The Effects of Neurofeedback in the Default Mode Network: Pilot Study Results of Medicated Children with ADHD

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THE EFFECTS OF NEUROFEEDBACK IN THE DEFAULT MODE NETWORK: PILOT STUDY RESULTS OF MEDICATED CHILDREN WITH ADHD

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Children with attention deficit hyperactivity disorder (ADHD) have difficulty activating the Default Mode Network (DMN) in a resting or quiet state. The DMN function assists in processing and understanding a person’s internal, reflective world and the world of self and others. Neurofeedback (NFB), a type of EEG operant conditioning, trains self-regulation skills using a brain–computer interface. The hardware and software have audio/video capabilities to correct irregular brainwave patterns and regional cerebral blood flow associated with mental health and cognitive concerns. Individual treatment sessions usually last approximately 20 min; to gain the largest overall treatment effect, NFB users need to experience about 30 to 40 sessions. This study randomly assigned 12 children diagnosed with ADHD and currently on a stimulant medication to a treatment or control group. Subjects in the treatment group completed 40 NFB sessions. Pre- and posttest fMRIs were administered on the treatment and control groups. Evidence showed that the forty 20-min sessions of Sensory Motor Rhythm NFB consolidated the DMN allowing for appropriate activation in the posterior cingulate, precuneus, the temporoparietal junction and the cerebellar tonsils. In addition to regulating and increasing SMR at 12–15 Hz, our research results showed activation of the DMN in a resting state after 40 NFB sessions. Assisting children with ADHD to appropriately activate the DMN may help them be more adaptive and reflective and to better understand their own internal world and the world of others.

INTRODUCTION

Neurofeedback

Neurofeedback (NFB) is a form of neuromodulation. Neuromodulation simply means the alteration of some aspect of neuronal functioning. Three common methods are transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), and NFB. These methods appear to be clinically useful in a variety of situations. In the laboratory, neuromodulation is used in the investigation of brain structure and function.

NFB is a technique involving a brain–computer interface (BCI) that maps certain aspects of a client’s neurophysiology (e.g., brain wave amplitudes for various frequency bands) to some form of feedback, usually audio
or video that allows the brain to monitor and manipulate the underlying EEG activity. NFB, sometimes called EEG operant conditioning, is a type of self-regulation training (Swingle, 2010). When applied correctly, NFB has been found to lead to clinical improvements in several mental health disorders (Yucha & Montgomery, 2008). According to Yucha and Montgomery’s thorough reviews, the authors rated the combined efficacy of biofeedback and neurofeedback as Level 4—“Efficacious” for anxiety reduction, attention disorders, chronic pain, epilepsy, and headaches. NFB “reinforces an optimal baseline of central nervous system self-regulation” (Legarda, McMahon, Othmer, & Othmer, 2011, p. 1050). This self-regulation often decreases the need for multiple medications.

Numerous studies have shown the effectiveness of EEG neurofeedback with attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD). One of the major researchers in this area is Dr. Joel F. Lubar (1991), who discovered that more than 80 to 90% of people with ADD/ADHD improved significantly from protocols of neurofeedback/EEG. In a large study of 100 children who were receiving Ritalin, parent counseling, and academic support, Monastra, Monastra, and George (2002) found that only the 50 children who had NFB and medication sustained their improvement without the Ritalin. A position paper on NFB and the treatment of ADHD cited meta-analyses, large multisite randomized controlled trials, historical studies, and studies demonstrating efficacy levels as support for using neurofeedback as an evidence-based treatment for children with ADHD (Sherlin, Arns, Lubar, & Sokhadze, 2010). In 2009, Arns, de Ridder, Strehl, Breteler, and Coenen published a meta-analysis that included 15 studies and 1,195 clients with ADHD. Six of the studies had randomized controlled trials. The same authors also found there was a large effect size on the symptoms of impulsivity and inattention and a medium, clinically relevant effect size on hyperactivity after NFB treatment regimes. These findings raised the joint efficacy levels from the Association for Applied Psychophysiology and Biofeedback and the International Society for Neuronal Regulation guidelines from a Level 3—“Probably efficacious” to a Level 5—“Efficacious and specific.”

Loftouse, Arnold, Hersch, Hurt, and DeBeus (2012) of Ohio State University completed a limited pilot study of NFB for children with ADHD in which 36 children, ages 6 to 12 years, were assigned to treatment and sham control conditions and provided with 40 sessions of NFB. Their results lead them to recommend that a team of both proponents and critics of NFB conduct a large sample, similarly sham-controlled study with improved subject selection criteria and treatment procedures. Short of this research, their review of NFB treatment of pediatric ADHD leads them to conclude that NFB is “probably efficacious” for the treatment of ADHD. The debate and the research continue. At its lowest rating by its strongest critics, NFB for ADHD has been found to be Level 3—“Probably efficacious”; at its highest rating by its strongest proponents, it has been found to be Level 5—“Efficacious and specific.”

**Attention Deficit Hyperactivity Disorder**

ADHD is the most common childhood psychiatric disorder with a cumulative incidence reaching 7.5% by age 19 (Barbaresi et al., 2004). The main behavioral symptoms of the disorder are inattention and hyperactivity/impulsivity (Diagnostic and Statistical Manual of Mental Disorders [4th ed., text rev.]; American Psychiatric Association, 2000), but there is increased recognition of a reward/motivation deficit too (Tomasi & Volkow, 2012). According to Konrad and Eickhoff (2010), there has been a shift of focus from regional brain pathology in children with ADHD to dysfunction in distributed network organization. Regardless of the etiology, ADHD symptoms lead to impaired functioning and often are associated with other problems such as learning disorders, poor academic performance and conduct disorders. For those diagnosed with ADHD, some (~30%) may simply “outgrow” it as the symptoms of hyperactivity decrease in late adolescence. However, between 30 and 70% of children will have symptoms that persist into adulthood.
For many, stimulant medication is the treatment choice. Despite the proven efficacy of stimulant medication, these treatments still have a nonresponse rate of approximately 20% (Barkley, 2006). Those who have a variant of ADHD that will not remit will require a different treatment choice.

**Functional Magnetic Resonance Imaging**

By using functional magnetic resonance brain imaging (fMRI), neural activity can be mapped measuring the hemodynamic response (blood flow) in activated areas. These activated portions of the brain reflect differences in cerebral blood flow conditions. Typically, custom-designed paradigms emphasizing a specific focus, such as reading, rhyming, or motor-related Go or No Go tasks (response or nonresponse to a stimuli), are required of an fMRI subject.

In addition to observing the ADHD brain with EEG NFB, previous fMRI studies show children diagnosed with ADHD have anatomic and functional abnormalities in the rostral supplementary motor area (pre-SMA) of the brain (Suskauer, Simmonds, Fotedar, et al., 2008). This portion of the brain is responsible for behavioral “response preparation and response selection” (Suskauer, Simmonds, Caffo, et al., 2008, p. 1142). Tamm, Menon, Ringel, and Reiss (2004) found evidence that, during motor tasks, children with ADHD compensate for these functional abnormalities by relying on the prefrontal cortex excessively, thus precluding prefrontal resources typically used for higher order executive functioning. Structural abnormalities have been found in children with ADHD such as smaller prefrontal and premotor volumes in the brain (Mostofsky, Cooper, Kates, Dencikia, & Kaufmann, 2002) and cortical thinning (Shaw et al., 2006). Levesque, Beauregard, and Mensour (2006) researched 20 unmedicated children with ADHD and found that the 15 children treated with NFB had activation of several subcortical areas as compared to the five children in the control group. These researchers stated, “These results suggest that in AD/HD children, NFT has the capacity to normalize the functioning of the ACC (anterior cingulate cortex), the key neural substrate of selective attention” (p. 216).

**Default Mode Network**

Raichle and colleagues’ (2001) seminal work on the default mode network (DMN) described its primary network in the medial orbital prefrontal cortex, the anterior cingulate, the posterior cingulate, the precuneus region, the inferior parietal lobes, and the hippocampus. Researchers in the last decade have produced an abundance of new information concerning the function and purpose of the DMN in children diagnosed with ADHD (Liston, Cohen, Teslovich, Levenson, & Casey, 2011; Sestieri, Corbetta, Romani, & Shulman, 2011; Tomasi & Volkow, 2012; Yang et al., 2011). According to the Sestieri team (2011), the DMN, a set of brain regions, “is often considered a functionally homogeneous system that is broadly associated with internally directed cognition (e.g., episodic memory, theory of mind, self-evaluation)” (p. 4407). When fMRIs are administered and clients are requested to remain passive, quiet, or in a resting state, normal populations consistently activate the DMN. The opposite seems to occur with children who have ADHD.

The neuropathology associated with ADHD in the DMN has been demonstrated by abnormal signal fluctuations in the inferior frontal and superior parietal cortices, cingulum, and cerebellum (Cao et al. 2009; Liston et al., 2011; Yang et al., 2011; Zang et al., 2007). Tian et al. (2006) found higher resting state functional connectivity in the anterior cingulum, pons, insula, cerebellum, and thalamus. These studies tend to imply that there is altered connectivity in the parietal cortex (Uddin et al., 2008) and anterior cingulum (Fair et al., 2010), supporting the involvement of both executive attention and reward-motivational networks in ADHD (Rubia et al., 2009; Tomasi & Volkow, 2012).

Tomasi and Volkow (2012) studied an open-access resting state functional connectivity database of 247 ADHD children and 305 typically developing children and discovered that children with ADHD had lower connectivity in regions of the superior parietal cortex and
precuneus or default mode and in the cerebellum than the control subjects. This work is expansive and validating, as previous research studies have had much smaller sample sizes that have provided limitations to many of the results.

However, little research is available on the effects of NFB and the brain’s functioning anatomy with the DMN, the brain’s baseline state of normal activity, and the brain oxygen extraction fraction (Raichle et al., 2001). By examining the effect of NFB on DMN functioning and ADHD, we may better understand the clinical implications for ADHD.

PURPOSE

The purpose of this study was to examine the effect of NFB on ADHD and scan each participant’s brain for functional changes in the DMN regions. Given the similar range of influences of NFB and default mode network functions, we hypothesized that NFB would normalize DMN functions during resting states. Our hypothesis, if accepted, might be of interest to the neuroscience community for a couple of reasons:

- How do we explain the ability of standard NFB at Cz to strengthen the DMN function?
- What is the optimal method for improving DMN function using neuromodulation?

METHODS

Participants

Included in the study were 12 children and adolescents, male and female, between 9 and 15 years of age who were previously diagnosed with ADHD and were on a stimulant medication prescribed by a licensed provider. The subjects were screened for appropriateness of inclusion in the study using the inattentive or hyperactive/impulsive criteria from the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; American Psychiatric Association, 2000) and the Amen ADHD Survey. These criteria were included in a screening questionnaire. The Tests of Variable Attention was administered to all subjects before and after treatment (Greenberg & Kindschi, 1996). Consent and participation forms were signed.

Data were obtained from 12 subjects (11 male and one female; age range = 9–15 years; M age = 12.4 years, all were right-handed). Subjects were randomly assigned either to receive NFB treatment or to receive no additional treatment.

Experimental Design and Procedure

Treatment subjects (n = 6) received 40 NFB sessions occurring over a period of 13 weeks and 1 day, which consisted of increasing Sensory Motor Response (SMR) at 12–15 Hz at Cz (top of the head). NFB was performed by two trained neurotherapists following the protocol by J. O. Lubar and Lubar (1984) and Hirschberg (2007). All NFB sessions were conducted on a Nexus 10 using Biotrace software. Unipolar montages were used with the active electrode attached at the midsection of the head at Cz with the reference attached to the left mastoid bone behind the ear and the ground sensor attached to the right mastoid bone behind the ear. The goal of the NFB training was to raise the amplitude of the SMR (at 12–15 Hz) and inhibit the amplitude of high beta (20–30 Hz) and theta (4–7 Hz).

The desired frequencies were obtained from EEG recordings and feedback using music and puzzles with a feedback loop in the form of puzzles that unfolded into pictures when the correct SMR amplitude was obtained. At the beginning of each treatment session, participants were asked to complete a standardized symptom checklist stipulating whether their previously stated symptoms were “better, worse, or stayed the same” from session to session.

All subjects were scanned by a General Electric Signa 3 Tesla whole body scanner (GEMS, Wisconsin, USA) using an eight-channel, high-resolution head coil (GEMS, Wisconsin, USA). Subjects were scanned at two points, approximately 3 months apart, which we refer to as “pretreatment” and “posttreatment” for both the treatment and
the control groups. Participants were verbally instructed to “relax, try not to wiggle around, and remain awake during the scan.”

Before the functional imaging, a high-resolution, 3D, whole head image utilizing the fast spoil gradient echo sequence was acquired with 25 cm field of view, 256 × 256 matrix, and 128 division in a slab, with an in-plain resolution of 0.98 × 0.98 × 1 mm. The BOLD functional imaging used a gradient echo EPI sequence of 24 cm field of view, TR/TE = 3000/35 ms, 64 × 64 matrix size, 90° flip angle, in trans-axial direction, 3 mm slice thickness with no gap, and 50 slices to cover the whole brain. This functional scan provides a pixel resolution of 3.75 × 3.75 × 3 mm.

Spontaneous brain activity during default mode data acquisition was monitored using blood-oxygen-level-dependent fMRI (BOLD fMRI). Multislice T2*-weighted echo-planar images were acquired.

The acquired fMRI data were processed using FSL 4.1 (FMRIB analysis group, Oxford, UK). For default mode fMRI data, an Independent Component Analysis based program called Multivariate Exploratory Linear Optimized Decomposition into Independent Components in FSL was employed.

RESULTS

Our data were analyzed within each individual and as groups. The brain was normalized to a standard brain template in children, which was generated from Cincinnati Children’s Hospital (n.d.) children template. At the end, the brains were resampled into a resolution of 4 mm.

After the independent components (ICs) were generated, a denoising was processed manually by removing all the motion-artifact related independent components. This denoising procedure was repeated until a reasonable amount of ICs were obtained.

The DMN from each group was identified from the ICs and used for the higher level group comparison using the fMRI Expert Analysis Tool. The GLM method used in first-level (time-series) data analysis is known as FILM (FMRIB’s Improved Linear Model). For higher level analysis, the fMRI Expert Analysis Tool uses FLAME (FMRIB’s Local Analysis and Mixed Effects). The statistical threshold for the Z score is $Z > 2.29$. The $p$ threshold is $> .05$ (see Figure 1). The NFB data were analyzed using the mean amplitude scores from the first SMR neurofeedback sessions and comparing it to the mean amplitude score of the 40th neurofeedback session. A paired $t$ test was calculated using SSPS. There was a significant difference, paired $t(5) = -1.83$, $p = .05$, in the mean amplitude scores between the first and last sessions with lower scores on the first session compared to the last session (see Figure 2).

DISCUSSION AND CONCLUSION

In this study the DMN was generated successfully as seen in Figure 1. Comparing the experimental and control groups, Figure 1 shows that the effect of treatment with NFB leads to a more consolidated DMN than the effects of time alone would cause.

There has been difficulty in reaching a consensus as to what brain regions are responsible for producing the symptoms of ADHD.
(Dickstein, Bannon, Castellanos, & Milham, 2006). This is some of the first data supporting changes in the DMN using NFB with children and ADHD. The results of this study indicate that NFB has the ability to decrease the tonic activity of the posterior cingulate, precuneus, the temporoparietal junction, and the cerebellar tonsils of the DMN. Our evidence also shows that NFB consolidates the area of the DMN. These results suggest that NFB provides a greater change to the DMN, over a shorter period, than would be expected with typical development.

Our study showed that NFB treatment of medicated ADHD subjects led to clinical improvement that was accompanied by improvement in the DMN functions. Of interest is the group average pretreatment fMRI. This image suggests the limited anterior to posterior connectivity and the ectopic DMN components that are seen in the 9- to 15-year-old brain. The absence of these findings posttreatment suggests that the NFB also resulted in maturation of the DMN toward that of the adult brain in a period of several months.

Andrews-Hanna (2012) conducted meta-analyses on DMN research in the last decade and addressed the necessary, adaptive nature of the DMN. The importance of mind wandering and the need for “internal mentation” was discussed (p. 259). If NFB can assist children with ADHD in consolidating the DMN, the clinical implications are essential to their everyday living. Productive internal mentation allows for processing and possibly preparing for the unpredictable aspects of life. This would certainly help children with ADHD to access another resource, facilitating processing and understanding of past and future events. In addition, another benefit of a more consolidated DMN for children with ADHD is that it assists these children with selective attention, replicating the results of Levesque et al. (2006).

The purpose of this research was to serve as a pilot study for larger studies. Limitations include a small sample size and a large male-to-female ratio, and only children who were currently being treated with stimulant medications were included. Future directions of this study would address the limitations just stated. Studying this further may give us additional insight into the effects of NFB as well as its role in the modulation of the default mode.

We hope that these findings will lead to a reevaluation of the current theoretical foundations of NFB. For example, might the trajectory of network maturation influence client management? How does SMR training at Cz strengthen DMN function? What other aspects of network function are affected by NFB? These are the questions that need to be further researched.

REFERENCES


