Effect of neurofeedback training on the neural substrates of selective attention in children with attention-deficit/hyperactivity disorder: A functional magnetic resonance imaging study

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Abstract

Attention Deficit Hyperactivity Disorder (AD/HD) is a neurodevelopmental disorder mainly characterized by impairments in cognitive functions. Functional neuroimaging studies carried out in individuals with AD/HD have shown abnormal functioning of the anterior cingulate cortex (ACC) during tasks involving selective attention. In other respects, there is mounting evidence that neurofeedback training (NFT) can significantly improve cognitive functioning in AD/HD children. In this context, the present functional magnetic resonance imaging (fMRI) study was conducted to measure the effect of NFT on the neural substrates of selective attention in children with AD/HD. Twenty AD/HD children—not taking any psychostimulant and without co-morbidity—participated in the study. Fifteen children were randomly assigned to the Experimental (EXP) group (NFT), whereas the other five children were assigned to the Control (CON) group (no NFT). Subjects from both groups were scanned 1 week before the beginning of the NFT (Time 1) and 1 week after the end of this training (Time 2), while they performed a Counting Stroop task. At Time 1, for both groups, the Counting Stroop task was associated with significant loci of activation in the left superior parietal lobule. No activation was noted in the ACC. At Time 2, for both groups, the Counting Stroop task was still associated with significant activation of the left superior parietal lobule. This time, however, for the EXP group only there was a significant activation of the right ACC. These results suggest that in AD/HD children, NFT has the capacity to normalize the functioning of the ACC, the key neural substrate of selective attention.

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Keywords: Attention; AD/HD children; Neurofeedback; fMRI; Anterior cingulate cortex

Attention Deficit Hyperactivity Disorder (AD/HD), a frequent developmental disorder of childhood, affects 3–7% of children and often continues into adulthood [2]. It is mainly characterized by inattention, hyperactivity, and impulsivity. These symptoms reflect impairments in cognitive functions. These functions have been largely associated with the brain systems found in the prefrontal lobes. In line with this, structural magnetic resonance imaging (MRI) studies have found significant volumetric reduction of the prefrontal cortices in children with AD/HD [8,13,22]. In addition, single photon emission computed tomography (SPECT) studies have shown decreased perfusion in prefrontal areas implicated in the control of attentional processes in AD/HD individuals [1,15]. Of note, a functional MRI (fMRI) study has demonstrated a dysfunction of the anterior cingulate cortex (ACC) in adults with AD/HD while they performed a Stroop task [4], a variant of the Stroop [30]. This task, which involves 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 lines of evidence from positron emission tomography (PET) and fMRI indicate that the dorsal division of the ACC (or ACd, Brodmann area–BA-32) plays a pivotal role in various cognitive processes implicated in the Stroop task [5,6]. The results of several clinical studies conducted during the last three decades suggest that neurofeedback (or EEG
biofeedback)—an operant conditioning procedure whereby an individual learns to self-regulate the electrical activity of his/her own brain—may be efficient in treating children with AD/HD [14,16–21,26,28,32–34]. In this context, the present fMRI study was conducted to measure the effect of NFT, in children with AD/HD, on the neural substrates of the selective attentional processes involved in the Counting Stroop task.

Twenty AD/HD children comprised the study sample. 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, S.D.: 1.3; range: 8–12) and five AD/HD children comprised the CON group (5 boys, mean age: 10.2, S.D.: 0.8, range: 9–11). The EXP group received NFT whereas the CON group received no treatment. The parents of the subjects gave written informed consent and the study—which was conducted in accordance with the Declaration of Helsinki—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 8–12 years; (2) right-handedness (Edinburgh Handedness Inventory, [23]); (3) IQ > 85 (based on the age 8–12 years; (2) right-handedness (Edinburgh Handedness Inventory, [23])); (3) IQ > 85 (based on the Structured Clinical Interview[29] and an AD/HD symptom checklist from DSM-IV [10]. Exclusion criteria for all subjects were the presence of: (1) any current Axis I psychiatric diagnosis other than AD/HD; (2) a learning disability; (3) a neurologic disorder; (4) a neuropsychiatric disorder.

No subjects were taking psychostimulants 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. Assessment included: (1) psychiatric, medical, and neurologic evaluations by a board certified child psychiatrist; (2) structured diagnostic interview with the Structured Clinical Interview [29] and an AD/HD symptom checklist from DSM-IV [10]. Neuropsychological testing included the Digit Span subtest of the Wechsler Intelligence Scale for Children—Revised (WISC-R) [36] to assess attention span, the Integrated Visual and Auditory Continuous Performance Test (IV A, version 4.3) to evaluate visual and auditory attention [35], and the Conners Parent Rating Scale—Revised (CPRS-R) (Attention Quotient and Response Control Quotient), to obtain parental reports of subjects’ behavioral problems regarding specifically inattention and hyperactivity [9]. Scaled scores were used for data analysis.

The Digit Span, the IV A, 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 1). Within- and between-group comparisons were performed using two-tailed t-tests.

The behavioral protocol used was based on the protocol developed by Bush et al. [6] with respect to the Counting Stroop task. Subjects were instructed that they would see sets of one—four identical words appear on the screen. They were told also to report, through button-press, the number of words in each set, independently 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.” Subjects were instructed that the sets would change every 1.5 s. During the functional scan, which started with nine sec 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 trials total. During each type during the functional scan session. The order of presentation of the blocks was counterbalanced across subjects. 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). Subjects viewed the stimuli on a tilted mirror placed in front of their head.

NFT was based on a protocol previously proposed by Lubar and Lubar [18]. 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 Biodex 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 utilized. Skin impedance was less than 5 KΩ.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Neurropsychological and CPRS-R data</th>
<th>Time 1</th>
<th>Time 2</th>
<th>EXP</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRPS-R inattention</td>
<td>Mean</td>
<td>73.4</td>
<td>71.6</td>
<td>71.2</td>
<td>58.9</td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td>9.9</td>
<td>8.4</td>
<td>12.1</td>
<td>7.2</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>Mean</td>
<td>75.8</td>
<td>79.4</td>
<td>73.8</td>
<td>64.3</td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td>9.9</td>
<td>10.8</td>
<td>9.3</td>
<td>18.9</td>
</tr>
</tbody>
</table>


*P < 0.05.
***P < 0.005.
****P < 0.001.
The relevant 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 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.

Twenty-eight slices (4 mm thick) were acquired on a 1.5 T system (Sonata, Siemens Electric, Erlangen, Germany) every 2.65 s using an echo-planar (EPI) pulse sequence. Following functional scanning, high-resolution anatomical data were acquired using a gradient echo pulse sequence.

Data were analyzed using Statistical Parametric Mapping software (SPM2, Wellcome Department of Cognitive Neurology, London, UK). The images for all subjects were spatially normalized into an MRI stereotactic space [31]. 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). 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). 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 versus 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.

At Time 1, there was no significant difference between CON and EXP subjects with respect to the average scores on the Digit Span, the IVA, and the CPRS-R (Table 1). This indicates that before EXP subjects start the NFT, inattention and hyperactivity were comparable in both groups. At Time 2, the scores on the Digit Span and the IVA significantly increased at Time 2, relative to Time 1 (Digit Span: \( P < 0.05 \); IVA: \( P < 0.005 \)) (Table 1).

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

For the Interference trials, the pattern was very similar, i.e. at Time 1 the average accuracy scores (percentage of correct responses) of the CON (55.8%, S.D.: 23.8) and EXP (48.2%, S.D.: 23.8) groups were comparable (Table 2). At Time 2, the average accuracy score of the CON subjects (56.8%, S.D.: 24.3) was not different than that of Time 1. For the EXP group, this score was significantly higher (\( P < 0.05 \)) at Time 2 (68%, S.D.: 13.9) than Time 1 (Table 2).

For the CON group, the Interference minus Neutral contrast produced a significant locus of activation in the left superior parietal lobule (BA 7) (Table 3 and Fig. 1). At Time 2, this contrast was associated with another locus of activation in the left superior parietal lobule (BA 7) (Table 3 and Fig. 1). The two-sample

### Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Region</th>
<th>Talairach coordinates (mm)</th>
<th>Z-statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( x )</td>
<td>( y )</td>
</tr>
<tr>
<td><strong>Time 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXP</td>
<td>L. Superior parietal lobule</td>
<td>7</td>
<td>-36</td>
</tr>
<tr>
<td>CON</td>
<td>L. Superior parietal lobule</td>
<td>7</td>
<td>-16</td>
</tr>
<tr>
<td><strong>Time 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXP</td>
<td>R. Acurol</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>L. Caudate nucleus</td>
<td></td>
<td>-12</td>
</tr>
<tr>
<td></td>
<td>L. Superior parietal lobule</td>
<td>7</td>
<td>-23</td>
</tr>
<tr>
<td></td>
<td>L. Substantia reta</td>
<td></td>
<td>-12</td>
</tr>
<tr>
<td>CON</td>
<td>L. Superior parietal lobule</td>
<td>7</td>
<td>-12</td>
</tr>
</tbody>
</table>

Stereotactic coordinates are derived from the human atlas of Talairach and Tournoux [32] and refer to medial–lateral position (\( x \)) relative to midline (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.
t-test conducted to compare BOLD responses at Time 1 and Time 2 did not reveal anything significant.

For the EXP group, the Interference minus Neutral contrast produced a significant locus of activation in the left superior parietal lobule (BA 7) (Table 3 and Fig. 1). At Time 2, this contrast produced another locus of activation in the left superior parietal lobule (BA 7) (Table 3 and Fig. 1). In addition, significant loci of activation were noted in the right ACcd (BA 32), left caudate nucleus and left substantia nigra (Table 3 and Fig. 1). Of note, a two-sample t-test revealed that BOLD activation in the right ACcd (BA 32) and left caudate nucleus was significantly greater at Time 2 than Time 1 (Table 4 and Fig. 2).

The Time 2 versus Time 1 comparison of the average scores on the Digit Span, the IVA, and the CPRS-R indicate that the neurofeedback protocol used here led to a significant reduction of primary symptoms of AD/HD, such as inattention and hyperactivity. These neuropsychological and behavioral findings are consistent with those of previous studies which showed that NFT can lead to clinically significant improvement of attention, motor control, and impulse regulation in AD/HD children [14,16–21,25,26,28,32–34]. Our neuropsychological and behavioral findings provide further empirical support to the view that neurofeedback may constitute an effective treatment for children with AD/HD. Yet, one cannot exclude the possibility that the cognitive improvement in the EXP group and the absence of cognitive improvement in the CON group may be ascribable to the fact that CON subjects did not receive an attentional training.

Table 4
EXP Group: Time 1 vs. Time 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Region</th>
<th>Brodmann area</th>
<th>Talairach coordinates (mm)</th>
<th>Z-statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
<td>R ACcd</td>
<td>32</td>
<td>3 30 27</td>
<td>3.42</td>
</tr>
<tr>
<td></td>
<td>L Caudate nucleus</td>
<td>–12 17 8</td>
<td></td>
<td>3.16</td>
</tr>
</tbody>
</table>

Stereotaxic coordinates are derived from the human atlas of Talairach and Tournoux (1988) and refer to medio-lateral position (x) relative to midline (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.
lasting the same time duration than the NFT received by EXP subjects. Further studies are awaited to tackle this important issue.

Neurally, for both groups of subjects, no activation of the ACcd was detected at Time 1. This finding is compatible with the results of a fMRI study recently carried by Bush et al. [4]. In this study, adults with ADHD failed to activate the ACcd while they performed a Counting Stroop task. For the EXP group at Time 2, however, significant loci of activation were noted in the right ACcd (BA 32), left cingulate, and left substantia nigra. For the CON group, no activation was detected in these three brain regions. With regard to the ACcd, a large body of functional neuroimaging data indicates that this brain region exerts a key role in the cognitive processes involved in the Stroop task [5,6], being crucially involved in selective attention, the selection of an appropriate response, and the suppression of inappropriate responses [24]. Given this, we submit that the better performance of the EXP subjects at Time 2 versus Time 1 was ascribable to the normalization, following NFT, of neural activity in the ACcd, a central component of the anterior attentional system.

The significant activations of the left cingulate and left substantia nigra seen in EXP subjects at Time 2 suggest that the normalizing effect of NFT upon ACcd was mediated, at least partially, by dopamine. Various lines of evidence suggest that a dysfunction in dopaminergic transmission in fronto-striatal circuits is related to AD/HD. Thus, AD/HD symptoms can be treated with methylphenidate, a potent blocker of the reuptake of dopamine which increases the availability of this neuromodulator [25].

There is some evidence indicating that dopamine underlies the integrative properties of the fronto-striatal circuits, which may serve as a support of synaptic plasticity processes, such as long-term potentiation [7]. Given this, we posited that the neurofeedback protocol used here led to the neuromodulation by dopamine of neural activity in the anterior cingulate–striatal circuit. We also hypothesized that this neuropsychiatric phenomenon implicated long-term potentiation as well as D4 and D5 receptor genes for a review, see [3]). Lastly, dopamine modulation of fronto activity during the performance of the Stroop task has been previously demonstrated [11].

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References