-Go task, suggest that the normalizing effect of NFT was mediated, at least partially, by dopamine. This biogenic amine exerts a pivotal neuromodulatory effect in the brain (Seamans & Yang, 2004). Various lines of evidence indicate that a dysfunction in dopaminergic transmission in fronto-striatal circuits is related to AD/HD. First, AD/HD symptoms can be successfully treated with methylphenidate, a potent blocker of the reuptake of dopamine which augments the availability of this neuromodulator/neurotransmitter into the extraneuronal space (Dresel et al., 2000). Second, molecular genetic evidence suggests an association between AD/HD and polymorphism of the dopamine transporter gene, as well as the dopamine D4 and D5 receptor genes (for a review, see Bobb, Castellanos, Addington, & Rapoport, 2005). Third, structural MRI studies of individuals with AD/HD have reported volumetric reductions in the frontal lobes and striatum (Aylward et al., 1996; Castellanos et al., 1994, 1996; Durston et al., 2004; Filipek et al., 1997; Mataro et al., 1997; Mostofsky et al., 2002). Fourth, SPECT and PET studies carried out in AD/HD children, adolescents or adults have found decreased metabolism in diverse frontal and striatal regions (Amen & Carmichael, 1997; Kim et al., 2002; Lou et al., 1989; Sieg et al., 1995; Zametkin et al., 1990). Lastly, dopamine modulation of frontal activity during the performance of the Stroop task has been previously shown (Dolan et al., 1995).

The nigrostriatal dopaminergic system is involved in motor control whereas attention processes are regulated in part by mesocortical dopaminergic neurons (for a review, see Nieoullon & Coquerel, 2003). There is also some evidence indicating that dopamine underlies the integrative properties of the fronto-striatal circuits and supports synaptic plasticity processes such as long-term potentiation (Calabresi, Pisani, Mercuri, & Bernardi, 1996). On this basis, we postulate that the neurofeedback protocol used here led to the neuromodulation by dopamine of neural activity in fronto-striatal circuits. Furthermore, given the association between AD/HD and polymorphism of the D4 and D5 receptor genes, we also hypothesize that this neuroplastic phenomenon implicated long-term potentiation as well as the D4 and D5 receptors.

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