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Aim and Scope

NeuroRegulation is a peer-reviewed journal providing an integrated, multidisciplinary perspective on clinically relevant research, treatment, and public policy for neurofeedback, neuroregulation, and neurotherapy. The journal reviews important findings in clinical neurotherapy, biofeedback, and electroencephalography for use in assessing baselines and outcomes of various procedures. The journal draws from expertise inside and outside of the International Society for Neurofeedback and Research to deliver material which integrates the diverse aspects of the field. Instructions for submissions and Author Guidelines can be found on the journal website (http://www.neuroregulation.org).

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Welcome to Volume 4, Issue 1 of *NeuroRegulation*! As the increased exposure and interest in neurofeedback and applied neuroscience continues to grow, we are excited to see increased submissions to *NeuroRegulation*.

With this fourth volume of *NeuroRegulation* we are excited to introduce a special invited paper series focused on providing clear, unambiguous definitions for the concepts and methods used in neurofeedback and applied neuroscience. It is often very difficult to find clear operant definitions for many of the concepts used in the processes of neurofeedback, applied neuroscience, or quantitative electroencephalographic (qEEG) research. It is our goal to solicit experts and leaders to provide these reference articles so that young researchers and veteran clinicians can find clear information about neurofeedback, quantitative EEG, and applied neuroscience without proprietary conflicts being present. In this issue, Scott Decker, Paul Fillmore, and Alycia Roberts provide a reference article for coherence. Estate Sokhadze, Manuel Casanova, Emily Casanova, Eva Lamina, Desmond Kelly, and Irma Khachidze contribute a reference article for event-related potentials (ERP) in cognitive neuroscience. It is with great honor we received these contributions and we express sincere gratitude to these authors for kicking off this invited paper series. It is extremely important in science and clinical work to provide clear, definitions for the core components of a methodology. We will continue this series over the course of 2017 and hope to receive articles for all core concepts in neurofeedback and EEG.

Additionally in this issue, authors present numerous topics of interest to researchers, clinicians, and the public. Ed Pigott presents a thoughtful confrontation of difficulties in neuropharmacology and emphasizes the important role neuromodulation and learning techniques play in future evidence-based models for treating psychological issues. Elyse White, Kayleah Groeneveld, Rachel Tittle, Nicholas Bolhuis, Rachel Martin, Timothy Royer, and Majid Fotuhi present data examining the effects of combined neurofeedback and heart rate variability on symptoms of anxiety and depression. Erin MacInerney, Ronald Swatzyna, Alexandra Roark, Bianca Gonzalez, and Gerald Kozlowsi present a case study of the importance of breakfast and breakfast choices on the EEG.

NeuroRegulation thanks these authors for their valuable contributions to the scientific literature for neurofeedback and quantitative EEG. We strive for high quality and interesting empirical topics. We encourage the members of ISNR and other biofeedback and neuroscience disciplines to consider publishing with us. It is important to stress that publication of case reports is always useful in furthering the advancement of an intervention for both clinical and normative functioning. Thus, we encourage all individuals practicing neurofeedback to submit case studies! We thank you for reading *NeuroRegulation*! Additionally, *NeuroRegulation* is on Facebook, drop by and like our page.

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Coherence: The Measurement and Application of Brain Connectivity

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Abstract

While much knowledge has been gained by the endeavor to link specific brain sites with specific cognitive functions, modern conceptualizations of brain activity focus much more on the function of networks of brain regions. A key construct in defining these networks has been the study of connectivity across regions. In this review, we discuss several methods of measuring connectivity and focus primarily on the utility of electroencephalographic (EEG) coherence. While over- and under-connectivity have been related to numerous clinical phenomena, we focus our discussion on the role of connectivity in reading and language disorders, and present a Neurocognitive Connectivity (NCC) framework for understanding these disorders. We argue that EEG coherence presents a unique target for treatment of these and other populations, in that the ability to modulate connectivity via EEG neurofeedback has been shown to be of significant clinical utility.

Keywords: electroencephalography; coherence; neurocognitive connectivity; neurofeedback

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Introduction

Linking cognitive and behavioral functions with specific regions of the brain through case studies of individuals with brain injury has been the primary basis of understanding "brain-behavior" relationships in neuropsychology. This dates back at least as far as Pierre Paul Broca (1861), who famously attributed specific deficits in the production of speech to corresponding damage to the inferior frontal lobe. Although neuropsychological studies such as Broca's have been valuable, technological advances in neuroimaging have drastically expanded the types of questions we can ask about cognition, especially in the healthy brain. For example, neuroimaging techniques have uncovered and refined theories about brain areas being "dedicated" to some domains of cognition, such as face processing (Kanwisher, McDermott, & Chun, 1997), phonological decoding (Boukrina, Barrett, Alexander, Yao, & Graves, 2015; He at al., 2013,), and the planning of motor speech (Dronkers, 1996; Richardson, Fillmore, Rorden, LaPointe, & Fridriksson, 2012). However, on the whole, neuroimaging studies have also highlighted the limitations of simple localization perspectives of brain functions in demonstrating that most cognitive functions are not localized to just one area, but rather distributed across different regions of the brain.

Moving beyond simplistic theories of single-site localization, neuroimaging investigations of brain function have revealed that even relatively simple

cognitive functions involve a complex and dynamic pattern of brain network activation across diverse regions of the brain. This complexity in patterns of brain activation parallels the complexity of human cognition found in even mundane everyday endeavors. Not only refuting simplistic localization theories of brain functioning, contemporary neuroimaging research also provides suggestion of deeper principles of brain function to explain cognition. Indeed, brain-behavior relationships extend beyond merely understanding the relationships between brain injury and behavior. Utilizing both structural and functional magnetic resonance imaging (MRI), numerous anatomical and functional properties of the brain have been uncovered. Most commonly, these studies involve combining detailed pictures of structure (e.g., T1-weighted images), collected over several minutes, with estimates of blood flow over time (i.e., blood-oxygenation level-dependent [BOLD] contrasts), collected every several seconds. While this works well in many contexts, many cognitive functions unfold on timescales of tens or hundreds of milliseconds, requiring additional sources of information to fully understand them. Electromagnetic imaging techniques such as electroencephalography (EEG) and magnetoencephalography (MEG) fill this gap well, and have excellent temporal resolution (e.g., Breier , Simos, Zouridakis, & Papanicolaou, 1999; Thierry, Boulanouar, Kherif, Ranjeva & Démonet, 1999), thus providing unique perspectives on the function of brain "networks."

One important discovery in the past few decades has been the role of brain networks as an intermediary link between brain structure, cognition, and behavior. Understanding functions of the brain in terms of networks rather than specific anatomical structures has been a considerable development in modern neuroscience (Bullmore & Sporns, 2009). There are numerous networks in the brain, without clear differentiation; however, the various networks are characterized by specific patterns of connectivity (Sporns, 2011; van den Heuvel & Sporns, 2013). Similar to how different cities are connected by a network of airports, brain networks have hubs or central nodes with high connectivity, and other regions with low connectivity. The specific model of network connectivity in the brain has been described as a "small-world" network (Bassett & Bullmore, 2006).

More importantly, connectivity, or lack thereof, in brain networks has proven to be an important theoretical construct with considerable applied applications. An emerging view in contemporary neuroscience is that many functional neurocognitive deficits for which individuals seek treatment are caused by problems in brain connectivity within specific brain networks, such as those that are important for academic learning (Paulesu et al., 1996; Rippon, Brock, Brown, & Boucher, 2007), sustaining attention (Kucyi, Hove, Esterman, Hutchison, & Valera, 2016), social communication (Coben, Clarke, Hudspeth, & Barry, 2008; Grossmann, 2015), and fulfilling activities of daily living (Bieńkiewicz, Brandi, Goldenberg, Hughes, & Hermsdörfer, 2014).

Despite the numerous studies demonstrating the importance of brain connectivity for different clinical conditions, measurement of brain connectivity has not typically been incorporated in general applications of psychological diagnostic procedures. The problem appears twofold. First, the rationale for including measures of brain network connectivity and how such measures can be connected to behavior is not clearly understood. Second, the measurement of brain connectivity is often confusing and also not well understood.

The rationale for differentially connected brain networks as an intermediary between brain structure and behavioral functioning is not derived from any one particular study but inducted through hundreds of studies (i.e., Bullmore & Sporns, 2009; Fox et al., 2005; Mišić, & Sporns, 2016, etc.). Collectively, broad assumptions are emerging that clarify the nature of the brain, brain-behavior relationships, and clinical applications thereof. While far from definitive, Table 1 provides an attempt to logically derive the role of connectivity through a list of assumptions, each supported by modern neuroscientific research.

Table 1

Assumptions regarding brain connectivity and cognitive functions.

1. For any given cognitive function, there are multiple brain structures or sets of structures that are primarily involved in performing that function.
2. In most cases, these areas are functionally (and often structurally) connected, forming a specific network.
3. Dysfunction of a network via over- or under-connectivity will result in reduced proficiency in cognitive functions reliant upon connectivity of the involved brain regions.

As derived from Table 1, there is an intricate relationship between "cognition" and "brain connectivity." In recognizing the emerging importance of the link between cognition and measures of brain connectivity, the term Neurocognitive Connectivity (NCC) will be used to provide a framework for linking cognition with brain connectivity through the assumptions of Table 1. The NCC framework implicitly suggests that while having some theoretical importance when measured in isolation, brain connectivity is of primary interest when it can be linked to cognition or behavior. Similarly, therapeutic techniques for changing brain connectivity with no relevance for cognition or behavior are of little clinical value. Thus, the NCC framework is used to provide explicit assumptions regarding the clinical utility of measuring brain connectivity as a link to measures of cognition. Theoretically, NCC provides integration across empirical findings that extend beyond neuroscience and include development, cognition, genetics, and behavior. The remaining sections of this manuscript will provide additional details of the NCC framework and its clinical application. Additionally, we will discuss specific methods of objectively measuring and/or modulating brain network connectivity, focusing primarily on a metric referred to as EEG coherence (Bowyer, 2016).

Importance of Connectivity

Although the above rationale provides a strong theoretical foundation for an increased focus on the investigation of brain connectivity, the details of how we define and measure connectivity can be quite varied. Structural connectivity is often measured by MRI and diffusion tensor imaging (DTI), and yields information about both local and global directionality (via maps of fractional anisotropy; e.g., Feldman, Lee, Yeatman, & Yeom, 2012; Lebel et al., 2013) as well as robustness of connections between defined points (via fiber-tracking methods; e.g., Vandermosten et al., 2012). While structure provides a vital substrate for the presence of networked brain function, it does not give the full picture of which networks actually exist, performing coordinated functions. Thus, the notion of functional connectivity has gained great traction in recent years (Glasser et al., 2016; Smith et al., 2013), including spawning large-scale projects to systematically map the human functional brain networks and their key nodes (http://www.humanconnectome.org/; Glasser et al., 2016). The term *functional connectivity* is used to describe the correlated neuronal activity of these various regions (Bowyer, 2016). However, this term is not only conceptual but also refers to the measurement basis of brain connectivity using fMRI and EEG methodologies. Functional connectivity refers to the cross-temporal correlation of measured brain activity in different regions of the brain (Bowyer, 2016; Honey et al., 2009). While much of the work in defining functional connectivity has utilized resting-state fMRI (RS-fMRI; e.g., Smith et al., 2013), as noted above, more temporally sensitive methods such as EEG and MEG are also necessary to evaluate how functional connectivity might change over brief timescales (Bowyer, 2016; also see discussion of functional versus effective connectivity in Friston, 2011). Coherence is one commonly used metric for deriving functional brain connectivity in EEG, which will be discussed in detail below.

Defining Coherence

Electroencephalographic measures provide excellent temporal resolution of brain activity and are based on electrical properties of the brain as measured by electrodes on the scalp. The measured electrical potentials on the scalp are small (microvolts: *u*V) and can be decomposed into frequency bands (i.e., Delta, Theta, Alpha, Beta, Gamma) or further into single hertz bins generally via the Fast Fourier Transform (FFT). The measured microvolts are typically squared (uV^2) to derive Absolute Power, which is typically used as an underlying indicator of brain activation.

Coherence measures, on the other hand, quantify the degree of association between two brain regions, which is used to infer a functional relationship between two different regions of the brain. Similar to a correlation coefficient, coherence measures take values between 0 (no coherence) and 1 (absolute coherence). Coherence is calculated following transformation from the time domain to the frequency domain, and compares similarity of the power spectra, with regions showing greatest similarity being assumed to be the most functionally connected. It incorporates information on synchrony including both amplitude and phase, but is independent of power (Bowyer, 2016).

Most commonly, EEG coherence describes the inter-relationship between two surface electrodes, though summaries such as site coherence (the average coherence for one electrode's coherences to all others) or global coherence (the average of all site coherences) can be useful; see Kaiser (2008) for a more comprehensive review. Recent methods (e.g., LORETA/eLORETA; Pascual-Marqui, Michel, & Lehmann, 1994; Pascual-Marqui et al., 2011) also allow coherence to be estimated between brain

regions themselves, using source analysis to infer the generators of EEG signals. In its most common formulation, EEG coherence is calculated by the form:

$$y^2xy(f) = \frac{\left(Gxy(f)\right)^2}{(Gxx(f)Gyy(f))}$$

where Gxy(f) is the cross-power spectral density and Gxx(f) and Gyy(f) are the respective auto-power spectral densities (Thatcher, Krause, & Hrybyk, 1986). Though summarizing frequency content necessarily requires a defined time window, which is commonly at least tens of seconds for quantitative EEG (qEEG) analyses (Bowyer, 2016), these time windows can be shortened to allow for near-real-time estimates of coherence, making coherence a malleable metric for use in neurotherapeutic contexts such as neurofeedback.

Given the dynamic properties of brain activity, it would seem the correspondence between distantly located electrodes on different regions of the scalp would be, on the whole, erratic and unreliable. Surprisingly, coherence measures have been found to be quite reliable. For instance, reliability coefficients above *r* = .80 were first found in 1961 (Adey, Walter, & Hendrix, as cited in Thatcher, 2010), with many later studies finding similar levels of stability (Cannon et al., 2012; Chabot et al., 1996; Corsi-Cabrera, Galindo-Vilchis, del-Río-Portilla, Arce, & Ramos-Loyo, 2007; Corsi-Cabrera, Solís-Ortiz, Guevara, 1997; John, 1977; Roberts, Fillmore, & Decker, 2016; Thatcher, Walker, Biver, North, & Curtin, 2003; though see Gudmundsson, Runarsson, Sigurdsson, Eiriksdottir, & Johnsen, 2007, for an alternate perspective). One study (Fernández, Harmony, Rodríguez, Reyes, Marosi, & Bernal, 1993) reported coherence reliability coefficients as high as *r* = .95 for both resting state and a verbal cognitive task, even with a test-retest interval of 1 month. Indeed, due to its high reliability, coherence is often targeted in neurofeedback treatment (i.e., Friedrich et al., 2014; Gruzelier, 2014; Keizer, Verment, & Hommel, 2010). However, as demonstrated in Roberts, Fillmore, and Decker (2016), the effects of such a treatment protocol are highly dependent on the reliability of the targeted metric itself.

Several factors have been shown to affect coherence reliability. For instance, Shaw (1984) found that coherence was higher in eyes-closed than eyes-open resting state. This difference was the most pronounced in the alpha range; in which eyes-closed coherence reliability coefficients approached unity. Other patterns have emerged as well, including interhemispheric and gender differences in coherence (i.e., Gootjes, Bouma, Van Strien, Scheltens, & Stam, 2006; Koles, Lind, & Flor-Henry, 2010; Miskovic, Schmidt, Boyle, & Saigal, 2009; Tucker, Roth, & Bair, 1986). Thatcher et al. (1986) also reported reliable patterns of coherence, which prompted the proposal of a two-compartmental model of coherence describing the importance of different types of cells for short- (i.e., basal dendrites) and long- (i.e., pyramidal cells) range communication.

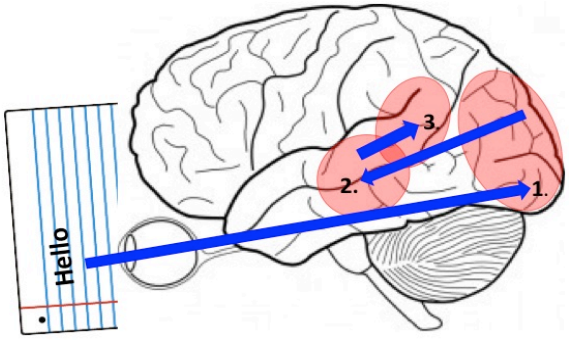
Neurocognitive Connectivity and Clinical Connections

To demonstrate the basic assumptions of the importance of brain connectivity, a simplified demonstration involving reading cognition will be given and further expanded to discuss clinical implications for understanding Specific Learning Disabilities. The applicability of the framework for other neurodevelopmental disorders will also be discussed.

First, reading is a multi-dimensional cognitive task, and the specific cognitive demands change throughout its development. The early stages of reading involve "word decoding." Decoding involves, first, a *visual analysis* of letters and *visual recognition* of letter patterns or groups of letters. Next, letter groups must be associated with language sounds (*phonology*). To read a word, the letter sounds of different letters in the word must be blended. Finally, the blended letter sounds must be recognized as a word that is already stored in the individual's vocabulary (*lexical semantics*).

Specific cognitive processes involved in word decoding are linked to specific brain networks in different areas of the brain. First, the visual analysis of letters primarily involves brain networks beginning in the occipital lobe in the most posterior region of the brain. In contrast, the second step of phonology involves auditory sound representations that are primarily localized in the temporal regions of the brain, more specifically in the superior temporal region. Third, closely associated with auditory sound representations are the receptive languages areas, which involve networks in close proximity to auditory sound representation regions because language is learned through sound. However, language goes beyond sound to involve semantic representations or word meanings, which involve even more distributed networks in the brain. Thus, reading involves all the assumptions of an NCC

framework as provided in Table 1 (see also Figure 1 for a pictorial representation of the NCC framework as it applies to reading). First, word decoding involves cognitive processes in different regions of the brain, which subsequently involve networks from different regions of the brain. Second, these different networks involved in reading must have functional connections for the normal development of reading to occur. Finally, reduced connectivity between brain networks involved in specific learning tasks reduces learning efficiency. Reduced learning efficiency of academic task(s) due to individual differences in atypical brain connectivity is the underlying cause of specific learning disabilities (SLD).



1. **Decode**: Visual analysis of letters and visual recognition of letter patterns occurs in the *occipital lobe* after the individual has viewed the word.
2. **Phonology**: Visual letter groups are associated with the language sounds and sound blending occurs primarily in the *superior temporal lobe*.
3. **Semantics**: Blended sounds are compared to words in stored vocabulary in neurological areas in *close proximity* to where phonological processing occurred.

Figure 1. NCC Framework of Word Recognition: Corresponding cognitive and coherence measures in different brain regions.

Numerous studies involving brain imaging support an NCC framework for SLD. One of the first studies investigating brain connectivity differences between children with dyslexia and typically developing peers found that children with dyslexia had "disconnected" language areas of the brain that corresponded to deficits in phonology (Paulesu et al., 1996). Here, it was proposed that weak connectivity between the anterior and posterior brain regions in the left hemisphere resulted in phonological deficits characteristic of many children with reading problems. Sally Shaywitz's work has also consistently demonstrated functional connectivity disruptions in the brains of individuals with dyslexia (e.g., Shaywitz, B. A., et al., 2002; Shaywitz, S. E., et al., 1998). Differences in brain connectivity in children with learning disabilities has also been linked to white matter structures of the brain, which serve as the major "highways" for connecting different brain regions (Silani et al., 2005; Temple, 2002). Additionally, reduced functional connectivity has been associated with deficits in integrating orthography and phonology in children with dyslexia (Cao, Bitan, & Booth, 2008) and has been predictive of differences between children with dyslexia and neurotypical readers (Quaglino et al., 2008). Moreover, specific patterns of brain connectivity are linked to specific types of learning problems (Fields, 2008; Pugh et al., 2000).

Additionally, the NCC framework is not limited to reading disabilities. Recent research has demonstrated differentiated functional connectivity in brain regions involved in word processing amongst fMRI data for children with dysgraphia and oral and written language learning disabilities (Berninger, Richards, & Abbott, 2015). Disruptions in neurocognitive connectivity have also been found in children with developmental dyscalculia (Rosenberg-Lee et al., 2015). These networks often dissociate from those important for language-based SLD. For example, it has been found that individuals with math learning disabilities (MLD) exhibit disturbances in the left parietal and prefrontal brain areas (Geary, 2013). Another study found children with dyscalculia display decreased fractional anisotropy (a marker of white matter integrity) in the superior longitudinal fasciculus, as well as significant insufficiencies in fibers of the superior longitudinal fasciculus—a tract theorized to provide essential connections for numerical processing (Kucian et al., 2014). This is in contrast to children with dyslexia who typically have reduced connectivity in the left occipito-temporal cortex (Paulesu, Danelli, & Berlingeri, 2014). Many other studies have also highlighted the ways in which brain areas implicated in dyscalculia are different than those in dyslexia, due to the different neurocognitive demands inherent in learning math and reading (Ashkenazi, Black,

Abrams, Hoeft, & Menon, 2013; Butterworth, Varma, & Laurillard, 2011; Kucian & von Aster, 2015). This demonstrates the flexibility in network characterization for SLD via the NCC framework.

The NCC perspective for viewing cognitive deficits as a result of disconnection of brain networks not only provides a fresh perspective for understanding SLD but also for grasping neurological disorders at large (Stam, 2014). Abnormal patterns of brain connectivity have been linked to numerous developmental and psychiatric conditions, and reduced symptomatology in these conditions is dependent on the normalization of brain network connectivity (Voytek & Knight, 2015). For example, atypical patterns of connectivity have been found in individuals with schizophrenia (Su, Hsu, Lin & Lin, 2015), epilepsy (Widjaja et al., 2015), and Alzheimer's Disease (Qin et al., 2015), to name a few. The NCC framework may help to devise new and better identification and/or treatment options for individuals with these (and other) neuropsychiatric disorders.

Given the relevance of the NCC framework in the understanding of neuropsychiatric disorders, it follows logically that metrics capable of characterizing and/or modulating brain connectivity would be ideally suited for both diagnostic and treatment purposes. Accordingly, there is evidence to suggest that EEG coherence may be an ideal target for neurotherapeutic interventions. For example, Thatcher et al. (2003) have suggested that coherence is a better predictor of IQ (and other neurocognitive constructs) than other EEG metrics including absolute power. Additionally, several studies have examined this question in children and adults with neurodevelopmental disorders. For example, Coben, Wright, Decker, and Morgan (2015) demonstrated coherence training improved reading performance above and beyond that of traditional school-based reading interventions. Coben (2008, as cited in Linden, & Gunkelman, 2013) also demonstrated the efficacy of coherence training a sample of individuals with autism spectrum disorders. Furthermore, the authors completed a randomized control study of neurofeedback treatment for college students with ADHD, demonstrating significant changes in coherence, above and beyond that of other qEEG and behavioral metrics (Roberts & Decker, 2015). Thus, not only does coherence provide a valid indicator of brain network connectivity that directly links to cognitive functioning, it may also be the best target for therapeutic outcomes.

Clinical Applications for Coherence in Assessment and Treatment

Theoretical

Complex cognitive activity emerges from neuronal activity as part of an integrated network structure to exchange information throughout the brain (van den Heuvel & Sporns, 2013). Although the degree to which disconnected brain networks manifest as discrepancies between different types of behavioral measures is not precisely known, reasonable inferences can be made based on the theory. Nonetheless, there are only a few cognitive theories that have formally integrated the role of brain connectivity with performance on cognitive measures. One exception is the Parieto-Frontal Integration Theory (P-FIT) of Intelligence (Jung & Haier, 2007). This theory is derived from a review of literature on correlates of intelligence with a variety of brain imaging indicators, which provide a strong basis for intelligence being linked to the brain. Though current instantiations of the P-FIT model rely largely on MRI data, and thus do not take into account electrophysiological methods such as EEG and MEG that could shed light on the temporal dynamics of networks for intelligence, it provides a clear example of integrating connectivity with cognitive theory.

Assessment and Identification

Neuropsychological approaches to clinical disorders have recently grown in interest to practitioners (Decker, 2008). Historically, measures of cognition were limited to IQ scores. However, IQ scores were the basis of using such cognitive measures. Consistent with a contemporary neuropsychological view, *specific* cognitive deficits arise from connectivity problems in particular regions of the brain. The use of IQ scores, which is an amalgam of different cognitive tests compiled into a single score, lacks the specificity and sensitivity for capturing the exact cognitive deficits associated with different clinical disorders (Decker, Hale, & Flanagan, 2013).

Supporting an NCC framework, causal links have been made between experimental changes in brain connectivity and behavior. For example, reading interventions, which enhanced brain connectivity in the left occipital-temporal region of the brain resulted in improved reading scores in children (Shaywitz & Shaywitz, 2008). Similarly, meta-analytic research has supported clear changes in brain activity as a result of reading interventions (Barquero, Davis, & Cutting, 2014). Specifically, researchers found that children with reading difficulties exhibited different amounts of functional connectivity in the frontal lobe

compared to children without reading difficulties. However, after participating in different reading interventions, a difference in frontal connectivity no longer existed. Futhermore, recent literature suggests children with double-deficits (phonological and rapid naming deficits) have more atypical brain connectivity than children with only a single deficit (Norton et al., 2014), which demonstrates an additive relationship between atypical connectivity and learning problems. These findings indicate treatment outcomes of children with dyslexia, in comparison to a control group, are dependent on the normalization of brain connectivity in specific regions of the brain (Richards & Berninger, 2008)—a concept that has major implications for directing future neurological interventions, such as coherence-based neurofeedback.

Within the NCC framework, an uneven profile of cognitive skills may correspond to deficits in network hub functionality in the brain. Some preliminary research may already suggest this is likely the case (Adelstein et al., 2011; Bassett & Bullmore, 2006; Cole, Yarkoni, Repovš, Anticevic, & Braver, 2012; Shimono, Mano, & Niki, 2012; van den Huevel, Mandl, Luigjes, & Hulshoff Pol, 2008; Zalesky & Fornito, 2009).

Just as brain networks provide a common denominator for cognitive and academic weaknesses in phonology that change with intervention (Shaywitz & Shaywitz, 2008), there is promise that other interventions involving different brain networks will be similarly effective. Within the NCC framework described here, the value of cognitive tests in assessing brain networks can be clarified. First, and historically noted, cognitive tests provide a behavioral indicator of the functional integrity of brain networks. Second, different cognitive tests provide an indicator of the integrity of different brain networks. Finally, coherence provides a more direct measure of the functional integrity of different brain networks. Unfortunately, no cognitive measure is pure and variance in performance can be attributed to contextual, socioeconomic, and educational sources. Coherence provides a more direct measure of brain connectivity to verify the neurophysiological basis of cognitive problems. However, the practical utility of both measures is in their correspondence with each other.

Ultimately all cognition is dependent on brain connectivity, and cognitive measures provide ecological validity for better understanding challenges someone might face in everyday life. However, cognitive deficits as indicated by behavioral measures are ambiguous as to underlying causes. Coherence measures in conjunction with cognitive measures not only provide validation of diagnostic problems but also provide information to guide and select more targeted interventions. Evaluating the correspondence between cognitive test performance and brain hub involvement will likely be a future direction of neurocognitive and translational research.

In emphasizing the role of brain connectivity, the NCC perspective may provide an important theoretical foundation for guiding interventions. Essentially, children with SLD have weak connections in particular areas of the brain that reduce integration of associative learning that is involved in specific academic tasks. Similar functional deficits have been documented in a number of other neurodevelopmental and neurological disorders, as described above. Thus, interventions that facilitate connectivity of these brain regions should result in improved performance, or create the conditions for improving the efficiency of learning (as well as of attention, social skills attainment, etc., in other clinical disorders).

An important role emerging from NCC involves a revised understanding of attention, which has historically been difficult to define. Attention has been classically defined as a description of information held in awareness at a particular moment in time; it can become more or less focused and can shift; it involves both exogenous (environmental) influences as well as endogenous (within the person) influences. More contemporary research has found links between attention and brain connectivity. Specifically, attention is a cognitive mechanism that facilitates the binding or connectivity of different brain networks (Gootjes et al., 2006). Attention is important because it is influenced by both task demands and volitional control; thus, it is amendable to intervention.

Lastly, the NCC framework may provide a conceptual framework for explaining novel therapies that have been used in SLD and other clinical conditions. Neurofeedback (NF) has been one method used to directly change brain connectivity. This treatment involves a brain-computer interface for operant conditioning of brain activity, where patients are trained to direct their own EEG activity. Positive outcomes have been reported for various disabilities, including SLD. For instance, cases and experimental studies have demonstrated changes in brain connectivity from NF in children with dyslexia

that resulted in improved spelling (Breteler, Arns, Peters, Giepmans, & Verhoeven, 2010), improved reading (from 1.2 grade levels to upwards of 2 grade levels; Coben et al., 2015; Walker & Norman, 2006), and improved phonological skills (Nazari, Mosanezhad, Hashemi, & Jahan, 2012).

Summary

EEG Coherence is a metric derived from the electrical potentials in the brain to gauge the inter-relationship between two electrodes. The measured relationship can be used to infer the degree of connectivity between two distant regions of the brain. As discussed throughout this manuscript, neuroimaging techniques, and EEG in particular, have become integral physiological metrics in the identification and study of various brain networks. More and more, research is focusing less on structural differences, in lieu of understanding how these interconnected structures communicate in order to process the increasingly complex environments that we encounter on a daily basis.

The integration of cognitive and neuroscience investigations of SLD is converging to suggest specific brain regions, or networks, are explicitly engaged cognitive tasks. Additionally, education requires integrated, or connected, brain networks dedicated to the differential processing demands in learning. The Neurocognitive Connectivity (NCC) framework is offered to synthesize the emerging theme of neuroscientific investigations. The NCC framework is demonstrated using examples of specific learning disabilities which involve problems in learning due to specific cognitive deficits. Furthermore, research is emerging to suggest children with SLD have specific atypical patterns of brain connectivity and these patterns of reduced connectivity in brain networks are the underlying cause of SLD. These atypical patterns of connectivity correspond to different displays of learning disabilities. Implications of viewing SLD as a brain network connectivity problem are discussed with relevance to theory, assessment, and intervention. While research supporting a disconnectivity model of SLD has been reinforced by neuroscientific investigations, there is also emerging evidence for the role of coherence metrics to detect atypical patterns of connectivity in brain networks for a broad array of neuropsychological and neuropsychiatric conditions. However, additional research in the applied and practical applications of the NCC model is necessary. While coherence can be derived from a variety of brain imaging methodologies, EEG and QEEG have numerous advantages within clinical applications. In addition to the general benefits over other neuroimaging methodologies related to temporal resolution, EEG and QEEG metrics are easy to obtain, inexpensive, noninvasive, cost-effective, and provide reliable and valid indicators of brain connectivity. Furthermore, coherence measures are ideal therapeutic targets for gauging treatment outcomes as well as the target of treatments involving neurofeedback.

Although continued research is needed to further investigate the ever-growing web of connectivity within the human brain, EEG coherence is a metric particularly well suited to this endeavor. Future research will likely continue to refine methodological aspects of coherence measures in identifying the best approaches to identify discrete brain networks within source space based on sensor level recordings. Additionally, coherence measures will likely factor into the formation of future models of cognition and provide a substantial role in not only shaping theoretical models of cognition but also therapeutic applications for individuals with cognitive deficits.

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NeuroRegulation

Event-related Potentials (ERP) in Cognitive Neuroscience Research and Applications

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Abstract

This review is aimed at exploring the usefulness of measuring event-related potential (ERP) in cognitive tests and discusses several applications of the ERP technique. Analysis of ERP components is one of the most informative dynamic methods of investigation and monitoring of information processing stages in the human brain. Amplitude and latency of ERP components at specified topographies reflect early sensory perception processes and higher level processing including attention, cortical inhibition, memory update, error monitoring, and other cognitive activities. ERPs provide a method of studying cognitive processes in typical subjects, as well as a sensitive instrument to assess differences in individuals with neuro- and psychopathologies. Despite significant advances in functional neuroimaging, the ERP measure still represents an important tool for brain research in psychiatry, as many psychiatric diseases correlate with certain altered patterns of ERPs. Such ERP alterations can serve as valid biological markers for functional diagnostic or for better understanding of the cognitive functions which are disturbed in psychiatric disorders. Application of ERPs in psychiatric treatment research is an approach aimed at validation of specific ERP measures as sensitive functional outcomes of experimental neuromodulation interventions such as rTMS and neurofeedback. Also discussed are additional aspects of ERP usefulness in psychiatry research and treatment.

Keywords: ERP; qEEG; psychopathology; biomarkers; cognitive neuroscience

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Introduction

In addition to more traditional quantitative electroencephalography (qEEG) techniques, where EEG is assessed during resting conditions with eyes closed and eyes open, there is a recent trend towards a wider usage of event-related potential (ERP) recording methodology for research and clinical applications. This review is not aimed at describing the basic fundamentals of ERP technology, but rather is intended to discuss a rationale for the usefulness of this methodology in cognitive neuroscience research, functional diagnostic, and also as a valuable neurotherapetic interventions outcome measure. Event-related brain potentials are described as changes in electrocortical activity recorded from the scalp and are evoked by an external or internal event. This ERP activity is changing very rapidly in time and across cortical topographic fields and is recorded

with high temporal resolution in order of several milliseconds from different scalp locations (Otten & Rugg, 2005). Research based on ERP is an established tool to address various questions in psychology, psychiatry, and neuroscience. Our review is confined to the use of ERP in cognitive neuroscience with a focus on several psychopathologies such as autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), posttraumatic stress disorder (PTSD), and schizophrenia (SCZ) to name a few. From the very early period of ERP application there were numerous studies aimed at association of the certain features of ERP waveforms (e.g., ERP components) with specific cognitive processes and further using them as biomarkers of the engagement of these cognitive processes. This approach is based on prior knowledge about the functional significance of specific ERP components and is very useful for inferences about cognitive processes taking place during various experimental manipulations in typical controls and patients with psychiatric conditions. There are several measures used in ERP research, such as scalp topographic distribution, polarity (positive or negative), amplitude, latency, time course, and dipole source localization. These ERP variables may provide important insight about perceptual, cognitive, and motor functions in normal and in psychopathological conditions. Considering the high temporal resolution and low costs of ERP technology, it is logical to assume that ERPs will remain an essential instrument in cognitive neuroscience, neurotherapy, and clinical neurophysiology.

Event-related Potentials (ERP) as a Tool in Cognitive Neuroscience Research

Analysis of ERP components is one of the most informative dynamic methods of investigation of information processing stages in the brain. Amplitude and latency of ERP components at relevant scalp topographic regions-of-interest (ROI) provide information about early sensory perception processes and higher level processing including attention, cortical inhibition, response selection, error monitoring, memory update, and other cognitive activity (Duncan et al., 2009; Polich, 2007). ERP methodology represents a valuable technique for studying normative cognitive processes in typically developing subjects, and at the same time ERP may serve as a sensitive tool to assess differences in children with neurodevelopmental pathologies such as ASD and ADHD, or in adult individuals with various psychiatric conditions (e.g., PTSD, SCZ, substance use disorder [SUD], etc.). Despite significant advances in functional neuroimaging (e.g., functional magnetic resonance imaging [fMRI] or positron emission tomography [PET]), the ERP still represents an important brain research methodology in psychiatry, as many psychiatric diseases correlate with altered patterns of EEG responses detectable in ERP (Lenz et al., 2008). ERP alterations in psychopathologies can serve as valid and sensitive biomarkers for functional diagnostic purposes. On the other hand, investigation of differences in ERP measures can contribute to better understanding of the cognitive functions disturbed in neurodevelopmental disorders and other psychopathologies.

Stimulus-locked ERP

ERP locked to stimulus reflects the activation of neural structures in primary sensory cortex and in associative cortical areas related to higher order cognitive processes. ERP studies are especially interesting for the purpose of this review as they provide temporal information concerning processes such as attention. Earlier ERP components (such as the P100, N100, and P200) usually relate to attentional selection mechanisms, whereas later components (P300) are more often associated with organization and interpretation of the stimulus. ERP components can be categorized as short-latency (exogenous, e.g., N100) or long-latency (endogenous, e.g., P300) ERPs, which reflect early-stage, modality-specific and late-stage polymodal associative processing, respectively. The early ERP components (e.g., P100, N100) reflect exogenous processes modulated by the physical attributes of the stimulus (i.e., brightness for visual stimuli, loudness of auditory stimuli), rather than by endogenous cognitive processes (Coles & Rugg, 1995). However, it was noted that attention processes may operate even at the early stages of information intake and influence stimulus processing at the later stage (Herrmann & Knight, 2001). In such context, P100 may reflect a facilitation of early sensory processing of attended stimuli, while N100 may reflect the early stage of orienting of attention towards task-relevant target stimuli (Hillyard & Anllo-Vento, 1998; Luck, Heinze, Mangun, & Hillyard, 1990; Näätänen & Michie, 1979).

Posterior visual P100 is generated within the fusiform gyrus (Heinze et al., 1994), whereas N100 is probably generated by distributed dipoles in lateral extrastriate cortex (Gomez-Gonzales, Clark, Fan, Luck, & Hillyard, 1994) with contribution from parieto-occipital and occipito-temporal areas (Yamazaki et al., 2000). Anterior P100 and N100

components occurring within a comparable time window result from frontal generators (Clark, Fan, & Hillyard, 1994). The cognitive functional significance of the midlatency P200 component of ERP has not been completely resolved (Crowley & Colrain, 2004) and existing results are not consistent. Novak, Ritter, and Vaughan (1992) suggested that the P200 represents reflection of activity of an attention modulation process in oddball paradigms. García-Larrea, Lukaszewicz, and Mauguiére (1992) proposed that the P200 more probably reflects stimulus evaluation aspects during the classification process and facilitates a first rough stimulus appraisal. It was reported that the extent of required cognitive effort positively correlates with the P200 magnitude (Conley, Michalewski, & Starr, 1999). It could be concluded that P200 reflects attention and discrimination processes as well as task difficulty related variables.

There is a negative endogenous ERP component (N200 or N2b), located over centro-parietal scalp locations and occurring about 180 and 320 ms poststimulus (Näätänen, Gaillard, & Mäntysalo, 1978; Näätänen, Schröger, Karakas, Tervaniemi, & Paavilainen, 1993). This component is associated with categorization, perceptual closure, and attention focusing, ultimately signaling that a perceptual representation has been formed (Potts, Patel, & Azzam, 2004). The posterior visual N2b is enhanced if the presented stimulus contains a perceptual feature or attribute defining the target in the task. An anterior frontal positive component (P2a) in a latency range comparable with the posterior N2b has been reported in working memory and attention tasks. The P2a recorded over inferior prefrontal recording sites appears to be selectively responsive to the evaluation of the task relevance of presented visual stimuli, and source localization places dipoles of this component in the orbito-frontal cortex (Potts, Dien, Harty-Speiser, McDougal, & Tucker, 1998; Potts, Liotti, Tucker, & Posner, 1996). Kenemans, Kok, and Smulders (1993) described this frontal positivity as a component that indexes the hierarchical selection of task-relevant features for further processing. Information about processes related to response conflict detection and processing, as well as inappropriate response inhibition, can be extracted from the fronto-central ERP component N200 (West, 2003; West, Bowry, & McConville, 2004), which is thought to originate from the anterior cingulate cortex (ACC) and prefrontal sources (Donkers & van Boxtel, 2004).

The most studied endogenous ERP is the P300 (300–500 ms poststimulus). The P300 is obtained in an oddball paradigm, wherein two stimuli are presented in a random order, one of them frequent (standard) and another one rare (target; Polich, 2003; Pritchard, 1981). A modification of the task has been used where a third, also infrequent novel distracter is presented along with the standard and rare target stimuli. It was reported that these novels elicit a fronto-central P300, so-called P3a, whereas the rare targets elicit a centro-parietally distributed P300, so-called P3b (Katayama & Polich, 1998; Polich, 2003). The P3a is recorded at the anterior frontal locations and reflects frontal activity (Friedman, Simpson, & Hamberger, 1993; Knight, 1984). The P3a to novel distracter stimuli is generated by contribution of brain structures, including the hippocampus (Knight, 1996) and medial and inferior frontal (Baudena, Halgen, Heit, & Clarke, 1995; Elting et al., 2008), dorsal PFC and anterior cingulate cortex (Dien, Spencer, & Donchin, 2003). In a three-stimulus oddball task the P3a is interpreted as “orienting” to novel distracters, and the P3b as an index of ability to sustain attention to target. Source localization techniques have claimed that multiple brain areas are involved in the generation of the visual P3b: the hippocampus and parahippocampal areas, the insula, the temporal lobe, occipital cortex, and the thalamus (Goto, Brigell, & Parmeggiani, 1996; Herrmann & Knight, 2001; Mecklinger et al., 1998; Rogers, Basile, Papanicolaou, & Eisenberg, 1993). Most studies agree that the P3b has multiple dipole sources (Halgren, Marinkovic, & Chauvel, 1998; Knight, 1997; Townsend et al., 2001).

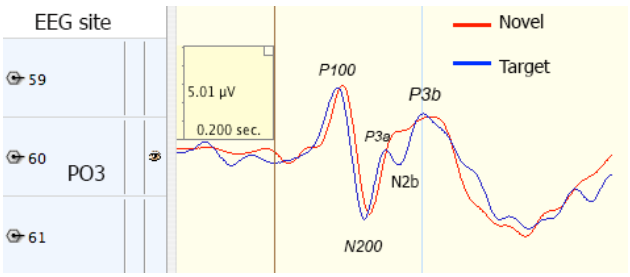

Figure 1. Screenshot of a stimulus-locked posterior ERP in a visual three-category oddball task with novel distracters. At the parieto-occipital PO3 site there are clearly visible P100, N200, N2b, P3a, and P3b components to target stimuli.

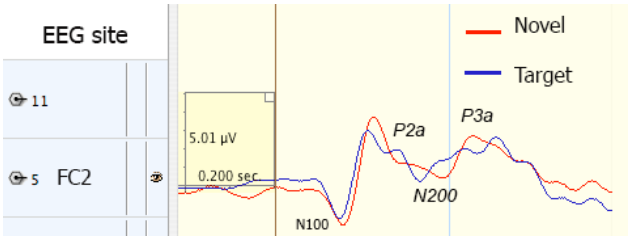

Figure 2. Screenshot of an anterior ERP in a visual three-category oddball task with novel distracters. At the fronto-central FC2 site there are clearly visible N100, P2a, and N200 components to target stimuli and P3a component to novel distracter stimuli.

Response-locked Error-related Potentials

Application of ERP methodology is not limited only to the evaluation of responses to sensory stimuli in various cognitive tasks; they also can be used to assess motor-response-related processes. Some type of ERPs can be used to understand response-related neural processes. One important executive function known to be compromised in psychopathologies is the ability to select a contextually appropriate response among several competing ones, and simultaneously inhibit contextually inappropriate responses to avoid committing an error. Another executive deficit observed during performance on speeded reaction time tasks in neuro- and psychopathologies (e.g., ASD, SCZ, SU disorders) is manifested in an abnormality related to response error monitoring, error recognition, and subsequent posterror response correction.

Error sensitivity can be readily examined by measuring response-locked ERP components associated with brain responses to errors. Two specific components relevant in this context are the error-related negativity (ERN, more rarely referred to as Ne) and the error-related positivity (Pe). The ERN is a response-locked negative ERP deflection, emerging between 40 and 150 ms after the onset of the incorrect behavioral response—a commission error (Falkenstein, Hoormnn, Christ, & Hohnsbein, 2000). Usually this negative wave is followed by a positive wave referred to as the Pe potential. Although there is discussion about the exact meaning of the Pe (Overbeek, Nieuwenhuis, & Ridderinkhof, 2005), most studies indicate that the Pe is related to the conscious recognition of the error (Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001) or the attribution of motivational significance to the committed error (Falkenstein et al., 2000). This suggests that the ERN reflects an initial automatic brain response as a result of an error, and the Pe possibly indicates the conscious reflection and comprehension of the error (Overbeek et al., 2005). The magnitude of the ERN is associated with behavioral evidence of self-monitoring (i.e., self-correction and posterror slowing responses) and therefore is interpreted as a biomarker of error processing (van Veen & Carter, 2002). Dipole modeling has localized ERN sources to the caudal ACC, while Pe has been localized to the more rostral ACC division (Bush, Luu, & Posner, 2000; Gehring & Knight, 2000; Herrmann, Römmler, Ehlis, Heidrich, & Fallgatter, 2004; van Veen & Carter, 2002; West, 2003). ERN and Pe are generally accepted as valid neural indices of response-monitoring processes in psychophysiological research and clinical neurophysiology.

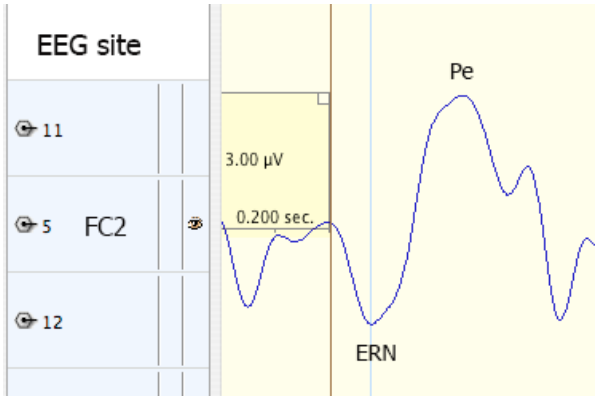

Figure 3. Screenshot of commission error-response locked ERP in a flanker task. There is a negative deflection around 100 ms posterror (i.e., error-related negativity—ERN) followed by an error-related positivity (Pe).

Performance on behavioral tasks is monitored by a brain system that is responsive to errors (Falkenstein et al., 2000; Gehring & Knight, 2000; Gehring, Goss, Coles, Meyer, & Donchin, 1993; Luu, Flaisch, & Tucker, 2000; Luu, Tucker, Derryberry, Reed, & Poulsen, 2003). Evidence from fMRI, qEEG, and ERP studies outlines that error monitoring is a function of the medial frontal cortex (MFC), including the supplementary eye fields, rostral cingulate motor area, and dorsal anterior cingulate cortex (ACC; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). One of the important research questions is whether the error-related frontal activity is associated with a premorbid trait reflecting an initial deficiency of behavioral control and regulation, and whether this deficit can be

generated as a result of neuropathological states associated with behavioral control deficits typical for psychiatric conditions. Several clinical research studies have demonstrated excessive error processing in patients with obsessive–compulsive disorders (OCD; Johannes et al., 2001), anxiety disorders (Markela-Lerenc et al., 2004) and Tourette syndrome (Gehring, Himle, & Nisenson, 2000). Yet, reduced error processing manifestations were reported in borderline personality disorder (de Bruijn et al., 2006) and schizophrenia (Mathalon et al., 2002). In psychiatric studies, a decreased ERN is typically related to increased severity of psychomotor poverty symptoms (Bates, Liddle, Kiehl, & Ngan, 2004). Furthermore, error processing has also been found to be reduced in nonclinical traits such as high impulsivity (Ruchsow, Spitzer, Grön, Grothe, & Kiefer, 2005).

Neuroanatomically and functionally, the anterior cingulate cortex (ACC) provides an interface between frontal action selection processes, limbic emotion or motivation processes, and motor output regulation (Coles, Scheffers, & Holroyd, 2001; Holroyd & Coles, 2002; Taylor, Stern, & Gehring, 2007). The integral role of the ACC in self-monitoring and guiding attention in goal-directed actions suggests that it may be an important focus for ADHD research. In ASD, disturbances in attention regulation and behavioral rigidity may result in social orienting deficits and a chronic disruption of social information processing and social learning that together may contribute to the social-cognitive and emotional deficits observed in autistic children (Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; Klin, Jones, Schultz, & Volkmar, 2003; Mundy, 1995; Mundy & Neal, 2001). In our studies on error monitoring in autism (Sokhadze, Baruth, El-Baz, et al., 2010; Sokhadze et al., 2012a; Sokhadze et al., 2012b) we showed that the ERN and the Pe component of the response-locked ERP were substantially decreased in children with autism as compared to typically developing (TD) controls and even as compared to children with ADHD. In particular, the amplitude of ERN was less negative and latency of both ERN and Pe were prolonged in the ASD group as compared to the TD children. The ERN is an EEG measure associated with the commission of errors, thought to be independent of conscious perception (Franken, van Strien, Franzek, & van de Wetering, 2007), while the Pe is thought to reflect the motivational or emotional significance of the error or, in another words, the conscious evaluation of the error (Overbeek et al., 2005). The findings that both ERN and Pe are altered in autism may suggest that ASD patients are not only less sensitive to committed errors but that they are also less aware of their errors, probably attributing less significance to them. Inadequate and inflexible responsiveness to errors may underlie one of the typical characteristics of autism spectrum disorders, namely, the persistence of stereotyped repetitive behaviors. The sum of the group differences across these behavioral and stimulus- and response-averaged ERP indices of the ASD patients' performance is that it reflects global deficits in attentional processes, more specifically deficits in effective differentiation of target and distracter stimuli. This latter interpretation is supported by the significant differences between the ASD patients and typically developing controls in terms of both the stimulus-locked and response-locked ERP amplitudes and latencies, and the correlation between subjects' behavioral performance measures and specific ERP components magnitude.

Structural and functional deficiencies of the ACC may contribute to the atypical development of joint attention and social cognition in autism (Mundy, 2003). Such interpretation of the results of the ERN/Pe deficits found in several studies (Bogte, Flamma, van der Meere, & van Engeland, 2007; Henderson et al., 2006; Sokhadze, Baruth, El-Baz, et al., 2010) is consistent with many aspects of theory and research that suggests that ACC-mediated response monitoring may contribute to social-emotional and social-cognitive development in autism (Mundy, 2003). However, while emphasizing the possible role of ACC-related self-monitoring deficits in autism, Mundy (2003) also noted that according to Devinsky and Luciano (1993) these ACC impairment-related behavioral deficits emerge only when they are combined with disturbances in other related functional neural networks, e.g., dorsolateral prefrontal cortex (DLPFC).

Perspectives of Application of ERP as Outcomes in Treatment Research

There are several important practical applications of ERP testing in neurodevelopmental disorders. The first one is the application of ERP tests for functional evaluation as this method has substantial diagnostic potential. The question of using ERP parameters as a diagnostic tool was discussed by Kemner, van der Gaag, Verbaten, and van Engeland (1999), who used multivariate analysis and found that several parameters (mainly P300) showed differences among patients with autism, ADHD, multiple complex developmental disorder (MCDD), and dyslexia. When ERP parameters were used as

variables in discriminate analysis, it was possible to classify several child psychiatric groups and a normal control group well above chance level, with classification occurring in 46% of the cases. When only clinical groups were compared (ASD, ADHD, MCDD, dyslexia), the classification correctness reached 60% (Kemner et al., 1999). However, autism is only one of numerous psychiatric and neurological disorders in which parietal P300 (P3b) is abnormal. Attenuated P3b was found in schizophrenia (Ford, 1999), bipolar disorder, ADHD, and alcoholism to name a few (review in Picton, 1992; Polich & Herbst, 2000; Pritchard, 1986) and cannot be considered as a specific marker for ASD. Expanding the topographical areas of ERP measurements (e.g., frontal, parietal, etc.) and adding earlier potentials (e.g., N100) and error-related potentials (i.e., ERN and Pe) may increase the diagnostic potential for clinical and functional evaluations of ASD.

Our error-related potential findings (Sokhadze, Baruth, El-Baz, et al., 2010; Sokhadze et al., 2012a; Sokhadze et al., 2012b; Sokhadze, El-Baz, Sears, Opris, & Casanova, 2014; Sokhadze, El-Baz, Tasman, et al., 2014; Sokhadze, Tasman, Sokhadze, El-Baz, & Casanova, 2016) revealed that autism is associated with reduced error processing and impaired behavioral correction after an error is committed. Because adequate error processing is necessary for optimal behavioral performance, it is plausible that these deficits contribute to the maintenance of the preservative behaviors typical for autism. Impairments in an ability to correctly and timely evaluate committed errors and to learn from errors may lead to behavior that is rigid and repetitive rather than adaptively guided by action outcomes. Deficits in adjustments of erratic behavior during interaction with peers may as well affect social interaction of children with autism and in those with ADHD. Elucidating the neurobiological basis and clinical significance of response monitoring and correction deficits in ASD and ADHD represents a promising direction for further qEEG, and specifically ERP-based, research. The ERP variables along with behavioral performance measures can be used as functional outcome measures to assess the effectiveness of behavioral interventions (e.g., Applied Behavioral Analysis [ABA] in ASD), cognitive-behavioral therapies (CBT; e.g., exposure therapy in PTSD) or neurotherapies (e.g., repetitive transcranial magnetic stimulation [rTMS] in ASD, or neurofeedback in children with ADHD or neurofeedback in adult patients with SUD) and thus may have important practical implications. The application of ERP indices in standardized visual or auditory oddball tasks as an outcome measure in diagnostic and posttreatment evaluations seems to be a feasible approach considering the growing interest in qEEG assessments of individuals with neurological and psychiatric disorders.

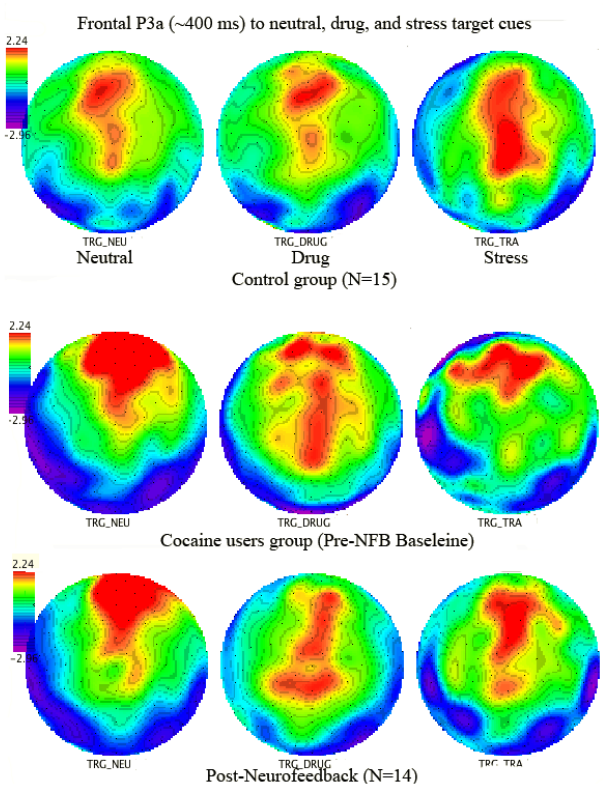

Figure 4. Topographic maps during drug- and traumatic-stress-related cue reactivity task in typical controls and patients with cocaine substance use disorder (CUD). There are depicted responses around 400 ms to neutral, drug-, and stress-related target cues in control and SUD group before and after Theta/SMR neurofeedback training course. Drug users as compared to controls showed at baseline test higher response in a form of enhanced P3a (red color) to drug cues at the fronto-central regions that were reduced post-neurofeedback training. It should be also noted that typical controls showed normative enhanced P3a to stress cues, while the SUD group had lower reactivity to stress cues at the baseline.

ERP Components as Biomarkers

To be useful as a biological marker, the changes in ERP biomarkers during cognitive tests have to be both sensitive and specific. Traditional neurophysiological studies compare a group of healthy controls with a group of patients and report significant differences in selected ERP measures.

This is a useful approach for diagnostic purposes, but it also needs to be linked with theoretical models that may advance understanding of brain function and neuropathology specific psychopathologies, for example, when comparing ASD and ADHD. To achieve this goal, it is necessary to use cognitive functioning tests and demonstrate that specific function abnormality is reflected in and correlates with specific ERP changes (Başar & Güntekin, 2008). A potential approach to achieve this goal is to identify the cognitive deficit typical for a patient group and use already known, or potentially useful, ERP correlates of this impaired function (e.g., the degree of attention deficit with ASD and ADHD). During performance on a cognitive task, patients with the pathologies of interest (ASD, ADHD) are proposed to yield ERP markers assessing the attention-related deficits as compared to the matched control group. The approach of studies for our group (Sokhadze, Stewart, Tasman, Daniels, & Trudeau, 2011) was based on using both stimulus-locked ERPs (e.g., frontal N100, P2a, P3a, parietal N200, P3b, etc.) and response-locked ERPs (ERN/Pe) during cognitive tests aimed to identify specifics of their alterations in ASD and in ADHD groups, as well as their differences from the neurotypical typical (NT) children, and consider them as useful biomarkers of above conditions.

Event-related Potentials in ASD and ADHD

ASD

ERP studies of visual processing commonly employ an oddball discrimination task of selective attention in which the participant responds to an infrequent target stimulus among more frequent nontarget stimuli (Vohs et al., 2008). Most investigations into visual processing in ASD have focused on higher level, long-latency ERPs, like the P300 (Courchesne, Courchesne, Hicks, & Lincoln, 1985; Courchesne, Lincoln, Kilman, & Galambos, 1985; Courschesne, Lincoln, Yeung-Courchesne, Elmasian, & Grillon, 1989; Hoeksma, Kemner, Kenemans, & van Engeland, 2006; Kemner et al., 1999; Townsend et al., 2001; Verbaten et al., 1991). The centro-parietal P3b amplitude has been found to be similar (Courchesne, Courchesne, et al., 1985; Courchesne, Lincoln, et al., 1985; Courchesne et al., 1989; Hoeksma et al., 2006), reduced (Townsend et al., 2001; Verbaten et al., 1991) and augmented (Kemner et al., 1999) in ASD to target stimuli compared to controls. There have been fewer studies on early-stage (i.e., 50–200 ms) visual processing in ASD (Jeste & Nelson, 2009). In our prior ERP study (Baruth, Casanova, Sears, & Sokhadze, 2010; Sokhadze, Baruth, et al., 2009) on novelty processing in ASD, we reported that the ASD group showed significantly higher amplitudes and longer latencies of early frontal ERPs and delayed latency of P3a to novel distractor stimuli. Our results suggest low selectivity in pre-processing and late-stage overprocessing in integrative regions in the prefrontal cortices. Shorter latency and higher amplitude of the early frontal negativity in the autism group with minimal differentiation of response magnitude to either target or nontarget stimuli is an interesting finding that was replicated in several of our reports (Sokhadze, Baruth, Tasman, et al., 2010; Sokhadze et al., 2012a; Sokhadze et al., 2012b; Sokhadze, Casanova, & Baruth, 2013) where different visual oddball tasks were used. The visual N100 is considered as an index of stimulus discrimination **(**Hopf, Vogel, Woodman, Heinze, & Luck, 2002). The visual N100 generally is augmented during preattentional stimulus processing (Hillyard, Hink, Schwent, & Picton, 1973) and is larger towards task-relevant target stimuli (Luck et al., 1990). The ASD group shows clearly augmented and delayed frontal P3a that might result in an impaired early differentiation of target and nontarget items (e.g., on N100 stage) and more effortful compensatory strategies involved for successful target identification, as well as following correct motor response selection. In addition, frontal P200 (P2a) was found to be equally more positive to all stimuli in the ASD group with a lack of stimulus discrimination; as P2a were indiscernible between target and distracter stimuli in the ASD group, wherein in the control group P2a was more positive to targets. The P200 over frontal ROI has been associated with the hierarchal selection of task-relevant features (Kenemans et al.,1993). In ASD globally augmented cortical responses, especially to irrelevant stimuli at early stages of visual processing, probably are complicating stimulus discrimination processes at the stage of the P200. In general, the ASD group showed prolonged latencies to standard and rare nontarget illusory Kanizsa figures in a visual oddball task. These results suggest that individuals with ASD probably overprocess information needed for the successful differentiation of target and distractor stimuli. One of the possible explanations might be sought in the local hyperconnectivity hypothesis of autism. The topic of neural and functional connectivity abnormalities was always considered as an extremely important one in current ASD neuropathology theories (Belmonte et al., 2004; Courchesne & Pierce, 2005; Just, Cherkassky, Keller, & Minshew, 2004; Minshew & Williams, 2007**;** Welchew et al., 2005). Some authors consider ASD as disorder of neural connectivity (Coben, Chabot, & Hirshberg, 2013).

Our studies (Baruth, Casanova, El-Baz, et al., 2010; Baruth, Casanova, Sears, et al., 2010; Baruth et al., 2011; Casanova et al., 2012; Sokhadze, Baruth, El-Baz, et al., 2010; Sokhadze et al., 2012a; Sokhadze et al., 2012b; Sokhadze, Baruth, et al., 2009; Sokhadze, El-Baz, et al., 2009; Sokhadze, El-Baz, Sears, et al., 2014; Sokhadze, El-Baz, Tasman, et al. 2014) suggest that nontarget ERP responses in oddball paradigms should be routinely studied along with target responses in order to improve the diagnostic capabilities of cognitive ERPs. Notably, nontarget responses may help to decide whether abnormal responses to target (P3a, P3b) are related or not to a deficit in the mobilization of attentional resources (García-Larrea et al., 1992).

ADHD

Studies of P300 in ADHD have suggested that children with this diagnosis have attenuated P300 to both auditory and visual stimuli (Barry, Johnstone, & Clarke, 2003; Klorman et al., 1983; Klorman, Salzman, Pass, Borgstedt, & Dainer, 1979). A decreased P3b has been reported in conjunction with an augmentation at frontal sites (Banaschewski et al., 2003; Banaschewski, Roessner, Dittmann, Santosh, & Rothenberger, 2004; Dimoska, Johnstone, Barry, & Clarke, 2003; Duncan et al., 2009; Johnstone & Barry, 1996; Johnston, Madden, Bramham, & Russell, 2011; Jonkman et al., 1997; Jonkman, Kenemans, Kemner, Verbaten, & van Engeland, 2004; Smith, Johnstone, & Barry, 2004). In ADHD populations, ERP studies which concentrated on visual selective attention found a smaller early frontal negativity in ADHD as compared to controls, suggesting deficiencies in early attention processes (Jonkman et al., 2004; Satterfield, Schnell, & Nicholas, 1994; van der Stelt, van der Molen, Gunning, & Kok, 2001), while no abnormalities were found for the N200. Studies using other attention paradigms (e.g., continuous performance, oddball and choice reaction time tasks) have provided evidence for smaller P3b in visual oddball tasks (Barry et al., 2003). In sum, several studies found reduced frontal amplitudes (e.g., N100, N200) in ADHD, which can be taken as suggesting a deficit in selective attention manifested in ERP alterations.

ERP as Trauma-related Cue Reactivity in PTSD

Whereas the P300 in general is thought to represent “context updating/closure” (Donchin & Coles, 1988), in three-stimuli oddball task the P3a is interpreted as “orienting,” and the P3b as an index of an ability to maintain sustained attention to target (Alho, Lavikainen, Reinikainen, Sams, & Näätänen, 1990; Potts et al., 2004). The anterior P3a indexes the contextual salience of the rare stimuli, whereas posterior P3b is indexing task-relevance of the stimuli (Gaeta, Friedman, & Hunt, 2003). The three-stimulus category oddball paradigm provides possibilities for delineating the cognitive processes engaged in this task when motivational salience of novel distracter stimuli is manipulated. Among the most widely used manipulations are the selection of pictorial, auditory, or audio-visual modality cues related to trauma in patients with PTSD (e.g., gun shot in combat-related PTSD). These stimuli are used as rare novel distracters and the main ERP component of interest is usually fronto-central P300 (P3a). Higher novelty P3a amplitudes have been observed in responses to phobia-related images among persons with spider phobias and dental phobias (Kolassa, Musial, Mohr, Trippe, & Miltner, 2005; Schienle, Köchel, & Leutgeb, 2011). Meta-analysis of PTSD studies using ERP (Karl, Malta, & Maercker, 2006) noted higher P3a amplitudes to trauma-related pictorial cues in PTSD trauma-exposed subjects than in trauma-exposed subjects without PTSD.

Most of the studies on PTSD report abnormalities in the P300, which provide presumptive evidence for impaired cognitive processing in this disorder (Attias, Bleich, Furman, & Zinger, 1996; Blomhoff, Reinvang, & Malt, 1998; Charles et al., 1995; Felmingham, Bryant, Kendall, & Gordon, 2002; Karl et al., 2006; Kimble, Kaloupek, Kaufman, & Deldin, 2000; Stanford, Vasterling, Mathias, Constans, & Houston, 2001). Studies finding attenuated P300 attribute their results to concentration impairment (McFarlane, Weber, & Clark, 1993) or attention deficits (Charles et al., 1995; Metzger, Orr, Lasko, McNally, & Pitman, 1997; Metzger, Orr, Lasko, & Pitman, 1997). Increased P300 amplitude was explained as due to altered selective attention (Attias et al., 1996) or heightened orientation to threatening stimuli (Kimble et al., 2000). Several studies emphasize that P3a enhancement in PTSD is expressed when distracters are either trauma-related or novel stimuli in oddball tasks (Bleich, Attias, & Furman, 1996; Drake, Pakalnis, Phillips, Padamadan, & Hietter, 1991; Felmingham et al., 2002; Weinstein, 1995). Increased P300 (P3b) amplitude in PTSD is thought to reflect attentional bias towards threat stimuli and reduced P300 (P3b) amplitude is thought to reflect a consequent reduction in attentional resources to nonthreatening stimuli.

Some ERP-based Psychophysiological Approaches to Schizophrenia Research

One of the most trivial applications of ERP methods in psychopathology diagnostics is directed to the search of specific ERP features typical for the psychopathology of interest. The goal of such searches is to identify sufficiently sensitive and specific ERP markers for the particular mental disorder (schizophrenia, PTSD, etc.). Following modern concepts in psychophysiology, however, it should be considered that it is not a search for a single marker (e.g., centro-parietal P3b amplitude), but rather for multivariate discriminators of the patterns of ERP measures, even though such approaches are not yet frequently used in research and clinical applications. Psychophysiological studies based on ERP have an important role in the study of symptomatically heterogeneous, clinically diverse, and differentially medically treated psychopathologies. It is important to note that in psychophysiologically oriented research it would be recommended, when possible, to analyze behavioral response during performance on tasks and concurrently analyze parameters of ERPs at preselected topographies, in order to identify the stage of information processing when cognitive dysfunction seems to be more obviously manifested. It seems feasible to illustrate some efficient applications of ERP methods, and in particular cognitive neuroscience techniques, for the understanding of the neurobiological basis and specifics of certain psychopathologies (e.g., schizophrenia) where auditory ERPs have been widely examined. Identification of those ERP altered in schizophrenia adds information about specifics of cognitive dysfunctions in this disorder. ERPs are a powerful tool to investigate the time course of brain wave activity during cognitive processing in schizophrenia because ERP components can serve as markers for cognitive processing stages. The ERP P300 analysis has already been routinely used in schizophrenia research in an oddball paradigm in auditory sensory modality. One of the main reasons for its broad application in psychopathology research is the fact that, in schizophrenia, attenuation of P300 amplitude and prolonged latency have been described by many researchers (Ford, 1999; Ford et al., 2001; Gallinat et al., 2002; Turetsky, Colbath, & Gur, 1998a, 1998b). P300 is often, but not always, observed to be more reduced over the left than right temporal lobes in patients with schizophrenia, as it was outlined by Ford et al. (2001). It can be definitely stated according to Turetsky et al. (1998a, 1998b) that reduced amplitude of the P300 ERP is a robust and consistent finding in schizophrenic patients. The relationship between the frontal P300 and hallucinations is consistent with both the cognitive orienting function of this component and the role of the anterior cingulate in this ERP activity. Correlated left temporal and frontal dysfunction is consistent with fronto-temporal disturbance in some schizophrenics (Turetsky et al., 1998b). However, ERP abnormalities are not manifested only in P300 responses (P3a, P3b). The majority of studies reported findings that schizophrenics patients had reduced P300, N200, and N100 amplitudes and increased P300 latencies. The ERP abnormalities shown in most studies appear to be enduring trait of the disorder.

Conclusion

ERPs are reflecting stages of information processing. The analysis of ERPs could provide for important outcome measures, a potential cortical “signature” of response patterns associated with core behavioral and cognitive abnormalities that characterize various psychopathologies. Furthermore, when analyzed along with behavioral (reaction time, accuracy, etc.), response-locked potentials (e.g., ERN), event-related potential data-based biomarkers will offer insights into the psychophysiology of psychopathologies. The relative low cost of ERP methods means that the proposed biomarker will be accessible to many individuals and to those studies requiring large samples. EEG modalities are noninvasive and can be tolerated by many individuals who would otherwise not be able to participate in alternative studies (e.g., fMRI).

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NeuroRegulation

The Crisis in Psychopharmacology Provides an Opportunity for Neuroregulation Treatments to Gain Widespread Acceptance

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Private practice

Abstract

Psychopharmacology is in crisis due to the increasing recognition that it does not work as claimed and has failed to meaningfully improve outcomes over what they were in the 1950s and '60s. Though still widely promoted to the public, the chemical imbalance theory of major mental health disorders is now openly acknowledged as not accurate by leading psychiatrists, thereby undermining the rational for this approach to care. A series of large comparative effectiveness studies funded by the National Institute of Mental Health (NIMH) were each essentially failed trials with disappointing results and found that second-generation psychotropic medications were no more effective than their first-generation cousins. The evidence from several of these studies are reviewed within the scope of major depression and attention-deficit/hyperactivity disorders, and then compared to research on promising neuroregulation treatments. The author then makes recommendations for neuroregulation clinicians to avoid a crisis similar to that experienced in psychopharmacology today.

Keywords: psychopharmacology; neurofeedback; depression; STAR*D; MTA cooperative study; ADHD

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Background

In the attempt to provide evidence-based guidance to clinical practice and improve outcomes, the National Institute of Mental Health (NIMH) funded a series of large comparative effectiveness studies for attention-deficit/hyperactivity disorder (ADHD), the multimodal treatment of attention deficit hyperactivity disorder (MTA cooperative study): cost $21 million (Jensen et al., 2007; Molina et al., 2009; MTA Cooperative Group, 2004a, 2004b); bipolar disorder, the systematic treatment enhancement program for bipolar disorder (STEP-BD): $26 million (Bowden et al., 2012); major depression, sequenced treatment alternatives to relieve depression (STAR*D): $35 million (Fava et al., 2003; Rush, 2002; Rush et al., 2006; Trivedi et al., 2006; Trivedi, Stegman, Rush, Wisniewski, & Nierenberg, 2002); and schizophrenia, clinical antipsychotic trials of intervention effectiveness (CATIE): $72 million (Lieberman et al., 2005), among other well-funded efforts. In an editorial, DePaulo (2006), past chairman of psychiatry at Johns Hopkins, termed these studies as *effectiveness-plus* because each used the best available treatment methods to optimize outcomes. Furthermore, there was no blinding of treatments in each of these trials, thus taking advantage of nonspecific placebo effects, which inflate outcomes. Despite the costs, and investigators' best efforts, each of these studies were essentially failed trials with outcomes far less than expected. DePaulo noted how the studies taken together "underline the suggestion that modern pharmacological treatments may be no more beneficial than older ones, despite their added cost" (2006, p. 175). Similarly, former NIMH Director Insel (2009) observed that in each of these effectiveness-plus studies second-generation psychotropic medications were no better than their first-generation cousins and then went on to

acknowledge, “The unfortunate reality is that current medications help too few people to get better and very few people to get well” (p. 704).

As evidenced in a 2012 editorial by Fibiger, former Vice President of Neuroscience at Eli Lilly, DePaulo (2006) and Insel (2009) are not alone in acknowledging the current state of psychopharmacology. Fibiger writes the following:

> Psychopharmacology is in crisis. The data are in, and it is clear that a massive experiment has failed: despite decades of research and billions of dollars invested, not a single mechanistically novel drug has reached the psychiatric market in more than 30 years. Indeed, despite enormous effort, the field has not been able to escape the “me too/me (questionably) better” straightjacket (p. 649).

Fibiger (2012) goes on to note that each of psychiatry’s classes of medication were discovered by “serendipitous clinical observation” (p. 649) and would likely not have been discovered using current drug discovery strategies. Thus, concluding that:

> What the field has been doing for the past 3 or 4 decades has failed to generate effective, mechanistically novel psychopharmaceuticals…there is no choice but to make changes in how we approach the study of disease mechanisms, drug discovery, and development in psychiatry. This will require major investments in neuroscience research, humility in the face of our ignorance, and a willingness to consider fundamental reconceptualizations of psychiatry itself (p. 650).

Hyman (2012), another former NIMH Director, acknowledges how the initial serendipitous findings from the 1950s “motivated path-breaking research on neurotransmitter release, receptors, and transporters” but “what has happened—*or rather not happened*—in the intervening half-century was as unexpected as the initial spate of discoveries” (p. 1). Hyman goes on to observe that:

> The molecular targets of all of today’s approved psychiatric drugs are the same as the targets of their pre-1960 prototypes and their mechanisms of action are not understood beyond a few initial molecular events…By capturing the imagination of researchers to excess, however, and in the absence of other robust biological tools to probe brain function, these drugs may have proved something of a scientific curse (p. 1–2).

The widely acknowledged failure to improve psychopharmacology outcomes has gotten so bad that not only are academic psychiatrists actively disavowing the neurochemical imbalance theory of major mental health disorders, but some apologists claim that it was never even a theory held by responsible psychiatrists in the first place. Pies (2011), Editor in Chief Emeritus of *Psychiatric Times*, writes, “In truth, the ‘chemical imbalance’ notion was always a kind of urban legend—never a theory seriously propounded by well-informed psychiatrists” (p. 1).

Pies concludes his editorial by stating that “the legend of the ‘chemical imbalance’ should be consigned to the dust-bin of ill-informed and malicious caricatures,” as though this horse that biological psychiatry rode to prominence—backed by billions in taxpayer- and industry-funded research and many billions more in pharmaceutical companies’ deceptive marketing efforts—was not only a half-century long fool’s errand/scientific curse “chasing down chemical imbalances that don’t exist” (Greenberg, 2013, p. 6) but it is now a “malicious caricature” (Pies, 2011, p. 2) to expose this fact. In response to Pies (2011), Hickey (2014) provides extensive documentation going back to the early 1970s of eminent biological psychiatrists as well as the American Psychiatric Association itself propagating the chemical imbalance theory of mental illness and how this theory is featured prominently on numerous authoritative websites as well as on TV today.

Major Depression

The STAR*D study (Fava et al., 2003; Rush, 2002; Rush et al., 2006; Trivedi et al., 2006) is the largest antidepressant study ever conducted with over 120 journal articles published by study investigators. STAR*D enrolled 4,041 patients diagnosed with major depression, including patients with comorbid conditions; thereby increasing the generalizability of its findings, while also providing 12 months of free follow-up care to monitor the durability of treatment effects. The study provided up to four drug trials per patient with the hope of being able to give guidance in selecting the best next-step treatment for the many patients who fail to get sufficient relief from their initial antidepressant and subsequent trials. Each drug trial/step lasted up to 12 weeks with an

additional 2 weeks added on for those patients deemed close to remission. Antidepressants were administered using measurement-based care that involved assessing symptoms and side effects at each visit to guide aggressive medication dosing in order to ensure that the likelihood of achieving remission was maximized and that those who did not reach remission were truly resistant to the medication (Trivedi et al., 2006).

The researchers allowed patients to select treatment options for randomization in steps 2–4 "to empower patients, strengthen the therapeutic alliance, optimize treatment adherence, and improve outcome" (Fava et al., 2003, p. 483) and evaluated the relative effectiveness of 11 pharmacologically distinct drug/drug combination treatments in five head-to-head comparisons. Patients who achieved remission during any step were encouraged to enter the 12 months of free follow-up care. The follow-up protocol "strongly recommended that participants continue the previously effective acute treatment medication(s) at the doses used in acute treatment" but treating physicians were allowed to make "any psychotherapy, medication, or medication dose change" they deemed necessary to sustain remission during follow-up, including scheduling additional visits if depressive symptoms returned and/or intolerable side effects emerged (Rush et al., 2006, p.1908).

In different publications, the author among others have criticized the STAR*D investigators for extensive evidence of researcher bias that significantly inflated their reports of outcomes (e.g., Pigott, 2011; Pigott, 2015; Pigott, Leventhal, Alter, & Boren, 2010). Despite it being over six years since the Pigott et al. (2010) publication, STAR*D's researchers have still not offered a defense for their biases documented therein. In 2011, Pigott and Alter published a response to two letters commenting on the first STAR*D article. Neither letter questioned the Pigott et al. analysis, though STAR*D's researchers could easily have published a counterargument since one of its principal investigators was an associate editor for the journal. This did not happen; instead the researchers continued publishing articles untethered to their pre-specified analytic plan and primary measure.

Figure 1 is a comparison between STAR*D researchers' predicated success rate, their post hoc concocted *theoretical* success rate, and STAR*D's actual step-by-step success rates (Pigott, 2015). The predicated success rate is taken from Figure 7 in STAR*D's Research Protocol's step-by-step predictions of dropout and the number of patients who would have a satisfactory response and enter follow-up (Rush, 2002). The author obtained the protocol through a Freedom of Information Act request. The predictions were made by STAR*D's three most highly published researchers who had over 1,900 published studies between them. Regarding the predictions, the protocol states that they were arrived at based on the independent estimates of Drs. Fava, Rush, and Thase, informed by the results of published randomized controlled trials (Rush, 2002).

While these predictions' purpose was to estimate the number of continuing patients available for randomization in steps 2–4 and to ensure adequate statistical power for the planned comparisons, at the metalevel, these predictions are the central hypothesis STAR*D tested by assessing how well these experts could predict the aggregate step-by-step outcomes from optimally delivered antidepressant drug treatment. Evaluating these predictions is important in learning the correct lessons from STAR*D, since there were no significant group differences between any of the 11 drug/drug combination treatments, even though there was adequate statistical power to discern differences, if any existed. Furthermore, no post hoc secondary analyses have yielded significant predictors of outcomes between the pharmacologically distinct treatments. Therefore, this $35 million taxpayer-funded study provides no next-step guidance to give hope for improving outcomes from the optimal administration of antidepressants beyond that found in the study itself.

In STAR*D's summary article the researchers calculated a "theoretical cumulative remission rate of 67%" with the scientifically baseless provisos that "this estimate assumes no dropouts, and it assumes that those who exited the study would have had the same remission rates as those who stayed in the protocol" (Rush et al., 2006, p. 1910–1911). As Pigott et al. (2010) document, however, the researchers' assumptions in calculating their theoretical remission rate are simply not true in the real world—and was certainly not true in STAR*D, since more patients dropped out in each step than remitted. Today, STAR*D researchers' baseless provisos are commonly dropped when portraying its findings. For example, an *American Journal of Psychiatry* editorial states STAR*D found, "after four optimized, well-delivered treatments, approximately 70% of patients achieve remission" (Greden, 2013, p. 580), as though this is a factual statement of what occurred.

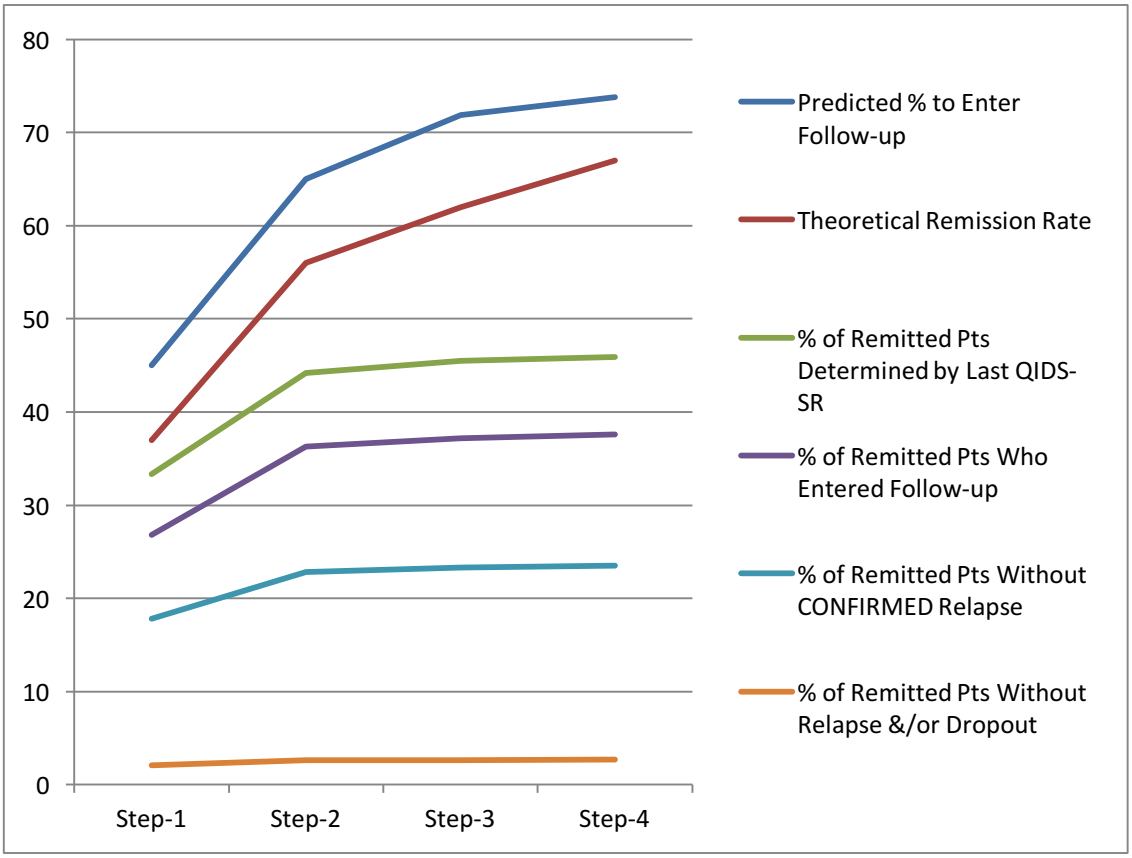

Figure 1. Comparison between predicted, theoretical, and actual step-by-step success rates (Pigott, 2015, used with permission).

As is evident in Figure 1, STAR*D's predicted (73.8%) and theoretical (67.0%) success rates are similar, yet highly divergent from what actually occurred after up to four drug trials, in that the cumulative percent of patients who had a remission was only 45.9% and, by step 4, the cumulative percent of patients who had a remission and entered free follow-up care was a mere 37.6%.

The data STAR*D investigators provide for accessing the durability of treatment gains are even more discouraging. For step 1, only 17.8% of patients had a remission and during follow-up did not have a confirmed relapse. After up to four rounds of antidepressant drug/drug combination treatments, the cumulative rate of patients who did not have a confirmed relapse improved to only 23.5% (and this from optimal acute and follow-up care). When dropout is added, the durability of treatment effects is even paltrier; only 2.7% of the 4,041 enrolled patients had a remission after up to four rounds of optimal care and neither relapsed nor dropped out during the 12 months of free follow-up services.

On the other hand, whereas psychopharmacology has not worked as claimed, neurofeedback (NFB) and other neuroregulation strategies are suitable alternative treatments (Choi et al., 2011; Peeters et al., 2014). While there are many studies demonstrating the effectiveness of these strategies for treating major depression, the Cantor and Stevens (2009) study is exemplary in its experimental design, use of quantitative electroencephalography (qEEG) biomarkers of depression for study inclusion, and incorporation of both neurophysiologic and rating scale measures to evaluate outcomes. The researchers randomly assigned 16 treatment-resistant depressed patients into two groups of eight (simulated and active 14 Hz audio-visual entrainment) in a crossover research design. Patients received either simulated or active auditory-visual EEG entrainment (AVE) 5 days per week for 4 weeks and then crossed over. As reported by the researchers, "all participants were required to have increased frontal relative alpha or increased relative frontal beta on a neurometric qEEG evaluation to qualify for the study based on

previous studies indicating such deviations in depression samples" (p. 102). Key findings were:

- Significant improvements on the Beck Depression Inventory-II (BDI) and neurophysiologic measures were only associated with active AVE treatment (p > .01);
- AVE resulted in 50% or greater improvement on the BDI for all patients;
- AVE resulted in significant EEG changes in cortical regions associated with mood regulation; and
- AVE treatment gains were sustained for 1 month following termination for the group who received AVE first.

The opportunity for neuroregulation strategies to have a significant impact on the treatment of major depression is not going away, only increasing. A recent article by Kelland (2017) reports that experts believe it will be more than decade "before any new generation of antidepressants comes to market" and cites the Kantor et al. (2015) study finding a near-doubling in the number of American adults taking antidepressants between 1999 and 2012, rising to 13.0 percent from 6.9.

Echoing the observations of Fibiger (2012) and Hyman (2012), Kelland's article quotes Oxford psychiatry professor Guy Goodwin acknowledging that psychopharmacology's lack of progress is "partly a failure of science, to be frank...Scientists have to get more of an understanding about how these things actually work before we can then propose ways to improve them." Despite negligible research funding, the neuroregulation field is in many ways ahead of psychopharmacology in finding effective treatments in that we have validated qEEG biomarkers for depression (e.g., John, Prichep, Friedman & Eastman, 1988; John et al., 2007) and both NFB and neurostimulation-based strategies to correct them; to date, there is nothing comparable in psychopharmacology.

ADHD

There have been two large NIMH-funded ADHD studies that included long-term follow-up assessments, the MTA Cooperative study (Jensen at al., 2007; Molina et al., 2009; MTA Cooperative Group, 1999, 2004a, 2004b) and the Preschool Attention-Deficit/Hyperactivity Disorder Treatment Study (PATS; Riddle et al., 2013). Pigott and Cannon (2014) provide a detailed critique and deconstruction of these studies. They conclude that the evidence from these NIMH-funded studies is pharmacological treatments do not result in sustained benefit for the vast majority of ADHD children and thus do not warrant being the first option for treating ADHD.

In fact, what evidence is available during the follow-up phases found a deleterious effect from the ongoing use of stimulant medications to treat ADHD. Jensen et al. (2007) reported that in the 22-month MTA follow-up, "medication use was a significant marker, not of beneficial outcome, but of deterioration" (p. 996); and Molina et al. (2009) noted in the final follow-up assessment that stimulant medication use "was associated with worse hyperactivity-impulsivity and ODD symptoms and CIS impairment at 6 years" (p. 488). Similarly, Riddle et al. (2013) reported in the PATS follow-up study, "medication treatment in the original PATS predicted higher ADHD symptom severity between follow-up years 3 and 6" (p. 10); raising again the issue identified in the MTA follow-up assessments of the increased risk of harm resulting from ongoing stimulant medication treatment.

Currie, Stabile, and Jones (2014) provide additional evidence of the increased risk of harm by the use of stimulant medications to treat ADHD. These three economists studied the medium- and long-term impact of adding prescription drug insurance coverage in Quebec. The summary of their findings is as follows:

> We find that the introduction of the prescription drug insurance program increased the use of stimulants in Quebec relative to the rest of Canada. However, we find no evidence that the performance of children with ADHD improved. In fact, the increase in medication use among children with ADHD is associated with increases in the probability of grade repetition, lower math scores, and a deterioration in relationships with parents. When we turn to an examination of long-term outcomes, we find that increases in medication use are associated with increases in the probability that a child has ever suffered from depression and decreases in the probability of post-secondary education among girls (p. 59).

This repeated pattern of the loss of efficacy and increased risk of harm in studies assessing the impact from the ongoing use of stimulant medications likely accounts for much of the dramatic

increase in the prescribing of antipsychotics to children (Pigott & Cannon, 2014). Olfson, Blanco, Liu, Wang, and Correll (2012) report that between 1993–1998 and 2005–2009, the rate of antipsychotics prescribed to children increased by over 750%. They found that disruptive behavior disorders (primarily ADHD) were the most common diagnoses in children that were prescribed an antipsychotic medication, accounting for 63% of such cases; and that in 54.1% of the outpatient visits, whenever an antipsychotic was prescribed, there was also an ADHD medication prescribed to the same child. In the PATS study, by the third year (age seven), an antipsychotic had been added to 8.3% of the preschoolers' medication regimen (and for 10.7%, a norepinephrine reuptake inhibitor) and by age 10, 12.9% were taking an antipsychotic (and for 8.6%, a selective serotonin reuptake inhibitor was added); adding further evidence that stimulant medications act as gateway drugs to more psychiatric drugs, in the often fruitless pursuit of a chemical cure. Thus, as summarized in Pigott and Cannon (2014):

> When the documented adverse effects of stimulants on ADHD children's growth, neural functioning, and cardiovascular system (Graham et al., 2011) are combined with their lack of long-term efficacy and gateway effect to other psychiatric drugs, stimulant medications must be displaced from their current status as the primary first-line treatment for ADHD (p.9).

Pigott and Cannon (2014) review the extensive evidence documenting NFB as the best available first-line treatment for ADHD. This treatment is based on Sterman and colleagues research finding that when hungry cats were fed contingent upon the increase in 12–16 Hz neuronal activity in the sensorimotor cortex (subsequently named the sensory motor rhythm [SMR]) the cats ''became very alert'' and displayed ''an almost intense cessation of movement," behaviors which are key deficits in children with ADHD (Sterman & Wyrwicka, 1967, p. 149). Building on Sterman's findings and using a rigorous double-blind within-subject reversal design, Lubar and Shouse demonstrated that, through real-time feedback of SMR paired with operant conditioning, ADHD children learned to self-regulate SMR with the resulting improvements or worsening of their ADHD symptoms based on whether they were reinforced to increase or decrease their SMR activity level (Lubar & Shouse, 1976; Shouse & Lubar, 1979).

NFB's evidence-base has now grown to over 70 published studies which find it effective in treating ADHD's core symptoms with the vast majority of these studies using standardized protocols targeting either SMR, the theta/beta ratio, or slow cortical potential training. Meta-analyses have found these standardized protocols to be efficacious and specific in treating ADHD's core symptoms (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009), with medium-to-large effect sizes in randomized controlled trials when compared to semi-active (e.g., EMG biofeedback) and fully-active (e.g., computerized cognitive training) treatments (Arns, Heinrich, & Strehl, 2014). Furthermore, unlike stimulant medication, reports of adverse effects from NFB are uncommon. More importantly, no other ADHD treatment has demonstrated credible evidence of sustained benefit following treatment termination, whereas this is the consistent finding of NFB studies that included follow-up assessments at 6 months (Gevensleben et al., 2010; Leins et al., 2007; Meisel, Servera, Garcia-Banda, Cardo, & Moreno, 2013; Steiner, Frenette, Rene, Brennan, & Perrin, 2014; Strehl et al., 2006) and 2 years (Gani, Birbaumer, & Strehl, 2008; Monastra, 2005).

Conclusions and Recommendations

Psychopharmacology's increasingly acknowledged 50+ year failure to identify any new molecular targets and to meaningfully improve outcomes, combined with the growing recognition that for many patients these medications cause more harm than benefit when used over time (e.g., Gøtzsche, 2015; Whitaker, 2010; Whitaker & Cosgrove, 2015), provides an opportunity for neuroregulation treatments to gain widespread acceptance. Critical to gaining such acceptance is for the NFB and neuromodulation professional communities to maintain high scientific and clinical standards of practice. In recent years, high-quality NFB research has been published in mainstream peer-reviewed journals such as *Pediatrics* (e.g., Steiner et al., 2014; Strehl et al., 2006), the *Journal of Attention Disorders* (e.g., Mayer, Wyckoff & Strehl, 2013; Wigton & Krigbaum, 2015), and *Biological Psychology* with their entire January 2014 issue dedicated to NFB. While Insel argues that psychiatry needs to be remade into the discipline of clinical neuroscience (Insel, 2009; Insel & Quirion, 2005), from inception that is our discipline. Thus, it is necessary to protect its validity and grow it through close adherence to high standards.

Given psychopharmacology's crisis and the growing recognition of neuroregulation interventions' effectiveness and promise, there has been a significant increase in interest and investments in the field. This is a blessing and a curse. On the one hand, it funds increased research and development efforts to build more effective and user-friendly treatments, thereby accelerating acceptance. On the other hand, it increases outside scrutiny while simultaneously opening the gates for opportunists to make unsubstantiated claims for their products and methods and thereby tarnish the field. Therefore, it is important to establish a culture of responsibility, evidenced by a willingness to learn from failure and the courage to call out unsubstantiated claims. Professional NFB and neuromodulation membership societies need to foster such a culture or else we too may find ourselves in a crisis similar to that which psychopharmacology finds itself in today.

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Statement of Competing Interests

Dr. Pigott has consulted for Amen Clinics, Brain Resources, CNS Response, the International Society of Neurofeedback and Research, and Neuronetics. He also owns stock options in CNS Response, a company that markets a qEEG database to predict medication response.

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NeuroRegulation

Combined Neurofeedback and Heart Rate Variability Training for Individuals with Symptoms of Anxiety and Depression: A Retrospective Study

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Abstract

Introduction. Neurofeedback (NFB) and heart rate variability (HRV) training present promising, nonpharmaceutical intervention strategies for anxiety and depression. This report is the first to address whether concurrent NFB and HRV (NFB+HRV) provides a viable intervention for symptoms of anxiety and depression, measured by the Achenbach System of Empirically Based Assessment (ASEBA) questionnaire. **Methods.** 183 children and adults with symptoms of anxiety and/or depression underwent NFB+HRV training. Psychological symptom rating, EEG, blood pressure, breathing pattern, and HRV were measured before and after treatment. **Results**. After NFB+HRV training, symptoms of anxiety ($p < .001$, $d_z = 1.42$) and depression ($p < .001$, $d_z = 1.34$) were reduced in children and adults. The majority of individuals with pretreatment symptoms of anxiety (82.8%) or depression (81.1%) experienced ASEBA improvements of clinical importance. There were also significant changes in EEG, breathing rate, and HRV. For the 16 individuals copresenting with hypertension, systolic and diastolic blood pressure were significantly reduced. **Conclusion.** We present evidence that NFB+HRV training may provide an effective, nonpharmaceutical intervention to reduce symptoms of anxiety and depression in children and adults. Additionally, NFB+HRV training may improve EEG, blood pressure, resting breathing rate, and HRV.

Keywords: anxiety; depression; neurofeedback; heart rate variability; EEG

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Introduction

Generalized anxiety disorder (GAD) and major depressive disorder (MDD) are affective psychological disorders that affect millions of Americans. These diseases cause considerable morbidity and mortality, as well as substantial private and public economic burden (Asselmann & Beesdo-Baum, 2015; Kessler et al., 2007; Richards, 2011). Many people do not gain satisfactory results from pharmaceutical approaches such as anxiolytics or Selective Serotonin Reuptake Inhibitor medications, which furthermore cause substantial side effects (Abejuela & Osser, 2016; Carvalho, Sharma, Brunoni, Vieta, & Fava, 2016; Kirsch et al., 2008). Accordingly, nonpharmaceutical interventions to complement or replace treatment with psychoactive medications are of great importance.

Psychotherapeutic approaches to treat anxiety and depression are effective; however, psychotherapy only partially reduces the disease burden, does not work for everyone, and people often relapse after the conclusion of treatment (Andrews, Issakidis, Sanderson, Corry, & Lapsley, 2004; Cuijpers, 2015; Hollon et al., 2002; Hunot, Churchill, Teixeira, & Silva de Lima, 2007; Schneider, Arch, & Wolitzky-Taylor, 2015; Vittengl, Clark, Dunn, & Jarrett, 2007). While these therapies are effective in strictly controlled research settings, there is gathering evidence that such techniques are considerably less effective in "real-world" practice (see Goldfried et al., 2014). For example, Gibbons, Wiltsey Stirman, DeRubeis, Newman, and Beck (2013) reported that depressed individuals treated with cognitive therapy in a randomized controlled trial environment experienced a three-fold greater reduction in depressive symptoms, compared with similar people treated by the same therapists in a clinical setting. Such gaps between science and practice in psychotherapy have been variously attributed to differences in clinician training (Royal College of Psychiatrists, 2013), failure to adhere to standardized treatment protocols (Levita, Salas Duhne, Girling, & Waller, 2016), or "therapist drift," wherein clinicians become less effective over time (Waller, 2009). Personality characteristics of the anxious or depressed individuals themselves have been identified as a challenge to the clinical application of evidence-based psychotherapies. Some of these challenging behaviors include resistance to doing homework (Westra, 2011), the presence of comorbid conditions and personality factors, and even the unwillingness to give up beliefs on the utility of worry, in the case of GAD (Szkodny, Newman, & Goldfried, 2014). Therefore, the search for new and better treatment strategies for anxiety and depression is a high priority.

Affective psychological disorders have complex biological origins and are rarely the result of single insults, such as deficiencies in certain neurotransmitters, or focal lesions in specific brain locations. These disorders are instead characterized by abnormal electrical activity within networks of brain connections involving mood and behavior (Menon, 2011). Affective disorders can be influenced by abnormalities in intrinsic networks in the brain, such as the Default Mode Network (Broyd et al., 2009). Treatment protocols to harmonize the activity in such brain networks have the potential to mitigate the duration or severity of anxiety, depression, posttraumatic stress disorder, obsessive-compulsive disorder, or other affective disorders. Accumulating evidence suggests that neurofeedback therapy, which provides the clinician with the ability to modify and optimize aberrant brain wave activity in people with psychiatric conditions, can become a form of treatment in this field (Niv, 2013).

Neurofeedback Training

Neurofeedback is a form of biofeedback that provides live information about brain activity via electroencephalography (EEG) recordings from the scalp. Neurofeedback protocols are based on operant-conditioning paradigms and reward individuals when they increase or decrease the specific EEG component that is being "trained." These EEG components may include: brain waves (e.g., sensorimotor rhythm [SMR] training), ratios of brain waves (e.g., theta/beta ratio training), or connectivity between specific brain regions (e.g., coherence training). Without receiving any direct stimulation, individuals learn to optimize their brain activity to approach the target in the EEG component that is being rewarded. Repeated neurofeedback sessions reinforce or create new brain connections and pathways through the mechanism of neuroplasticity. These alterations correspond to positive changes in the individual's behavior and feelings (Niv, 2013).

Alpha-asymmetry (ALAY) training is one of the most common neurofeedback protocols for treatment of affective disorders (Baehr, Rosenfeld, & Baehr, 2001), and it has been successfully applied to individuals with anxiety and/or depression. Choi et al. (2011) found positive results with the ALAY protocol in their pilot trial of 24 people with MDD. Participants in the active arm of this randomized, placebo-controlled pilot study who received 10 sessions of neurofeedback at F3 and F4 experienced significant improvement in their depression scores. In a small study with treatment of eight people who had an anxiety disorder, application of the ALAY protocol resulted in significant clinical benefits present 6 months after completion of treatment (Kerson, Sherman, & Kozlowski, 2009).

Several other neurofeedback protocols have also been shown to be effective for individuals with anxiety and/or depression. Cheon, Koo, and Choi (2016) found that 8 weeks of neurofeedback therapy (2 or 3 times a week, in which first beta waves at F3 were increased for 30 min followed by 30 min of increasing the alpha/theta ratio at Pz) significantly improved symptoms in people with a DSM-IV diagnosis of MDD. Among their 20 participants with MDD, 15% and 55% had remission of their condition

at 4 weeks and 8 weeks, respectively. In a study of 24 people with multiple sclerosis who had significant depression and fatigue, Choobforoushzadeh, Neshat-Doost, Molavi, and Abedi (2015) provided half of participants with neurofeedback and the other half with "treatment as usual." Their neurofeedback protocol consisted of down-training theta and alpha waves, and up-training first beta and then SMR, at F3. They saw a statistically significant improvement only in the neurofeedback group, and these benefits were still present at 2-month follow-up evaluations. Another group of researchers (Sadjadi & Hashemian., 2014) carried out a sham-controlled study to evaluate the benefits of 20 sessions of neurofeedback therapy in 24 children who had separation anxiety. Using a protocol that consisted of rewarding the alpha/theta ratio at F3, they found that children who received active neurofeedback treatment had less anxiety than the children who received the sham treatment. Walker and Lawson (2013) provided neurofeedback for 183 participants with MDD who were refractory to standard antidepressant medications. After six sessions of training in the right frontal-orbital area, rewarding a reduction of activity at 2–7 Hz and an increase of activity at 15–18 Hz, remission or significant improvements were noted in 84% of participants. At follow-up 1 year after treatment, these improvements remained in effect for nearly all participants. Walker (2009) also reported positive results from a protocol to correct specific abnormalities seen on the quantitative electroencephalogram (qEEG) for 19 individuals who were diagnosed with posttraumatic stress disorder. A neurofeedback protocol based on qEEG was also shown to be successful for a group of 14 participants who had general anxiety disorder (Dreis et al., 2015) and in a group of 20 children who had anxiety due to the fact that they were removed from their homes by Child Protective Services (Huang-Storms, Bodenhamer-Davis, Davis, & Dunn, 2006).

Heart Rate Variability Training

People with stress, anxiety, and depression have increased morbidity and mortality rates. This is likely due, in part, to increased activation of the sympathetic nervous system, which leads to increased incidence of cardiovascular disease. Increased cortisol released from the adrenal gland modulates the intrinsic neuronal pathways of the heart, which results in a higher pulse rate and reduced cardiac heart rate variability (HRV; Shaffer, McCraty, & Zerr, 2014). Activation of the sympathetic nervous system with stress and anxiety increases heart rate and is associated with low HRV. As would be expected, individuals with anxiety and difficulty in self-regulation of their emotions have high levels of sympathetic nervous system activity and low HRV (Williams et al., 2015). Recent studies have shown that vagal activation of the parasympathetic nervous system can slow down heart rate and enhance HRV. As such, a biofeedback modality that boosts the parasympathetic nervous system (e.g., deep slow abdominal breathing) can balance out the effects of sympathetic activation and increase HRV. In one study of 63 participants with coronary artery disease, training through deep abdominal breathing resulted in significant increase in HRV (Del Pozo, Gevirtz, Scher, & Guarneri, 2004). HRV biofeedback has also been utilized as an intervention to treat disorders—such as depression, anxiety, PTSD, and hypertension—with quite promising, albeit preliminary, results (reviewed in Gevirtz, 2013).

Combined Neurofeedback + Heart Rate Variability Training

The combination of NFB protocols with HRV training (NFB+HRV) may help individuals optimize mood, cognitive performance, and the balance between sympathetic and parasympathetic functions. A small pilot study (Reid-Chung, Thompson, & Thompson, 2015), found NFB+HRV training to be effective in reducing symptoms in participants with Post-Concussive Syndrome. To our knowledge, no research study has examined the potential benefits of such combined therapy in individuals with anxiety and depression.

To determine whether the combination of neurofeedback training and heart rate variability training is a viable treatment strategy for individuals with symptoms of anxiety and depression, we administered NFB+HRV to clients with these symptoms. A parallel group of clients who did not meet the threshold for either anxiety or depression, but who had symptoms of other conditions (such as migraine or attention-deficit/hyperactivity disorder), also received this combined treatment. Before and after the NFB+HRV treatment protocol, EEG, blood pressure, breathing pattern, and psychological symptom measurements were taken for each client, and these pretreatment and posttreatment measurements were compared.

Methods

Measurement of Psychological Symptoms

Achenbach System of Empirically Based Assessment. The Achenbach System of Empirically Based Assessment (ASEBA) symptom checklist was administered to measure the presence and severity of symptoms of anxiety and depression by questionnaire (Achenbach & Rescorla, 2001). Adult clients completed the Adult Self-Report (ASR; Achenbach & Rescorla, 2003), and parents completed the Child Behavioral Checklist (CBCL; Achenbach & Rescorla, 2001) for children under age 18. The ASEBA provides *T* scores for each behavioral scale. These *T* scores are quantitative measures of the number and degree of symptoms reported, based on a gender- and age-normative database.

The ASEBA scale defines three possible conditions—Normal, Borderline, and Clinical—based on the degree of need for the individual to seek professional help (Figure 1).

Normal. Individuals have no need to seek professional help for anxiety or depression.

Borderline. Individuals have borderline need to seek professional help for anxiety or depression.

Clinical. Individuals need to seek professional help for anxiety or depression.

Deviant. Individuals with Borderline and Clinical designation can be combined as one Deviant group, to contrast them with individuals in the Normal group, who are deemed not to have any significant anxiety or depression symptoms. The ASEBA suggests using *T* scores < 65 to designate the Normal range vs. *T* scores ≥ 65 to designate the Deviant range (Achenbach & Rescorla, 2001).

Because the term Deviant *may cause offense when applied to individuals with psychological conditions, we instead refer to this group as* Divergent *herein.*

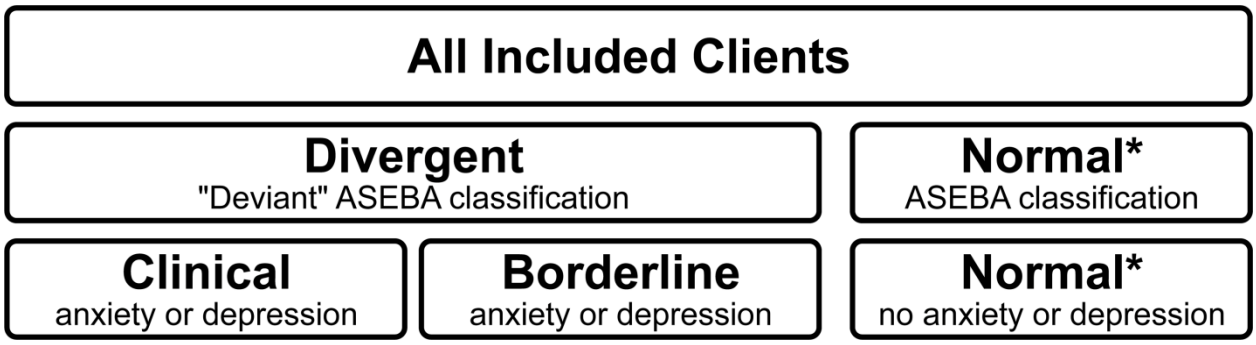

Figure 1. Diagram describing the ASEBA anxiety and depression classification system as it was utilized in this study. *These clients were Normal with regard to symptoms of anxiety and depression. However, all individuals in this study were clients of Neurocore, and likely experienced other symptoms such as migraine or ADHD.

Clients

The individuals in this study were child and adult clients of the Neurocore Brain Performance Center. Neurocore provides a combination of biofeedback and neurofeedback for individuals with a variety of symptoms, such as anxiety, depression, attention-deficit/hyperactivity disorder (ADHD), autism, memory concerns, migraines, sleep disturbances, or stress. The research protocol for this study was approved by the New England Independent Review Board, which provided an IRB Privacy Board Waiver of Authorization to conduct a retrospective analysis of findings from clients who started a 30-session NFB+HRV treatment program on or after October 15, 2015, and completed the program by July 15, 2016. All Personal Health Information Identifiers were removed from the dataset, which initially included a total of 378 clients. After exclusion criteria were applied, 334 clients remained in the current analysis. These criteria excluded eight individuals due to potential conflict of interest (employee or family member), three who were 60 years of age or older (due to age norms of the outcome measure), 10 who completed the program in less than 6 weeks or more than 6 months, and 14 extreme outliers who began the program with symptom rating scores higher than the 99th percentile (*T* score > 85) for symptoms of either

anxiety or depression (see Assessment section above on the ASEBA).

This report consists of outcomes measured from clients treated at eight Neurocore centers in the Michigan cities: Bloomfield Hills, Grand Rapids, Grandville, Holland, Kalamazoo, Livonia, Okemos, and Sterling Heights. Of the 334 clients included, there were 123 females and 211 males. Clients were separated into two groups: adults and children. Adults ranged in age from 18 to 59, with an average age of 37.7 years (*SD* = 11.8). Children ranged in age from 6 to 17, with an average age of 10.5 years (*SD* = 2.9). Table 1 depicts the demographic distribution of the 183 clients with ASEBA *T* scores in the Divergent range for symptoms of anxiety, depression, or both at baseline (labeled Divergent) and 151 clients who did not meet the criteria for these conditions (labeled Normal).

Table 1

Baseline Demographics of Clients with Divergent ASEBA T scores for Anxiety, Depression, Both, or Neither at Baseline: Gender and Age

		Anxiety Only				Depression Only			
		Adults		Children		Adults		Children	
		n	*M (SD)*	*n*	*M (SD)*	*n*	*M (SD)*	*n*	*M (SD)*
Age	Female	5	29.8 (7)	6	10.8 (2)	9	37.9 (13)	15	11.9 (3)
	Male	7	38.4 (12)	17	9.9 (1)	8	28.0 (9)	35	11.8 (3)
	Total	12	34.8 (11)	23	10.2 (3)	17	33.2 (12)	50	11.8 (3)

		Anxiety and Depression				Normal			
		Adults		Children		Adults		Children	
		n	*M (SD)*	*n*	*M (SD)*	*n*	*M (SD)*	*n*	*M (SD)*
Age	Female	13	37.9 (11)	18	10.9 (3.7)	30	39.5 (11.4)	27	9.7 (3.1)
	Male	6	30.8 (11)	44	10.2 (2.6)	25	42.4 (11.9)	69	10.1 (2.8)
	Total	19	35.6 (11)	62	10.4 (3)	55	40.8 (11.6)	96	10.0 (2.9)

Heart Rate Variability and Blood Pressure

HRV was measured using a photoplethysmography sensor (Thought Technology Ltd., Montreal, Canada) attached to the client's index finger. Data were collected for 3 min using a sampling rate of 128 Hz with a ProComp2 or a ProComp5 amplifier, and BioGraph 5.1 software (Thought Technology Ltd., Montreal, Canada). A ProComp5 was used for all initial and final assessments; either a ProComp2 or a ProComp5 was used for individual sessions. Interbeat intervals were calculated from the raw signal using a low cutoff of 30 ms and a high cutoff of 2,000 ms, and a power spectrum was formed from these data using fast Fourier transform. HRV measures collected include the density (in ms^2/Hz) of the following frequency domains: very low frequency (VLF; 0.016–0.040 Hz), low frequency (LF; 0.04–0.15 Hz) and high frequency (HF; 0.15–0.40 Hz). Data were expressed as percentages of each frequency band, with respect to the overall range of frequencies collected (0.016–0.500 Hz). High-frequency HRV is largely driven by activity of the Parasympathetic Nervous System (The Task Force Report, 1996). Activation of the low-frequency component of HRV is much more complex, with influences from both the Parasympathetic and the Sympathetic Nervous Systems (Billman, 2013). The VLF component is influenced by multiple homeostatic systems (including body temperature and circadian rhythms), and also by the heart itself (Shaffer et al., 2014). Respiration rate was measured by placing a strain-gauge belt (Thought Technology, Montreal, Canada) around the waist at the level of the umbilicus. Breaths per minute were calculated over the same 3-min intervals as HRV.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were collected using a standard digital blood pressure monitor (A&D Instruments, Abingdon, UK). Clients with either a systolic reading of at least 140 mmHg or a diastolic reading of at least 90 mmHg at baseline were defined as presenting with hypertension (*n* = 16 within the Divergent group).

Electroencephalography

Electroencephalographic (EEG) assessment data were collected at Cz (a region within the sensorimotor cortex), positioned using the International 10/20 electrode system. Gold cup electrodes were placed in a monopolar montage, with the ground electrode on the right ear and the reference electrode on the left ear. The scalp site was cleaned with NuPrep skin prep gel, and the electrodes were adhered using Ten20 conductive paste (both from Weaver and Company, Aurora, CO). Data were collected for 90 s with a ProComp2 or a ProComp5 device, and BioGraph 5.1 software (Thought Technology Ltd., Montreal, Canada) using a sampling rate of 256 Hz after ensuring skin impedance levels were below 10 kΩ. A ProComp5 device was used for all initial and final assessments, and either a ProComp2 or a ProComp5 device was used for individual sessions. Raw data were run through a Butterworth bandpass filter and average peak-to-peak amplitudes (in μV) were calculated for the following frequency bands: theta (4–8 Hz), sensorimotor rhythm (SMR; 13–15 Hz), low beta (16–20 Hz) and high beta (23–35 Hz). Two ratios were computed from these data: theta/beta ratio (theta/low beta) and high beta/SMR. These ratios were used to guide NFB training, as described below.

Therapeutic Intervention

Biofeedback and Neurofeedback. Clients included in the present report underwent 30 sessions of both neurofeedback and HRV training within a time period of 6 and 24 weeks. NFB+HRV training sessions were conducted by trained EEG technicians, under the supervision of licensed Masters of Social Work. Each feedback session began with 3 min of paced, slow breathing, with a goal of six to eight breaths per minute (0.10–0.13 Hz), and HRV training. Breathing depth and rate were visualized on a 23- or 24-inch monitor along with fluctuations in heart rate interbeat interval, both fitted to a sinusoidal shape moving with time across the screen. Clients were coached in the use of diaphragmatic breathing and instructed to make the two sinusoidal curves overlap to achieve "coherence" between these measures, which up-trained the %LF (low-frequency) band of HRV. Measurements collected at each session included average breaths per minute and %LF band, used as a surrogate measure of HRV.

Following 3 min of HRV training, each client received a personalized NFB session based on their baseline theta/beta ratio and high beta/SMR ratio values at Cz. The ProComp2 device and BioGraph 5.1 software were used to assess theta/beta ratio and high beta/SMR ratio in real time (frequencies and signal filtering detailed above), with feedback provided in the form of threshold-dependent presentation of a movie for a duration of 40 min. Reward thresholds were set and enacted automatically in the form of the movie pausing using the following rules and feedback paradigms. Compared to the value measured at initial assessment, theta/beta ratio values were driven in the direction of the historical group average value of Neurocore's database of clients who had completed 30 sessions previously (theta/beta ratio = 2.35). Therefore, clients with a baseline theta/beta ratio above 2.35 were trained to lower this ratio, and those with a theta/beta ratio below 2.35 were trained to raise it. High beta/SMR ratio values were consistently inhibited.

Two feedback mechanisms were provided simultaneously during each training session. One was a biofeedback mechanism for abdominal breathing rates, and the other was EEG feedback for brainwave activity. For respiratory biofeedback, if breathing had greater than 35% variation between breaths, then a negative stimulus of the video screen shrinking was provided. When clients were able to maintain variation of breathing under 35%, the screen would remain in full screen mode, acting as a positive reinforcer. All clients were encouraged to maintain an average abdominal breathing rate between six to eight breaths a minute with less than 35% variation between breaths. When clients exceeded 8.75 breaths per minute, or their breathing pace fluctuations exceeded lagged thresholding criteria, the movie screen would shrink, using a transition time of 10 s.

For EEG feedback, all treatment screens included positive feedback of the DVD playing for lowering high beta/SMR ratio (23–35/13–15) and maintaining theta/beta ratio (4–8/16–20) within therapeutic ranges (< 3.0 and > 1.7). A digital counter system within the BioGraph Infiniti software was employed to determine the percentage of reinforcement that was provided during training. An 80% (±15%) success rate was used as a benchmark for training

staff when choosing one of three available screens to begin the session (easy, average, difficult). Throughout the session, the software was configured to adjust between the three available screens seamlessly without notable interruption of DVD stimulus to maintain a reward rate of 80% (±15%). This ability to adjust treatment intensity screens while maintaining an 80% success rate was used to provide an achievable challenge for clients without overwhelming them.

Psychoeducation. All Neurocore clients received psychoeducation on a range of topics including sleep hygiene, diet, and exercise, in addition to learning coping skills like deep breathing. Roughly half of all clients in the present study (*n* = 176 / 334 all clients; *n* = 96 / 183 Divergent clients) met with a staff social worker for approximately 20 minutes before or after every session to review these topics. The remaining clients received similar educational input, but in a less formal manner. Because nonsignificant statistical regression models containing psychoeducation as a potentially confounding variable were not useful in predicting improvement in *T* score, this variable was not included in the analyses that follow. The models are explained in the section below.

Statistical Analysis

All parametric statistical analyses were performed using SAS® Enterprise Guide, Version 7.1. Calculations for confidence intervals for Cohen's effect sizes were performed using R (a language and environment for statistical computing (R Core Team, 2016). Within R, the "irr" package was used to analyze the Stuart-Maxwell test of marginal homogeneity (Gamer, Lemon, Fellows, & Singh, 2012). Other nonparametric statistical analyses, confidence intervals, and effect sizes were computed by hand. Statistical tables and formulae, from *Applied Nonparametric Statistics (2nd ed.)*, were used to calculate test statistics, *p*-values, and confidence intervals (Daniel, 1990) for blood pressure analyses. A separate formula $r = \frac{Z}{\sqrt{N}}$ was used to compute the nonparametric effect sizes (Pallant, 2007). All *p*-values were assessed using an experiment-wise error rate of α = 0.05 adjusted for multiple testing and comparisons with Bonferroni correction. With 19 comparisons, the Bonferroni corrected significance level was α_B = 0. All tests performed were two-sided. Due to the fact that some clients in this retrospective study could be biologically related, the statistical assumption of independence may be questionable.

Potentially confounding variables, such as age, gender, center (i.e., the specific Neurocore branch attended by the client), presence or absence of formal psychoeducation, and test type (CBCL or ASR) were first investigated using multiple linear regression. For both anxiety and depression, the models containing age, gender, center, formal psychoeducation, and test type (CBCL or ASR) were not useful in predicting the magnitude of improvement in *T* scores (*p* = .129, .123, respectively).

Mean *T* score changes from pretreatment to posttreatment were assessed with paired t-tests. The normality assumption was satisfied given the large sample size; however, it was confirmed by assessing box plots and histograms.

The Minimal Clinically Important Difference (MCID) for the change in ASEBA scores is defined for two age ranges within each gender for each type of test; CBCL or ASR. The MCID is defined as the Standard Error of Measure (*SE Meas*). The *SE Meas* is calculated using statistics from ASEBA's age- and gender-normed population. The standard deviation is multiplied by the square root of the test retest reliability subtracted from one, $SE\ Meas = SD\left(\sqrt{1 - Reliability}\right)$ (Achenbach & Rescorla, 2003). Given that these values for MCIDs for anxiety and depression range from 1.65 to 2.55 (see Appendix, Supplemental Table 1), we conservatively defined an improvement of at least three points as the minimal clinically important difference.

Additionally, crosstabulation tables were produced to show the changes in *T* scores for the three exhaustive categories per the ASEBA manual. The Stuart-Maxwell test for dependent proportions was used to test the statistical significance of the marginal homogeneity, or that row totals are equal to column totals, for all three classification levels from pretreatment to posttreatment (Everitt, 1992; Maxwell, 1970; Stuart, 1955). Assumptions for Stuart-Maxwell's were checked, with K x K mutually exclusive groups with pretreatment and posttreatment data and no categories with perfect agreement.

Due to the small number of clients in the anxiety and/or depression symptom Divergent groups who had hypertension at baseline (16/183) and the skewness of histogram of the differences from pre- to posttreatment, the nonparametric Wilcoxon Signed Rank test for paired differences was used to assess changes in blood pressure.

Results

Anxiety and Depression Levels Pretreatment and Posttreatment

Assessment of all clients was performed with the ASEBA symptom checklist, both before and after the NFB+HRV training protocol. At baseline, 183 of the 334 clients had abnormal ASEBA scores for anxiety, depression, or both. These clients make up the Divergent group (Figure 1). ASEBA scores for the remaining 151 clients were within the Normal range for anxiety and depression symptoms (the Normal group). Among the Divergent group, 44% (n = 81) presented with comorbid symptoms of both anxiety and depression. Of the 116 clients with Divergent ASEBA levels of anxiety symptoms (with or without comorbid depression symptoms), 35 exhibited symptoms of anxiety alone. Of the 148 clients with Divergent ASEBA levels of depression symptoms (with or without comorbid anxiety symptoms), 67 exhibited symptoms of depression alone.

Average change in *T* score was investigated from pretreatment to posttreatment for clients with symptoms of anxiety only, depression only, or comorbid anxiety and depression at baseline. Paired t-tests were used to assess these changes. Those with pretreatment ASEBA *T* scores in the Baseline or Clinical range for symptoms of anxiety only (without comorbid depression) experienced a significant decrease (improvement) in *T* score of M = 10.3 points after treatment, SD = 6.3, 95% CI = [8.1, 12.5], $t(34)$ = 9.64, p < .001. Similarly, those with pretreatment *T* scores in the Baseline or Clinical range for symptoms of depression only (without comorbid anxiety) experienced a significant decrease in *T* score of M = 8.8 points after treatment, SD = 6.2, 95% CI = [7.3, 10.3], $t(66)$ = 11.58, p < .001. Those with pretreatment *T* scores in the Baseline or Clinical range for symptoms of both anxiety and depression experienced a significant decrease in anxiety *T* score of M = 11.5 points, SD = 8.4, 95% CI = [9.6, 13.4], $t(80)$ = 12.26, p < .001; and a significant decrease in depression *T* score of M = 10.4 points, SD = 7.9, 95% CI = [8.6, 12.1], $t(80)$ = 11.83, p < .001.

With overlapping confidence intervals, there is not a statistically significant difference in the magnitude of change in *T* score among clients with symptoms of anxiety only, depression only, or comorbid anxiety and depression at baseline. For this reason, further analyses address clients with symptoms of anxiety as well as clients with symptoms of depression, regardless of comorbidity. To address any effects of the client's age, gender, test type, formal psychoeducation condition, and Neurocore center on outcomes, a regression model was run containing all of these potential confounders (described in the Methods section). This model was not significant, with a Global F test p-value of .129 for anxiety and .123 for depression. Separating the clients into subgroups based on these variables was, therefore, unnecessary. Additionally, client age and magnitude of improvement in *T* score were not significantly correlated for anxiety (r = -0.15, p = .116) or depression (r = -0.12, p = .135).

Table 2 shows the results of paired t-tests used to assess the average change in ASEBA *T* score for those with Borderline or Clinical baseline symptoms of anxiety and depression. Those with pretreatment anxiety symptoms had a mean decrease in *T* score of 11.1 points, SD = 7.8, 95% CI = [9.7, 12.6], $t(115)$ = 15.28, p < .001; and those with pretreatment depression symptoms had a mean decrease in *T* score of 9.7 points, SD = 7.2, 95% CI = [8.5, 10.8], $t(147)$ = 16.32, p < .001. The magnitude of these changes represents quite large effect sizes of d_z = 1.42 (95% CI = [1.16, 1.68]) for anxiety and d_z = 1.34 (95% CI = [1.12, 1.57]) for depression. The mean *T* scores before and after treatment for the two groups are displayed graphically (Figure 2). Table 2 also includes the percent of those who showed improvements of at least the MCID of three points. For anxiety, 82.8% improved by at least the MCID; for depression, 81.1% improved by at least the MCID.

Table 2

ASEBA: Mean Changes for Clients in the Divergent Group at Baseline, Pretreatment to Posttreatment

		M_d (SD_d) [95 % CI]					Improved ≥ MCID[a]
	n	Pre	Post	Decrease	d_z	*p*	% (*n*)
Anxiety	116	71.5 (5.7)	60.4 (7.9)	11.1 (7.8) [9.7, 12.6]	1.42	< .001	82.8% (96)
Depression	148	70.9 (4.8)	61.2 (8.0)	9.7 (7.2) [8.5, 10.8]	1.34	< .001	81.1% (120)

Note. M_d = Mean of differences; SD_d = Standard deviation of differences; d_z = Cohen's *d* for effect size of paired differences
[a]An improvement in ASEBA *T* score of at least the MCID of three.

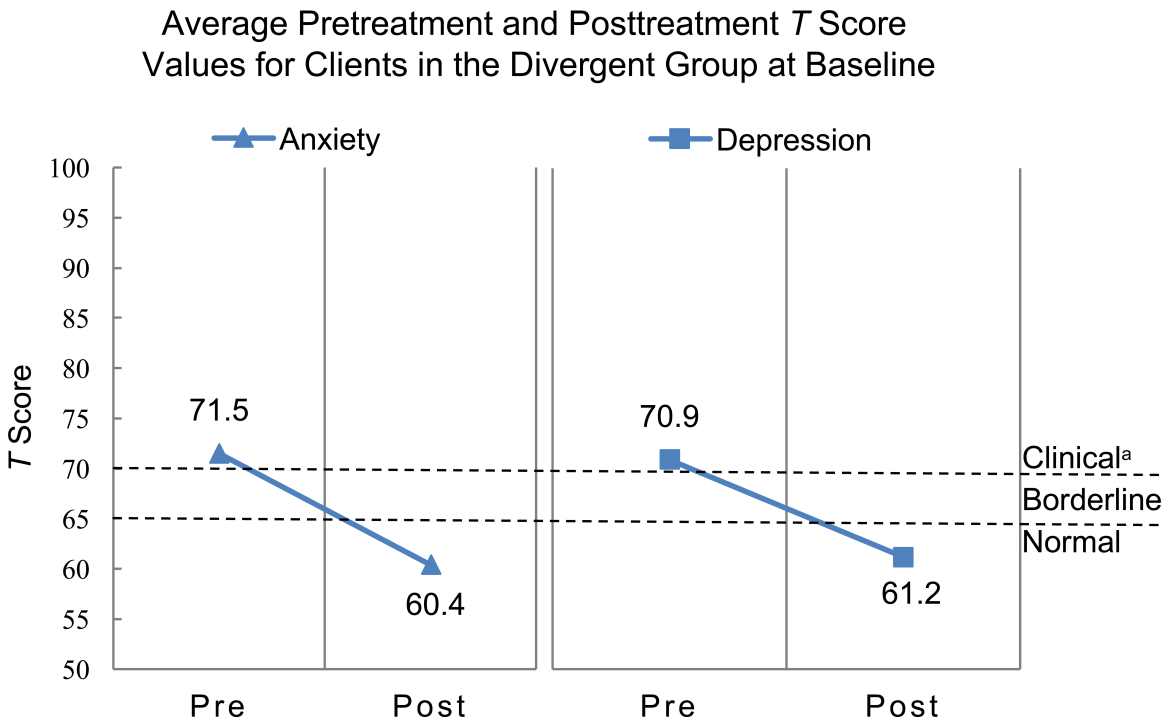

Figure 2. For clients in the Divergent Group at baseline: average ASEBA *T* scores at pre-treatment and post-treatment are shown for anxiety and depression. For both anxiety and depression, these average values are in the Normal range after treatment, and the mean change is statistically significant. [a]Clinical Range ≥ 70, Borderline Range 65–69, Normal Range < 65, ASEBA's defined minimum possible *T* score = 50.

To assess whether the observed changes in ASEBA score were likely to be due to placebo, a subset of the most severe clients (those who presented at baseline with scores in the upper quartile of Divergent scores) were evaluated (*T* score ≥ 76). Average *T* scores were reduced by 15.11 points for those with anxiety symptoms, *n* = 28, *SD* = 9.6, 95% CI = [11.40, 18.81], *t(27)* = 8.37, *p* < .001; and 13.29 points for those with depression symptoms, *n* = 24, *SD* = 10.4, 95% CI = [9.89, 17.69], *t(23)* = 6.25, *p* < .001, after treatment. For this anxiety symptom group, 89.3% of the upper quartile (25 out of 28) improved by at least the MCID of three, and 57.1% completely eliminated symptoms. The depression symptom group had similar results, with 79.2% of the upper quartile (19 out of 24) improving by at least the MCID of three, and 45.8% completely eliminating symptoms.

For both anxiety and depression, the Stuart-Maxwell test for marginal homogeneity was used to assess whether the proportion of clients with Clinical:Borderline:Normal ASEBA scores was different pretreatment compared to posttreatment. For each of the two tests run (one for anxiety and one for depression), all clients in the study were included. Each client was grouped according to whether they had Normal, Baseline, or Clinical

ASEBA *T* scores for the psychological disorder before treatment (pretreatment) and after treatment (posttreatment).

The proportion of clients with ASEBA *T* scores in the Clinical:Borderline:Normal range significantly differed from pretreatment to posttreatment for both anxiety ($\chi^2 = 54.8$, $p < .001$) and depression ($\chi^2 = 90.1$, $p < .001$; Table 3). Specifically, the proportion of clients with ASEBA *T* scores in the Clinical and Borderline range decreased from pretreatment to posttreatment, and the proportion of clients with ASEBA *T* scores in the Normal range increased from pretreatment to posttreatment, for both anxiety and depression. For clients with symptoms of anxiety, 60.3% of those with pretreatment Clinical status and 75.5% of those with pretreatment Borderline status experienced a posttreatment improvement in *T* score sufficient to be considered Normal. Similarly, for clients with symptoms of depression, 50.6% of those with pretreatment Clinical status and 88.5% of those with pretreatment Borderline status experienced a posttreatment improvement in *T* score sufficient to be considered Normal. Importantly, the majority of clients with pretreatment Clinical status for anxiety (79.5%) and depression (72.4%) were no longer in the Clinical range after treatment. These statistically significant results from the Stuart-Maxwell test are displayed graphically in Figure 3.

Table 3

Crosstabulation and Stuart-Maxwell Test of Marginal Homogeneity of ASEBA Classifications at Pretreatment by Posttreatment

	Anxiety	Post Row Percent (Frequency)					
		Normal	Borderline	Clinical	Total	χ^2	*p*
Pre	Normal	94.0% (205)	5.1% (11)	0.9% (2)	218		
	Borderline	75.5% (40)	20.8% (11)	3.8% (2)	53		
	Clinical	60.3% (38)	19.1% (12)	20.6% (13)	63		
	Total	283	34	17	334	54.8	< .001

	Depression	Post Row Percent (Frequency)					
		Normal	Borderline	Clinical	Total	χ^2	*p*
Pre	Normal	96.2% (179)	3.8% (7)	0.0% (0)	186		
	Borderline	88.5% (54)	8.2% (5)	3.3% (2)	61		
	Clinical	50.6% (44)	21.8% (19)	27.6% (24)	87		
	Total	277	31	26	334	90.1	< .001

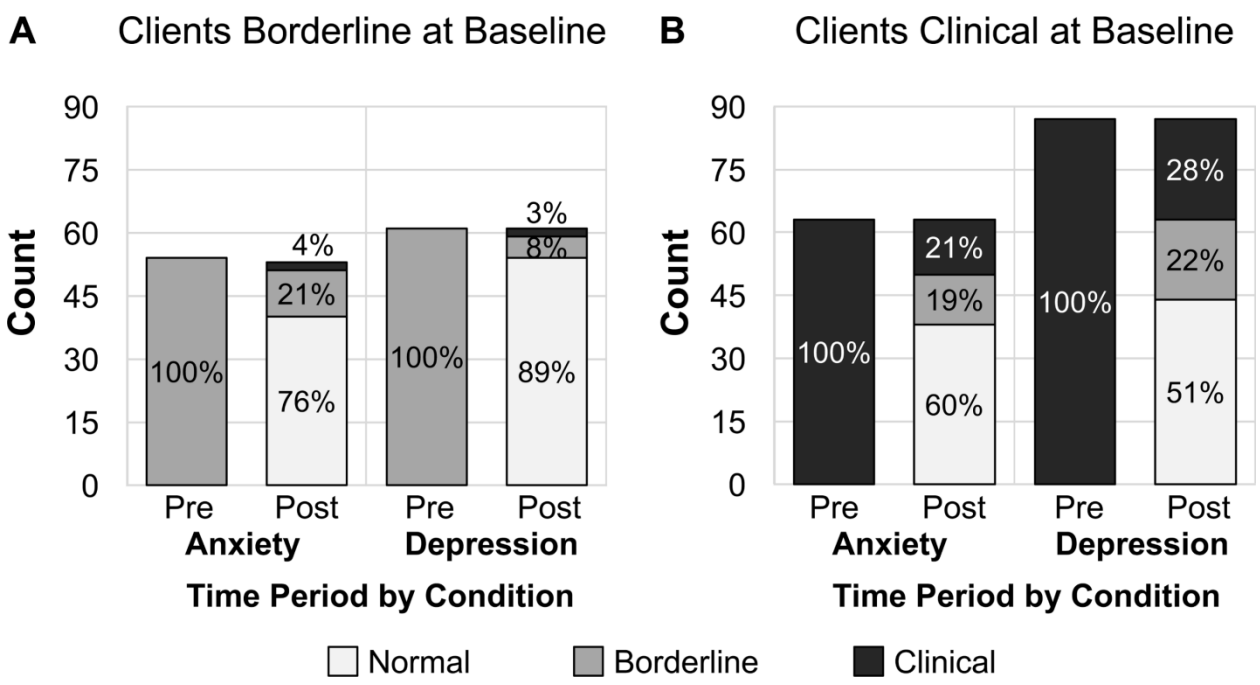

Figure 3. The majority of clients with Divergent ASEBA scores at baseline were in the Normal group after NFB+HRV treatment. These results are statistically significant, based on the Stuart-Maxwell test displayed in Table 3. (**A**) Clients in the pretreatment Borderline group for anxiety and depression are represented by the 100% Pre bars. After treatment (the Post bars), this group of clients was divided into Normal, Borderline, and Clinical groups, with the majority now in the Normal group. (**B**) The same is true for clients in the pretreatment Clinical group for both anxiety and depression.

Heart Rate Variability and Blood Pressure

HRV and Blood Pressure were recorded for a subset of clients (which includes 171 out of the 183 clients in the baseline Divergent group of clients with symptoms of anxiety and/or depression), due to missing data. HRV was evaluated using pretreatment to posttreatment changes in four measures: %VLF (very low-frequency) band of the heart rate interbeat interval power spectrum, %LF band, %HF (high-frequency) band, and respiration rate (breaths per minute). All four measures were significantly different after treatment, with *p*-values less than .001 (Table 4). On average, %VLF decreased by 6.1 (d_z = -0.58), %LF increased by 28.3 (d_z = 1.23), %HF decreased by 19.3 (d_z = -0.96), and respiration rate decreased by 6.4 breaths per minute (d_z = -2.29).

Table 4

Mean Changes in Heart Rate Variability Measures from Pretreatment to Posttreatment for Clients in the Divergent Group at Baseline

n = 171	*M* (*SD*)		M_d(SD_d)	[95 % CI]		
	Pre	Post	Change		d_z	*p*
%VLF	14.4 (8.1)	8.3 (7.2)	-6.1 (10.5)	-[4.5, 7.6]	-0.58	< .001
%LF	34.2 (12.7)	62.6 (21.8)	28.3 (23.1)	[24.8, 31.8]	1.23	< .001
%HF	44.4 (14.1)	25.1 (16.6)	-19.3 (20.1)	-[16.2, 22.3]	-0.96	< .001
BPM	14.0 (2.0)	7.6 (2.3)	-6.4 (2.8)	-[6.0, 6.8]	-2.29	< .001

Note. M_d = Mean of differences; SD_d = Standard deviation of differences; d_z = Cohen's d for effect size of paired differences; VLF = very low-frequency; LF = low-frequency; HF = high-frequency; BPM = breaths per minute.

Changes in blood pressure were assessed for the baseline Divergent group of clients with symptoms of anxiety and/or depression who also presented with hypertension at baseline (those with either a systolic reading of at least 140 mmHg or a diastolic reading of at least 90 mmHg; *n* = 16). These changes were assessed using the Wilcoxon Signed Rank test for matched pairs (Table 5). Significant improvement was found after treatment for both systolic and diastolic blood pressures, with *p*-values less than .001. Systolic blood pressure improved with a median decrease of 14.0 mmHg (*Z* = -3.15, 94.94% CI = [7.5, 35.5], *r* = -0.56). Diastolic blood pressure had similar results, with a median decrease of 11.00 mmHg (*Z* = -3.1, 94.94% CI = [.0, 17.0], *r* = -0.59). Large effect sizes were found after NFB+HRV training by Cohen (1988) criteria (small = 0.1, medium = 0.3, large = 0.5).

Table 5

Median Changes in Blood Pressure from Pretreatment to Posttreatment for Clients in the Divergent Group with Hypertension at Baseline, Based on the Wilcoxon Test

n = 16	*Mdn (IQR)*		Mdn_d (IQR_d)	[94.94 % CI]		
	Pre	Post	Change		d_z	*p*
SBP	142.5 (5.5)	130.5 (25.0)	-14.0 (19.5)	-[7.5, 35.5]	-0.56	< .001
DBP	87.5 (12.0)	74.5 (10.5)	-11.0 (14.5)	-[5.0, 17.0]	-0.59	< .001

Note. SBP = systolic blood pressure; DBP = diastolic blood pressure; *Mdn* = median; *IQR* = Interquartile Range; Mdn_d = Median of differences; IQR_d = Interquartile Range of differences.

EEG

For clients in the Divergent groups at baseline, changes in two ratios of interest (high beta/SMR and theta/beta) from pretreatment to posttreatment EEGs were assessed (Table 6). Baseline Divergent group clients experienced an average decrease in high beta/SMR ratio of 0.13, *SD* = 0.26, 95% CI = [0.09, 0.17], d_z = 0.500, *t(182)* = 6.79, *p* < .001. Because the NFB protocol drove the theta/beta ratio toward Neurocore's historic client group average value of 2.35 (see Methods), clients were split into two groups in order to assess whether the theta/beta ratio moved in the "expected" direction. One group included clients with a baseline theta/beta ratio above 2.35, and one group included those below 2.35. Clients with baseline Divergent scores for depression and/or anxiety symptoms, and who started out with a theta/beta ratio below 2.35, had an average increase of 0.19 after treatment, *SD* = 0.37, 95% CI = [0.08, 0.29], d_z = -0.513, *t(51)* = 3.63, *p* = .001. Clients with baseline Divergent scores in depression and/or anxiety symptoms, and who started out with a theta/beta ratio above 2.35 did not experience a statistically significant change from baseline, *t(131)* = -1.45, *p* = .149.

Table 6

Mean Changes in EEG Ratios for Clients with Divergent Scores at Baseline in Anxiety and/or Depression

		M (*SD*)		M_d(*SD*)	[95 % CI]		
	n	Pre	Post	Change		d_z	*p*
$\frac{HB}{SMR}$	183	1.43 (0.36)	1.30 (0.31)	-0.13 (0.26)	[-0.09, -0.17]	0.500	< .001
$\frac{Theta}{Beta} < 2.35$	52	1.88 (0.31)	2.07 (0.46)	0.19 (0.37)	[0.29, 0.08]	-0.513	< .001
$\frac{Theta}{Beta} > 2.35$	131	3.15 (0.57)	3.22 (0.74)	0.07 (0.53)	[-0.16, 0.02]	0.132	.149

Note. HB/SMR = high beta/sensorimotor rhythm.

Discussion

In the present retrospective study, we found that clients who suffered from symptoms of anxiety and/or depression experienced substantial improvement in symptoms after 30 sessions of NFB+HRV training. The majority of clients with pretreatment symptoms of anxiety (82.8%) or symptoms of depression (81.1%) experienced ASEBA *T* score improvements of clinical importance after treatment (by at least the MCID of three; see Methods). Most importantly, the majority of clients with baseline Divergent scores for anxiety or depression symptoms were in the Normal group after NFB+HRV treatment. Even for the clients for whom anxiety and depression symptoms were the most severe (the upper quartile of pretreatment *T* score), 57.1% of those with symptoms of anxiety and 45.8% of those with symptoms of depression were in the Normal group after treatment.

Neurofeedback can enhance the function of neuronal networks associated with mood and behavior (Simkin, Thatcher, & Lubar, 2014), and lead to alterations in brain structure that are observable via magnetic resonance imaging (MRI; Ghaziri et al., 2013). Ghaziri et al. performed MRI on participants before and after a course of treatment with NFB, which indicated that parts of the frontal lobe and association cortical areas increased in size. Although the majority of prior work in anxiety and depression neurofeedback involves modification of the alpha frequency band, the present study is unique in that we trained two ratios of frequencies that do not involve alpha: high beta/SMR ratio and theta/beta ratio.

Our protocol inhibited the high beta/SMR ratio, and comparison of pre- and postprogram EEG found that clients with symptoms of anxiety and/or depression had an average decrease of 0.13 in high beta/SMR ratio ($p < .001$, $d_z = 0.500$). This was the expected result, based on our specific NFB protocol. Because our protocol inhibited a ratio metric (high beta/SMR) rather than individual frequency bands, we cannot say whether the decrease in this ratio after NFB+HRV treatment was due to an increase in SMR, a decrease in high beta, or both. However, any of these changes would be predicted to improve mood. There is a large body of literature to support the benefits of increasing SMR at Cz (Sterman, 1996), while high beta is a frequency band associated with rumination, obsessional thoughts, and anxiety (Thompson & Thompson, 2006). Lowering high beta has been shown to reduce symptoms of anger (Walker, 2013) and is often used as an inhibit frequency in traditional NFB training paradigms (see Walker [2009] as an example).

Our NFB protocol was also designed to drive the theta/beta ratio toward Neurocore's historic client group average (2.35). For pretreatment Divergent group clients who had a theta/beta ratio below this value at baseline, there was a statistically significant increase in theta/beta ratio ($p < .001$), which was the expected result based on the protocol. For those with a theta/beta ratio greater than the historical group average at baseline, there was no significant change in theta/beta ratio after treatment. Based on our NFB protocol, we would have expected this ratio to go down. Therefore, the theta/beta ratio moved in the expected direction for some clients but not others, and we succeeded only in raising theta/beta. Because our protocol targeted a ratio metric (theta/beta), we cannot say whether this increase was due to an increase in theta, a decrease in beta, or both. Although an elevated theta/beta ratio has long been associated with ADHD (Arns, Conners, & Kraemer, 2013), this may not be the case for anxiety and depression. A low theta/beta ratio measured at O1 over the left occipital has been associated with poor quality of sleep and a feeling of exhaustion (Swingle, 2015). Although this has not yet been formally tested, in our clinical experience we have found that this association may also hold true for low theta/beta ratio measured at Cz (TGR, unpublished observations). If so, raising the theta/beta ratio in this subset of clients may also improve symptoms of anxiety and depression by relieving exhaustion. That being said, Walker and Lawson (2013) have reported improvements in depressive symptoms following an NFB protocol that lowered theta and raised beta (15–18 Hz) at FPO2.

Clients in this study with baseline anxiety or depression also experienced changes in breathing rate and in relative HRV frequency spectrum that were consistent with our NFB+HRV protocol. We trained both breathing rate and HRV to the range of six to eight cycles per minute (0.10–0.13 Hz). This corresponds to a breathing rate of six to eight breaths per minute and HRV in the low-frequency band (see Methods). Indeed, after treatment the average resting breathing rate was 7.6 breaths per minute (which was significantly decreased from the pretreatment value of 14.0), and the %LF band of the heart rate interbeat interval power spectrum was significantly increased. Importantly, there were also significant decreases in both systolic and diastolic blood pressure for pretreatment Divergent group clients who had hypertension at baseline.

The inclusion of HRV training before every NFB session might have contributed to the decreased psychological symptom severity and the other physiological changes observed in this study. HRV training is thought to work by enhancing the parasympathetic influences on the heart, producing significant benefits on cardiac function and HRV, although several theories about specific mechanism currently exist (Reviewed in Shaffer et al., 2014). In the present study, we found a significant increase in the %LF band of the heart rate interbeat interval power spectrum. Power increases within this band have been associated with strengthening the baroreflex system, which mediates reciprocal changes between blood pressure and heart rate (Lehrer, 2013). In support of this, we observed a significant decrease in blood pressure for clients who had elevated blood pressure levels at baseline. %LF range power increases could also be due to a shift in the frequency of Respiratory Sinus Arrhythmia (RSA), which usually corresponds to breathing frequency (Yasuma & Hayano, 2004).

RSA increases blood flow to oxygen-rich lung alveoli by raising heart rate during intake of breath and reduces blood flow to oxygen-poor alveoli by lowering heart rate during exhalation (Lehrer & Gevirtz, 2014; Vaschillo, Lehrer, Rishe, & Konstantinov, 2002). Individuals trained with biofeedback techniques to maximize the amplitude of RSA usually learn to achieve this by breathing at a rate of approximately six breaths per minute (Lehrer, Vaschillo, & Vaschillo, 2000), and intentional paced breathing at this frequency can produce very high-amplitude HRV (Vaschillo et al., 2002). One study in which HRV parameters were measured while participants breathed at specified rates found that total HRV amplitude peaked at four breaths per minute, as did low-frequency HRV amplitude (Song & Lehrer, 2003). This is also within the breathing frequency range utilized by Zen monks for the practice of “tanden breathing,” during which their HRV increases in the low-frequency band, and decreases in the high-frequency band (Lehrer, Sasaki, & Saito, 1999). The NFB+HRV protocol utilized in the current study combined biofeedback to encourage slow, deep breathing (at 6–8 breaths per minute) with HRV biofeedback to up-train the %LF band. Because RSA strength is postulated to represent an “index” of total cardiac vagal tone (Porges, 2007), it may be that the increase in %LF band that we observe is associated with enhanced activity of the parasympathetic nervous system. The current study was not designed to look at absolute changes within the HRV power spectrum, however, so no specific claims for a mechanism can be made.

The effects of HRV training are not thought to be solely on heart function. A recent study showed that healthy individuals who have an optimal high-frequency HRV often possess thicker cortex in the right anterior cingulate cortex (Winkelmann et al., 2016). Combining the NFB and HRV forms of biofeedback, which impact the physiology of both the central and autonomic nervous systems, may be the main reason we have seen such robust clinical benefits in our clients. Based on the results of the current study, as well as others in the field, we propose a model for how NFB and HRV interact to enhance mood and energy (Figure 5).

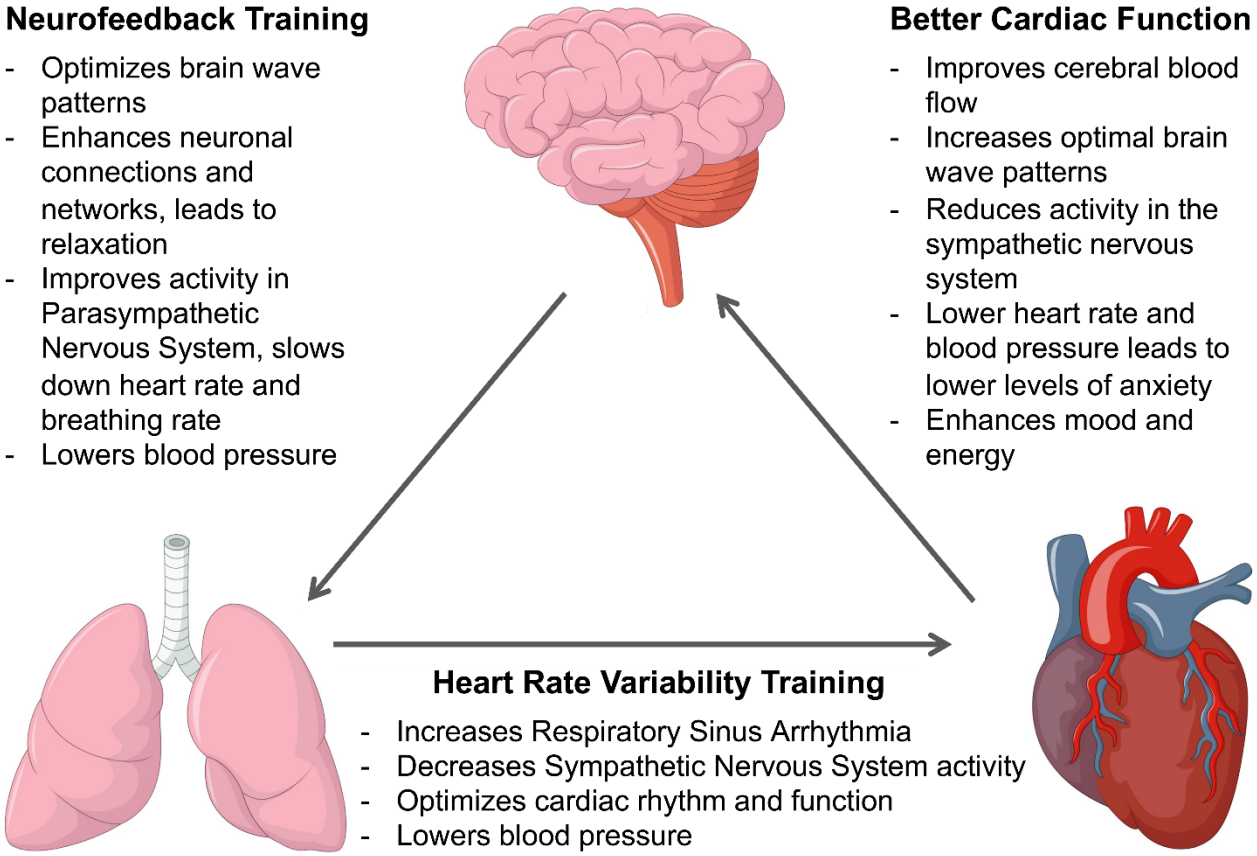

Figure 5. Model describing how concurrent neurofeedback and heart rate variability biofeedback training may interact to improve the function of both the nervous and cardiovascular systems.

Some studies (Khan & Brown, 2015) suggest that individuals with mild to moderate depression are prone to experience clinically significant improvement in symptoms due to placebo effects. Indeed, low symptom severity is among the best predictors of a large placebo effect for many different psychological conditions (Weimer, Colloca, & Enck, 2015). However, in this study, even those with severe symptoms gained clinically meaningful benefits from NFB+HRV. The presence of statistically significant changes in objective physiological parameters, such as EEG, HRV oscillations, and blood pressure, further suggests that improvements in ASEBA score (which are based on clients' subjective impression of their symptoms) might not be due to placebo effect. Finally, the large magnitude of effect sizes for both clients with anxiety and depression symptoms suggests the benefits of this treatment protocol.

A main strength of this study was combining NFB with HRV training for treating a large number of both adults and children (n = 183) with anxiety and/or depression. Because significant changes were found after training for both HRV variables as well as EEG ratios, it is likely that both of these interventions contributed to the significant decrease in symptom presence and severity. Another strength is the fact that data were collected from a geographically diverse cohort (in one of eight different Michigan cities). Interestingly, we found no difference in ASEBA or physiological outcome between clients of different age, gender, test type, or Neurocore center, which may indicate that our NFB+HRV protocol could be effective for clients from many different demographics.

Limitations of this study include its retrospective design and the lack of a sham control group. Further, a limited EEG, and not a full-cap 19-electrode quantitative EEG, was utilized to analyze brain wave activity at baseline and follow-up visits. Rather than training individual rhythms, our NFB protocol trained two ratio metrics; this means that for a given change in the trained ratio, we did not distinguish whether this was accomplished by a change in the numerator rhythm, an opposing change in the denominator rhythm, or both.

Measurement of psychological symptom presence and severity in this study was based on the ASEBA, which does not finely distinguish between subtypes of anxiety or depression (e.g., posttraumatic stress disorder or obsessive compulsive disorder). Any differential effects of the NFB+HRV protocol on various subtypes of anxiety and depression could therefore have been missed. For the HRV portion of the study, our study design enabled us to consider only relative changes within the HRV power spectrum (rather than absolute changes). Clients were also not reexamined after the conclusion of the program to determine whether the post-NFB+HRV changes were long-lasting. Finally, due to our study design, we were unable to distinguish between the potential benefits of NFB+HRV treatment versus either NFB or HRV treatment alone. Although some factors, such as our large sample size, robust effect size, use of standard diagnostic DSMV criteria and ASEBA scores, and presence of physiological biomarkers mitigate the negative impact of these limitations, a prospective, blinded study with appropriate sham control group, more stringent inclusion criteria, and long-term follow-up is needed to determine whether NFB+HRV can indeed produce robust and long-lasting results.

Conclusion

This report is the first to show that NFB+HRV training may have a robust effect on improving symptoms of anxiety and depression. NFB+HRV training may also improve physiological functions within the autonomic nervous system and cardiovascular system, including blood pressure and heart rate variability. Further prospective placebo-controlled longitudinal clinical trials are warranted.

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Appendix

Supplemental Table 1
ASEBA-Defined Minimal Clinically Important Difference

		Anxiety			Depression		
	Age	*SD*	Reliability	MCID	*SD*	Reliability	MCID
Boys	6–11	5.5	0.80	2.46	5.6	0.84	2.24
	12–18	5.7	0.80	2.55	5.8	0.84	2.32
Girls	6–11	5.4	0.80	2.41	5.4	0.84	2.16
	12–18	5.7	0.80	2.55	5.8	0.84	2.32
Men	18–35	5.3	0.86	1.98	5.9	0.86	2.21
	36–59	4.4	0.86	1.65	5.4	0.86	2.02
Women	18–35	5.4	0.86	2.02	5.6	0.86	2.10
	36–59	5.0	0.86	1.87	5.8	0.86	2.17

Note. Standard deviation (*SD*) and Reliability statistics are from ASEBA's age- and gender-normed population (Achenbach & Rescorla, 2001, 2003). MCID = Minimal Clinically Important Difference = $SD\left(\sqrt{1 - Reliability}\right)$.

NeuroRegulation

Breakfast Choices Influence Brainwave Activity: Single Case Study of a 12-year-old Female

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Abstract

Research into the benefits of children eating breakfast has previously focused on educational and cognitive performance as well as behavior. Few nutritional investigations have utilized brain imaging technology in order to examine how breakfast influences brain function. This single case study used quantitative electroencephalography (qEEG) in order to assess how three different breakfast choices affected a 12-year-old female's brainwave activity. The three different breakfast conditions included no breakfast, a high-sugar/high-carbohydrate breakfast, and a nutritionally balanced breakfast. The findings indicated that skipping breakfast significantly increased high beta activity associated with anxiety and focus issues. Eating a high-sugar/high-carbohydrate breakfast was also associated with increased high beta activity, but less significant than the no-breakfast option. Most importantly, eating a nutritionally balanced breakfast was found to normalize the qEEG. The variation in high beta activity in the different breakfast options suggested that eating a nutritionally balanced breakfast may reduce anxiety and increase focus compared to skipping breakfast. These results may help explain why previous research has found cognitive, academic, and behavioral improvements when children consume breakfast. Furthermore, the qEEG should be considered in future nutritional studies as a measurement of brain function.

Keywords: breakfast; nutrition; qEEG; children; performance; behavior

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Introduction

Breakfast is commonly considered the most important meal of the day. Previous research has emphasized the importance of a healthy and balanced breakfast. O'Neil et al. (2014) proposed the definition of breakfast as "the first meal of the day that breaks the fast after the longest period of sleep and is consumed within two to three hours of waking" (p. S9). They suggested that a quality breakfast should be composed from at least three food groups like lean proteins, fruits/vegetables, nonfat or low-fat dairy, and fiber-rich grains. In addition, O'Neil et al. (2014) advised that breakfast should consist of 15–25% of recommended total daily calories depending on their metabolic output.

Such guidelines have been widely disseminated, yet breakfast is commonly omitted by people of all ages. Deshmukh-Taskar et al. (2010) and Corder et al. (2011) found that approximately 20–30% of school-age children and adolescents skip breakfast in developed countries. Furthermore, it has been shown that children and adolescents who do eat breakfast often choose foods that are high in sugar

and carbohydrates. A study by Corcoran, Elbel, and Schwartz (2016) evaluated the federally subsidized school breakfast program for disadvantaged children in New York City and found no evidence of gains in academic performance. The study reported low turnout of children coming in early to eat a hot nutritious breakfast in the cafeteria. Because of this, they instituted an in-the-classroom breakfast that contained "cold prepacked items such as cereal, fresh fruit, or bagels" (p. 5). The academic performance gains that Corcoran et al. (2016) were expecting could have been nullified due to the high-sugar and high-carbohydrate nature of the in-classroom meals.

Breakfast has been previously recognized to improve educational outcomes (Littlecott, Moore, Moore, Lyons, & Murphy, 2015) and behavior (Ahadi et al., 2016). Adolphus, Lawton, and Dye (2013) conducted a systematic review of studies involving children and adolescents. They assessed 19 studies on the effects of breakfast on behavior and 21 studies on the effects of breakfast on academic performance. Overall, the evidence from these studies suggested that breakfast positively influences on-task behavior in classrooms, particularly in children under 13 years of age. In addition, Adolphus et al. (2013) found a positive association between the quality of school grades or achievement test scores and habitual breakfast frequency. This result was notably seen in children of deprived or low socioeconomic backgrounds and undernourished children. The conclusion of the review stated that the beneficial outcomes of breakfast were clearer on academic performance in comparison to behavior (Adolphus et al., 2013).

Although cognitive performance is related to academic performance, it is an area under separate investigation. Evidence indicates that consuming breakfast had a positive relationship to cognitive performance in schoolchildren (Hoyland, Dye, & Lawton, 2009; Wesnes, Pincock, & Scholey, 2012). In a study conducted on kindergarten children, those who consumed breakfast regularly had significantly higher full-scale, performance, and verbal scores on Intelligence Quotient (IQ) tests compared to children who consumed breakfast infrequently (Liu, Hwang, Dickerman, & Compher, 2013). Adolphus, Lawton, Champ, and Dye (2016) conducted a systematic review of studies assessing the impact breakfast had on the cognitive performance of children and adolescents. Their review found that breakfast consumption had a temporary beneficial increase in cognitive function within four hours of the meal. Their findings indicated that breakfast affected specific cognitive domains, specifically in tasks that require executive function, memory, and attention. Specifically, Cooper, Bandelow, and Nevill (2011) found that breakfast consumption improved accuracy on Stroop tests and responses on visual search tests, as well as improved response times on the Sternberg paradigm. The data from the review by Adolphus et al. (2016) also indicated that the beneficial effects on cognition were more apparent in undernourished children when breakfast was consumed as opposed to those who fasted. In the review, only a few studies were found to have compared the impact of breakfast composition. Brindal et al. (2012) compared lower glycemic breakfasts with higher glycemic breakfast and found some evidence that cognitive performance was enhanced when blood glucose concentrations returned to baseline. Similarly, Taki et al. (2010) found that the difference in the glycemic index of breakfasts modifies brain gray and white matter volumes, as well as cognitive function in healthy children. However, because of the paucity of studies that examine the outcomes of breakfast composition, firm conclusions cannot be drawn.

Prior studies on breakfast consumption discussed measuring changes in performance or behavior. Another area of investigation is changes in brain metabolism, structure, and function. Sizonenko et al. (2013) provided a comprehensive review of brain imaging techniques that could have utility in nutritional intervention studies. They evaluated multimodal magnetic resonance imaging (MRI), as well as electroencephalography (EEG), magnetoencephalography (MEG), near-IR spectroscopy (NIRS), positron emission tomography (PET), and single-photon emission computerized tomography (SPECT). Their review revealed that the number of nutritional studies using these techniques outside of clinical settings were limited and that this was likely due to the high cost of the technology, the imaging methodology not being sensitive enough to detect changes, and the lack of guidelines for standardization and data collection (Sizonenko et al., 2013). Pivik, Tennal, Chapman, and Gu (2012) performed spectral analysis of EEG activity to examine the influence of breakfast on mental arithmetic functions in children. Their findings suggested that brain activity involved in the processing of arithmetic calculations was enhanced when breakfast was consumed (Pivik et al., 2012). Spectral analysis has rarely been used to evaluate nutrition, although the study by Pivik et al. (2012) produced promising results. The quantitative EEG (qEEG) spectral analysis establishes parameters of normalcy for age-matched individuals, and this could

be a valuable investigative tool (Cantor & Chabot, 2009). These benchmarks could be used as references to compare changes under different experimental conditions, for example, the impact of nutritional.

In order to investigate the utility of qEEG when assessing the nutritional intake of children, we sought to design a single case study that would not only further the research of brain function but also investigate how different breakfast choices change measurable electrical output. This study will analyze qEEG data in order to determine how three different breakfast conditions affect brainwave activity in a 12-year-old female. We expect that conditions of no breakfast, high-sugar/high-carbohydrate breakfast, and nutritionally balanced breakfast will produce differential effects on the qEEG as compared to the normative sample. This data would suggest that children's eating habits in the morning have an effect on their performance and behavior due to the electrical state of their brain. In addition, we propose that the qEEG be utilized in future nutritional studies, as it provides an informative measure of change regarding educational and cognitive performance and behavior.

Methods

Subject

The subject of this single case study is a healthy, neurotypical 12-year-old female with no mental or physical health issues. At the time of the study, she was a high-performing 7th grade student at a private college preparatory school for girls. The subject reported herself as a breakfast skipper: she regularly did not eat breakfast before going to school. She also reported experiencing anxiety and difficulty to focus her attention prior to eating lunch. The subject has provided written consent for the publication of this study in accordance with the Declaration of Helsinki.

Procedure

Three sets of EEG/qEEG data were recorded with different breakfast conditions on separate days over a 3-week period. Each recording was done at 12:00 p.m. prior to the subject eating lunch. All three sets of data were recorded on a day when the subject was attending school. The first set of EEG/qEEG data was recorded on a day where the subject ate no breakfast. The second set was recorded on a day when the subject ate a high-sugar/high-carbohydrate breakfast. The high-sugar/high-carbohydrate breakfast condition consisted of one fruit-filled toaster pastry and one glass of orange juice. The third set of data was recorded when the subject ate a nutritionally balanced breakfast, following USDA guidelines (U.S. Department of Agriculture, 2000) that consisted of two scrambled eggs, one half slice of toasted wheat bread, one and one fourth cup of tomatoes, one half cup of fruit (strawberries, bananas, and apples), and one cup of whole milk.

In order to prevent variables other than the breakfast conditions from influencing the brainwave activity of the subject, controls were set. The following variables were consistent for each of the three EEG/qEEG recordings: 1) 8 hours of sleep prior to the day of data recording, 2) the time of the recording was 12:00 p.m. on a weekday (Monday–Friday), and 3) data was recorded while the subject was at a resting state with eyes closed.

EEG acquisition was done using TruScan EEG 32-channel equipment (DEYMED Diagnostic, Payette, ID). The subject was seated in a slightly reclining chair in a silent and low-light environment. Electro-Cap™ (Electro-Cap International, Inc., Eaton, OH) was used to collect the data according to the International 10–20 System with Linked Ears (LE) montage (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2). The data was processed and then sent to a board certified electroencephalographer for analysis.

Results

Absolute power eyes-closed data was analyzed for each of the three qEEGs with LE montage. The *Z*-score results are presented in Tables 1, 2, and 3. The hertz (Hz) range from 1 to 30 was assessed in each qEEG. The only significant range affected was high beta, with the delta, theta, alpha, and low beta ranges within the normal variation of the mean. The significant deviations from the mean found in absolute power were in the 26 to 28 Hz range in qEEG 1 and in the 27 to 30 Hz range in qEEG 2.

For qEEG 1 (no-breakfast condition): Table 1 shows 2.0 to 4.0 standard deviations (*SD*) above the mean in the 26 to 28 Hz range in the frontal, central, and left posterior temporal regions (F7, F3, Fz, F4, C3, C4, T5, P3) with a mean of 2.9 *SD*.

Table 1
Absolute Power LE High Beta Standard Deviations – qEEG 1 (No Breakfast)

	25 Hz	26 Hz	27 Hz	28 Hz	29 Hz	30 Hz
FP1	0.7	1.3	1.6	1.2	1.2	1.3
FP2	0.3	0.6	0.6	0.9	1.0	1.4
F7	0.8	1.3	2.0*	1.3	0.8	0.8
F3	1.3	3.3**	4.0**	2.5*	1.1	1.1
Fz	1.1	3.0**	4.0**	3.0**	1.7	1.5
F4	1.0	2.7*	3.9**	2.9*	1.6	1.2
F8	-0.1	0.3	0.8	0.5	0.5	1.0
T3	-0.1	0.5	0.8	0.2	0.0	0.0
C3	1.4	1.7	2.7*	1.6	0.5	1.2
Cz	0.9	1.4	1.8	1.3	0.8	1.3
C4	1.6	1.8	2.5*	1.6	0.9	0.9
T4	-0.3	0.2	0.7	0.2	0.0	0.0
T5	1.3	2.2*	2.5*	1.9	1.4	1.6
P3	1.3	2.0*	2.5*	1.9	1.3	1.3
Pz	1.0	0.9	1.2	1.6	1.2	1.5
P4	0.8	1.1	1.2	1.2	1.4	1.4
T6	0.8	1.3	1.9	1.4	1.7	1.7
O1	0.7	0.9	1.3	1.4	1.5	1.5
O2	0.4	0.8	1.2	1.1	1.1	1.4

* => 2.0 < 3.0 *SD*; ** => 3.0 *SD*.

For qEEG 2 (high-sugar/high-carbohydrate condition): Table 2 shows a 2.0 to 3.5 *SD* above the mean in the 27 through 30 Hz range in the left anterior temporal, frontal, central, left posterior temporal, and mid parietal regions (F7, F3, Fz, F4, C3, Cz, C4, T5, Pz) with a mean of 2.5 *SD*.

Table 2
Absolute Power LE High Beta Standard Deviations – qEEG 2 (High-Sugar/High-Carbohydrate Breakfast)

	25 Hz	26 Hz	27 Hz	28 Hz	29 Hz	30 Hz
FP1	0.5	1.0	1.6	1.4	1.4	1.3
FP2	-0.1	0.9	0.9	1.5	1.1	1.1
F7	0.5	1.0	2.1*	1.8	1.9	1.8
F3	0.7	1.9	3.5**	2.7*	2.4*	1.8
Fz	0.8	1.6	3.0**	3.3**	2.9*	1.9
F4	0.5	1.4	2.4*	3.2**	2.0*	1.3
F8	0.2	1.0	1.3	1.7	1.6	1.6
T3	-0.1	0.3	0.8	0.7	0.6	0.7

Table 2
Absolute Power LE High Beta Standard Deviations – qEEG 2 (High-Sugar/High-Carbohydrate Breakfast)

	25 Hz	26 Hz	27 Hz	28 Hz	29 Hz	30 Hz
C3	0.8	1.1	1.8	1.5	1.7	2.1*
Cz	1.1	0.8	1.4	1.3	1.9	2.2*
C4	1.0	1.1	1.6	2.1*	2.1*	1.7
T4	-0.2	0.1	0.5	0.6	0.2	0.2
T5	0.9	1.6	2.4*	1.9	1.4	1.6
P3	0.9	1.3	1.9	1.8	1.4	1.8
Pz	1.3	1.2	1.4	1.7	1.5	2.1*
P4	1.3	1.6	1.7	1.6	1.8	1.9
T6	1.3	1.2	1.8	1.7	1.4	1.3
O1	0.4	1.0	1.1	1.0	0.9	1.1
O2	0.2	0.8	1.2	0.8	0.6	0.8

* => 2.0 < 3.0 *SD*; ** => 3.0 *SD*.

For qEEG 3 (nutritionally balanced breakfast condition): Table 3 shows no significant *SD* from the mean in absolute power in any location in the high beta range.

Table 3
Absolute Power LE High Beta Standard Deviations – qEEG 3 (Nutritionally Balanced Breakfast)

	25 Hz	26 Hz	27 Hz	28 Hz	29 Hz	30 Hz
FP1	0.8	0.6	1.2	1.4	1.7	1.2
FP2	-0.2	-0.3	-0.1	0.3	0.1	0.2
F7	0.2	0.3	0.5	0.9	1.0	1.0
F3	0.0	0.1	0.6	0.9	1.1	0.8
Fz	0.3	0.3	0.8	1.1	1.2	1.0
F4	0.1	-0.2	0.4	0.8	0.7	0.6
F8	-0.4	-0.5	-0.1	0.3	0.2	0.7
T3	-0.8	-0.6	-0.2	-0.3	-0.2	-0.5
C3	0.0	-0.3	0.2	0.2	0.6	0.6
Cz	-0.1	-0.3	-0.2	-0.1	0.5	0.9
C4	0.0	-0.2	-0.1	0.1	0.3	0.6
T4	-0.7	-0.8	-0.4	-0.4	-0.6	-0.2
T5	-0.3	-0.1	0.8	0.5	1.0	0.5
P3	-0.1	-0.2	0.5	0.5	0.7	0.7
Pz	0.3	-0.4	0.2	0.6	0.5	1.2
P4	0.5	-0.1	0.3	0.5	0.7	1.0
T6	0.4	0.1	0.6	0.6	1.1	0.7

Table 3
Absolute Power LE High Beta Standard Deviations – qEEG 3 (Nutritionally Balanced Breakfast)

	25 Hz	26 Hz	27 Hz	28 Hz	29 Hz	30 Hz
O1	0.0	0.3	0.6	0.8	1.0	1.1
O2	-0.1	-0.1	-0.1	0.3	0.7	0.7

* => 2.0 < 3.0 *SD*; ** => 3.0 *SD*.

Discussion

In this young female, we found that her qEEGs differed significantly with each of the breakfast conditions. In the no-breakfast condition (qEEG 1), there was a significant increase in high beta (26–28 Hz) activity in the left anterior temporal, frontal, central, left posterior temporal, and central parietal regions. Statistically compared to norms, the standard deviation ranged from 2.0 to 4.0 above the mean.

The widespread distribution noted in the no-breakfast condition also involved electrode sites located over Wernicke's area. This suggests that expressive and receptive language areas may be altered when a child is a breakfast skipper. The widespread distribution of excessive high beta activity may help to explain research findings of improved cognitive performance (Adolphus et al., 2016; Cooper et al., 2011; Hoyland et al., 2009; Wesnes et al., 2012), educational outcomes (Adolphus et al., 2013; Littlecott et al., 2015) and behaviors (Adolphus et al., 2013; Ahadi et al., 2016) in those who eat breakfast compared to those who do not.

In the high-sugar/high-carbohydrate breakfast condition (qEEG 2), the excessive high beta was slightly reduced. The standard deviation was significantly less from 2.0 to 3.5 above the mean. The distribution was now seen in the 27 to 30 Hz range in the frontal, central, left posterior temporal, and central parietal sites (F7, F3, Fz, F4, C3, Cz, C4, T5, Pz). In addition, we found a 0.4 reduction in *SD* mean when comparing the high-sugar/high-carbohydrate breakfast condition to the no-breakfast condition. This finding suggests any food intake is better than no food intake in regard to brain function in children. Finally, the nutritionally balanced breakfast condition (qEEG 3) showed completely normalized high beta activity in all 19 sites assessed. A complete normalization was unexpected and is noteworthy, as we were expecting some residual deviation from the mean.

In an interview with the subject following the three testing conditions, the subject reported experiencing less anxiety with the high-sugar/high-carbohydrate condition than she did with the no-breakfast condition. Furthermore, when she ate the nutritionally balanced breakfast, her anxiety was reported as almost nonexistent and her ability to focus was superior to the other two conditions. Excessive high beta activity has been linked to a small subset of children with attention-deficit/hyperactivity disorder (ADHD) who are overaroused (Clarke, Barry, McCarthy, & Selikowtiz, 2001). Additionally, they found that these children often present as moody and with behavioral issues, anxiety, and obsessiveness. Clarke et al. (2001) found that excessive high beta in the frontal regions is associated with a deficit of frontal lobe self-regulation and inhibition control issues.

This was a case study of one, healthy neurotypical young female. Controlled studies are needed before any generalizations or conclusions can be made, because the subject is not representative of the general population. Furthermore, it would be logical to expect that in unhealthy and/or neuroatypical populations, the findings would be more significant. Future investigations may also want to consider the impact of stimulants on children's breakfast choices. It may help to explain why long-term stimulant use does not appear to improve grades (Currie, Stabile, & Jones, 2014), because stimulants, by their nature, suppress appetite. Thus, the appetite suppression may produce an excessive high beta ADHD subtype nullifying the stimulants gains.

Our findings suggest that breakfast is important in regulating children's anxiety and improving focus. This is the first study that utilized qEEG to investigate the impact of breakfast choices electroencephalographically. The findings are in support of prior research regarding nutrition being a critical component for cognitive and educational performance as well as behavior. To conclude, this single case study offers evidence to show why eating a nutritionally balanced breakfast is essential for healthy brain function in children.

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