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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 *NeuroRegulation* Volume 5, Issue 1; more so, welcome to our fifth year. We are excited to reach this goal and will continue to seek out further opportunities to advance the fields of neurofeedback, biofeedback, and applied neuroscience. It is important for the public to know about these methods of performance enhancement and therapeutic intervention. Neurofeedback is not a new technology. In fact, it has been in application for over 60 years. Technology has afforded great advancements in the methods and delivery; however, operant conditioning of the EEG is a veteran in terms of psychological interventions and should not be characterized as anything less. There is a large data demonstrating the effects across clinical symptoms as well as normative groups. Our goal is to provide sound learning principles in order to facilitate improvements in self-regulation and performance and reduce psychological distress and symptoms.

In the current issue Erik Peper and Richard Harvey discuss the implications of digital addiction and associated symptoms. In the age of technology and constant exposure to digital content, this is a timely topic given few recommendations have been given to define a healthy range of exposure and potential difficulties that may arise from overexposure. Matthew Goodman, Nicolette Castro, Mary Sloan, Rita Sharma, Michael Widdowson, Eduardo Herrera, and Jaime Pineda provide data concerning a neurovisceral approach to autism and aiding individuals in targeting self-regulation and core symptoms using a multimodal approach as well as a potential approach to aid symptom improvement in individuals with autism spectrum disorders. The authors utilize a variety of novel techniques and report interesting findings. Vera Grin-Yatsenko, Siegfried Othmer, Valery Ponomarev, Sergey Evdokimov, Yuri Konoplev, and Juri Kropotov provide case studies of infra-low neurofeedback effects in depression. There is a need for more case studies of this method in order to educate professionals and the general public on the variety of methods used to address the neural mechanisms associated with specific syndromes. Finally, Heidi Hillman and Charles Chapman provide a review of biofeedback as a method to intervene and improve difficulties with anger management. This article is informative and provides examples of published data to aid clients with difficulties managing affective processes, with an emphasis on anger.

NeuroRegulation thanks these authors for their valuable contributions to the scientific literature for neurofeedback and learning. 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. We encourage researchers, clinicians, and students practicing neurofeedback to submit case studies! Thank you for reading *NeuroRegulation*!

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NeuroRegulation

Digital Addiction: Increased Loneliness, Anxiety, and Depression

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Abstract

Digital addiction is defined by the American Society for Addiction Medicine (ASAM) as well as the American Psychiatric Association (APA) as "… a primary, chronic disease of brain reward, motivation, memory, and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social, and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors…" with examples such a such as internet gaming or similar behaviors. Symptoms of digital addiction such as increased loneliness (also called "phoneliness"), anxiety, and depression were observed in a sample of university undergraduates who completed a survey about smartphone use during and outside of class. Other observations included observations of "iNeck" (poor) posture as well as how multitasking/semitasking was prevalent in the sample. Implications of continued digital addition are discussed.

Keywords: digital addiction; smartphones; depression; loneliness; multitasking

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Background

"I felt dismissed and slighted when, in the middle of dinner, my friend picked up his phone and quickly glanced at the notification. The message appeared more important than me."

> The host at the dinner party asked us to turn our phone off or leave it at the door. At first, I felt the impulse to check my phone, but during the evening I really connected with the other people.

"I had accidentally left my phone at home and, the whole day long, I kept reaching for it to check email and social media feeds—I felt emotionally lost."

> As I was running on the trail behind UC Berkeley enjoying the expansive view of the San Francisco Bay, another idea for this article popped into my head. Namely, the importance of taking time to reflect and allow neural regeneration. I rushed back to add these concepts to this article.

Classroom Observations

When observing university students sitting in the classroom, we see them alone with their heads down looking at their mobile phone. When students enter a classroom, during class breaks, or after class, they are continually texting, scrolling, clicking, or looking at their smartphone instead of engaging with the people next to them. The same habits exist outside the classroom, whether they are leaning against the walls in the hallways, walking between classes, eating pizzas, or standing on the bus. A term that describes the phenomenon is an "iNeck" posture which has become all too common a body position.

Push Notifications

Notifications from email, Facebook, Instagram, Snapchat, and Twitter can feel so important that we interrupt what we are doing and look at the screen. A few decades ago, some physicians wore portable pagers that notified them of medical emergencies that demanded their attention, albeit on a relatively infrequent basis. Similarly, a notification such as a ringing sound that someone is calling you, or such as an image appearing on a screen from a friend via social media, triggers a cascade of orienting reactions. Should I ignore the notification, or should I interrupt what I am doing to respond? Unfortunately, the auditory or visual notifications activate neurological pathways that are powerful and similar to what would have been triggered by a surprise (Kouider et al., 2015), or even as if we had perceived a danger signal in our environment (e.g., a predatory carnivore) that would threaten our survival, causing us to momentarily "freeze" and orient to the source (Roelofs, 2017). Modern marketing and advertising strategies take advantage of the evolutionarily preserved orienting response that demands attention when, for example, notifications from advertisers as well as from our friends are "pushed" to us in the form of auditory, visual, or vibratory signals called push notifications (Albuquerque et al., 2016; Mikulic, 2016).

In addition, smartphone push notifications provide updates on our social environment which would be necessary for our group's survival; however, too many notifications pushed our way can become distractions from group survival, so the balance between a constant demand to orient towards a notification versus ignoring all notifications requires choices by the users of smartphone technology (Lee, Kwon, & Kim, 2016).

Even when push notifications from friends or advertisers lack content that demands attention, the process of orienting towards almost any form of auditory, visual, and/or vibrational sources of information is automatic. For example, in almost all cases, when you sit next to someone and they focus on a smartphone or computer screen—without being prompted and in many situations against social etiquette—you automatically orient to a visual and/or auditory source after glancing at their screen. Current neuroscience research suggests that with repeated exposure to certain content (e.g., video gaming, pornography) a form of dependency may form making it difficult to "pull away" from the screen. For example, Park and Kim (2015) describe neuronal mechanisms associated with "internet addiction," and Weinstein and Lejoyeux (2015) state:

> Excessive internet game use was shown to be associated with abnormal neurobiological mechanisms in the orbitofrontal cortex (OFC), striatum, and sensory regions, which are implicated in impulse control, reward processing, and somatic representation of previous experiences in a study measuring regional cerebral metabolic rates of glucose in positron emission tomography (PET) in normal and excessive internet game users.

Evolutionary Traps

The changing visual stimulation, especially in the peripheral vision, triggers us to orient to the cause of the visual changes. In the past these peripheral changes would indicate that there is something going on to which we need to pay attention. It could be the tiger shadowing us, or a possible enemy. Now the ongoing visual display changes on the screen hijacks our vigilance that evolved over millions of years for survival. Looking at and being captured by the screen has now become an evolutionary trap (Peper, 2015). A fictional account of the stress generated during texting when there is not an immediate response is superbly described by Aziz Ansari and Eric Klinenberg (2015) in their book *Modern Romance*.

Digital Addiction Pathways

Besides automatically responding to the novel stimuli, our neural reward pathways are activated when we respond to the stimulus, click, and scroll and are rewarded by text, videos, etc. The rewards from our scrolling, clicking, and surfing are intermittent. This provides the intermittent rewards which activate reward circuits in the brain and lead to behaviors that would be labeled internet addiction. The American Society for Addiction Medicine (ASAM) as well as the American Psychiatric Association (APA) have updated their definitions of addiction to include not only exposure to and dependency on a variety of substances but also exposure to and dependency on a variety of behaviors such as video gaming (Love, Laier, Brand, Hatch, & Hajela, 2015). In a way similar to dependency formation on content such as video gaming or pornography, push notifications (e.g., texts, social network services [SNS] alerts, social media service [SMS] messages) from friends and/or advertisers may lead to developing "smartphone dependency" (SPD) behavior or addiction (Enez et

al., 2016; Gola et al., 2017; Jeong, Kim, Yum, & Hwang, 2016; Kühn & Gallinat, 2014). As a result, many people preemptively check their phone or automatically respond to push notifications from social network services such as Twitter and Facebook (SNS/SMS) during their waking hours (Grinols & Rajesh, 2014; Hu, Long, Lyu, Zhou, & Chen, 2017; Jeong et al., 2016). In social situations, constant phone interruptions cause those involved to feel slighted and snubbed (Chun et al., 2017; Vaghefi & Lapointe, 2014).

Symptoms of Digital Addiction

In our research students who use their phone the most report experiencing significantly higher levels of isolation/loneliness, depression, and anxiety than those who use their phone the least, as shown in Figure 1.

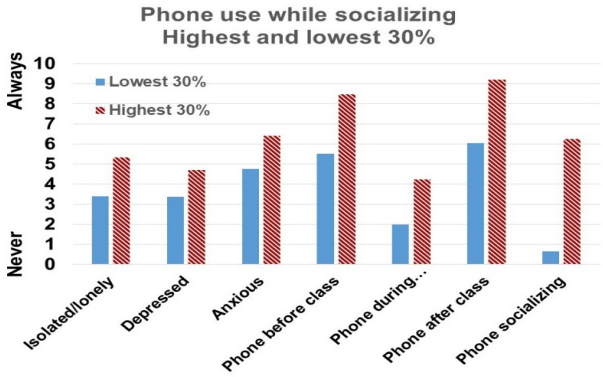

Figure 1. Self-report of isolation, depression, and anxiety which is significantly higher in students who use their phone the most as compared to those who use their phone the least.

Being "on call" by vigilantly and continuously checking the phone for anticipated, forthcoming content also contributes to multitasking, which subsequently interrupts attention and performance (Grinols & Rajesh, 2014; Jarmon, 2008). Many students no longer focus on one task at hand; instead, they are multitasking and interrupted by social media, music, and surfing the web (Lim & Shim, 2016).

Multitasking/Semitasking

In our recent survey of 135 university students who participated as part of an in-class pedagogy improvement evaluation, almost all reported that they multitask even though it would be better to focus on the required task and only shift focus after the task is done as is shown in Figure 2. Unfortunately, multitasking may more accurately be described as "semitasking" or doing twice as much half as well. Examples of multitasking have been described by Lim and Shim (2016) as falling into a few categories such as: non-media multitasking (e.g., eating while talking), cross-media multitasking (e.g., watching TV while texting), and single-device multitasking (e.g., playing an internet game while texting). The types of multitasking or semitasking of greatest interest in this article are cross-media or single-device examples.

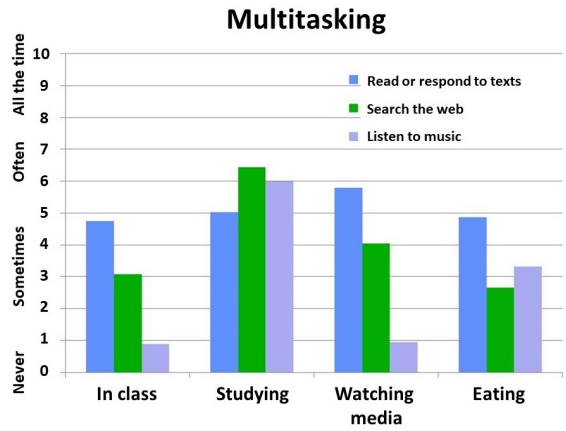

Figure 2. Self-report of multitasking.

Skepticism About Corporate Motives

Why have we become so addicted that we feel the urgency to check our phones day and night even when there are no notifications? The screen is the first focus of attention when we wake up and the last one before sleep. We cannot even wait to finish a meal or talk to a friend before checking the screen for possible updates. For the technology that is associated with addictive behavior, we can thank the major tech companies who have hired the smartest and brightest engineers, programmers, and scientists to develop software and hardware to capture our attention. They condition us to be addicted to increase corporate profit: more eyeballs, more clicks, more money. For a detailed analysis of how tech companies created our addiction, see Michael Schulson's (2015) essay "User Behaviour: Websites and apps are designed for compulsion, even addiction. Should the net be regulated like drugs or casinos?"

Avoid blaming children or adults who claim lack of self-control. The addictive nature of smartphone interactions was predominantly created by tech companies in their quest to capture market share by exploiting our natural, evolutionary survival responses to orient and attend to a change in our visual and auditory world that builds on an "evolutionary trap." The behavioral addiction of smartphone use begins forming neurological connections in the brain in ways similar to how opioid addiction is experienced by people taking Oxycontin for pain relief—gradually. An obvious skeptical question would be: "Are addictive substances or addictive behaviors created, encouraged, or reinforced by corporations more so in their ongoing quest to increase profits than to benefit the users of their products?"

Future Considerations and Concerns About Digital Addiction

There is cause for worry about the long-term harm of internet addiction as well as smartphone addiction, since overuse or abuse of behavioral technologies may have a worse effect than opioid addiction (Swingle, 2016). For example, because internet or smartphone addiction can lead to reduced social connections and emotional regulation, as well as increased attention-deficit disorders and distractibility or decreased self-initiative (proactive versus reactive behavior) there will likely be compromises to health and well-being (Holt-Lunstad, Smith, Baker, Harris, & Stephenson, 2015; Swingle, 2016). For example, in a meta-analysis by Holt et al. (2015), actual social isolation along with perceived feelings of loneliness increased mortality by 30%. Furthermore, Cacioppo, Cacioppo, Capitanio, and Cole (2015) have summarized the neuroendocrine effects of social isolation and perceived loneliness on specific brain systems, suggesting that perceived loneliness associated with smartphone addiction can have negative impacts on physical health. Similarly, Pittman (2017) suggests the term "phoneliness" to refer specifically to the types of perceived loneliness associated with smartphone addiction behaviors.

Being plugged in and connected limits the time for reflection and regeneration. Unprogrammed time allows new ideas and concepts to emerge, giving time to assess your own and other people's actions from a distant perspective. It offers the pause that refreshes and allows time for neural regeneration. Our nervous system, just like our muscular system, grows when there is enough time to regenerate after being stressed. Ongoing stress or stimulation without time to regenerate leads to illness and neural death. The phenomena can be seen in the development of rat brains.

Neuroanatomist Professor Marion Diamond showed that rats who were brought up in an impoverished environment and had very little stimulation possessed a thinner cortex and less dendritic connections than rats brought up in an enriched environment (Diamond et al., 1975; Rosenzweig, 1966). More importantly, an excessively enriched environment was associated to a reduction of neurogenesis and synaptic plasticity (Joëls et al., 2004). The more hours of television a child between age 1 and 3 watched was directly correlated with associated attentional problems at age 7 (Christakis, Zimmerman, DiGiuseppe, & McCarty, 2004), indicating that excessive stimulation during brain development may be harmful.

Strategies to Address Digital Addiction

From a biological perspective, health is the alternation between activity and regeneration. If you do not allow the system time to regenerate, neural degeneration may occur. Even though it is very challenging to break the addiction, it is possible. Mobilize your health and disconnect to allow regeneration. Take charge, regain social connections, and develop proactive attention.

1. Recognize that you have been manipulated into addiction by the tech companies, which have covertly conditioned you to react to notifications and have created the desire to check frequently for updates.

2. Become proactive by limiting interruptions when you work and play.

    - Turn off of notifications of your apps so that they do not interrupt your work.
    - Schedule time to look and respond to email, Facebook, Twitter, Instagram, or Snapchat and notify your colleagues that you will only respond to messages and information during prescheduled time periods such as 11 a.m.–12 p.m. or 3–4 p.m.
    - Schedule uninterrupted time when you are most alert. For most people this is morning time. Do your creative concentrated work first and then answer social media during times when your attention and concentration has decreased.

- Turn off your digital devices during social events (e.g., dinner or talking to friends, coworkers, and family).
- Make an active choice to be present with friends and family.
- Make a game out of avoiding smartphone use. For example, when going out to dinner, have everyone place their phone in the middle of the table and make an agreement that the first person who touches their smartphone before dinner ends will pay for the entire meal.
- Create unstructured time without stimulation to allow the opportunity for self-reflection and regeneration. As journalist Daniel A. Gross (2014) points out, "Freedom from noise and goal-directed tasks, it appears, unites the quiet without and within, allowing our conscious workspace to do its thing, to weave ourselves into the world, to discover where we fit in. That's the power of silence."

There is a simple aphorism that says: "Pay attention to shift intention," suggesting that training related to better intentional behaviors may allow breaking the cycle of smartphone addiction associated with falling into the evolutionary trap of "mindless attention."

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A Neurovisceral Approach to Autism: Targeting Self-Regulation and Core Symptoms Using Neurofeedback and Biofeedback

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Abstract

Mu Rhythm Synchrony Neurofeedback (MRS-NFB) has shown promise in improving electrophysiological and behavioral deficits in autism spectrum disorder (ASD). Heart rate variability biofeedback (HRV-BFB), a method for improving self-regulation of the autonomic nervous system (ANS), has yet to be tested as a clinical intervention for ASD. This study evaluated the impact of HRV-BFB on symptoms of ASD; and whether a combined HRV-BFB + MRS-NFB intervention would be more efficacious than HRV-BFB alone. Fifteen children with a verified diagnosis of ASD completed the study. Participants were assigned to either an HRV-BFB group (Group 1) or a combined HRV-BFB + MRS-NFB group (Group 2). All children underwent pre- and postassessments of electroencephalography (EEG), heart rate variability (HRV), and parent-reported behaviors. No significant between-groups differences were observed on any parent-reported behaviors. Group 1 showed significant pre–post improvements in emotion regulation and social behavior, while Group 2 showed significant pre–post improvements in emotional lability and autistic behaviors. Group 2 also showed significant improvements in RMSSD and lnHF (vagal tone) indices of HRV over time, while Group 1 displayed no significant changes in HRV over time. Group 1 showed an increase in mu suppression posttraining, and Group 2 showed a reduction in mu suppression posttraining. The results suggest that HRV-BFB, alone or in combination with MRS-NFB, may improve behavioral features of autism. A combined approach may be more efficacious in enhancing HRV, while the implications of each approach on mu suppression are mixed. Neurovisceral approaches that teach self-regulation offer a novel treatment avenue for ASD.

Keywords: autism; neurofeedback; biofeedback; heart rate variability; mu rhythms; mirror neuron system; neurovisceral integration

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Autism spectrum disorder (ASD) is characterized by social impairments and restricted, repetitive behaviors, in addition to broader deficits in executive functioning, emotion regulation, and the presence of comorbid disorders like anxiety (American Psychiatric Association, 2013; Hill, 2004; Mazefsky et al., 2013; White, Oswald, Ollendick, & Scahill, 2009). In the past decade, neurobiological explanations of ASD have expanded from identifying regional brain impairments (e.g., amygdala, fusiform face area; Adolphs, Sears, & Piven, 2001; Schultz et al., 2003) to focusing on networks, including the interaction of multiple networks (e.g., Default Mode Network [DMN], Salience Network [SN], and Executive Control Network [ECN]; Kennedy, Redcay, & Courchesne, 2006; Uddin & Menon,

2009). It is argued that impairments may result not so much from aberrant anatomy but from alterations in functional connectivity within and across networks, defined as interregional correlations in the time-course of the fMRI blood oxygenation level-dependent (BOLD) signal (Biswal, Yetkin, Haughton, & Hyde, 1995; Vissers, Cohen, & Geurts, 2012). These atypical patterns of functional connectivity may underlie the disordered and idiosyncratic information integration that is characteristic of the ASD brain, accounting for the myriad symptoms along the autism spectrum (Belmonte et al., 2004; Brock, Brown, Boucher, & Rippon, 2002).

One network proposed to exhibit the hyper- and hypoconnectivity characteristic of ASD, and which might contribute specifically to deficits in the social domain, is the human Mirror Neuron System (MNS; Fishman, Keown, Lincoln, Pineda, & Müller, 2014; Shih et al., 2010). The MNS consists of a group of frontoparietal regions associated with imitation and empathic behavior (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Iacoboni, 2009; Williams et al., 2006). Desynchronization or suppression of electrophysiological oscillations over the sensorimotor cortex, known as mu rhythm (alpha mu: 8–13 Hz; beta mu: 15–25 Hz) and recorded with electroencephalography (EEG), has been hypothesized to indirectly reflect MNS activity (Cochin, Barthelemy, Roux, & Martineau, 1999; Pineda, Allison, & Vankov, 2000; for a review see Pineda, 2005). While the MNS theory of autism has been a subject of debate (Enticott et al., 2013; Hamilton, 2013), it is generally agreed that mu rhythms are linked to the MNS and that both are involved in imitation and social behavior (Bernier, Aaronson, & McPartland, 2013; Braadbaart, Williams, & Waiter, 2013; Pineda, 2008). In typically developing (TD) individuals, suppression of this rhythm occurs during self-initiated motor actions and when observing another individual's meaningful action (i.e., "mirroring"; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996). In children with autism, however, this suppression occurs during self-movement (execution), but not while observing others move (Oberman et al., 2005). Furthermore, the observation deficit in ASD disappears when observing familiar, as opposed to unfamiliar, individuals (Oberman, Ramachandran, & Pineda, 2008). This has led researchers to conclude that under certain circumstances the MNS is functional and therefore to test clinical applications like neurofeedback that seek to remediate mu rhythm dysfunction in ASD.

Neurofeedback uses brain-computer interface technology to teach self-regulation of endogenous brain rhythms through principles of operant conditioning. Real-time display of EEG activity rewards the participant for modulating power in specific neurophysiological rhythms. A variety of neurofeedback interventions have led to improvements in attention, executive functioning, language, and social behavior in children with ASD (Coben, Linden, & Myers, 2010; Coben & Padolsky, 2007; Kouijzer, van Schie, de Moor, Gerrits, & Buitelaar, 2010). Mu Rhythm Synchrony Neurofeedback (MRS-NFB), which specifically focuses on training mu rhythms, has shown promise in reducing core symptoms of autism, including language, social cognition, and emotional responsiveness (Friedrich et al., 2015; Pineda, Carrasco, Datko, Pillen, & Schalles, 2014; Pineda et al., 2008). Note that while MRS-NFB aims to train the frequency and amplitude of centro-parietal rhythms, it does not train the morphology of the waveform itself. Previous studies of MRS-NFB in ASD have focused on enhancing mu power during training, as it is thought that the ability to enhance mu is a prerequisite for being able to perform mu suppression (Pineda, 2005; Pineda et al., 2008; Pineda, Carrasco, et al., 2014). One recent study trained children with ASD to either a) increase mu power, or b) increase and decrease mu power via a NFB paradigm utilizing a social video game. Children in both groups learned to regulate mu rhythms and did not significantly differ in the ability to suppress mu at the end of the training (Friedrich et al., 2015). Thus, the current study continued the protocol of mu enhancement.

While much attention has been given to central nervous system (CNS) dysfunction in ASD, the role of the peripheral nervous system (PNS) has also begun to attract interest. Porges (2001, 2003, 2007) initially proposed the Polyvagal Theory to describe how the vagus nerve (specifically its phylogenetically-recent myelinated pathway) mediates social behavior in mammals; and thus, how vagal dysfunction may contribute to social disorders like autism. The vagus is the 10th cranial nerve and helps regulate autonomic nervous system (ANS) activity via connections to the heart and other visceral organs. It is anatomically and functionally involved in the Social Engagement System (e.g., gaze, facial expression, extraction of the human voice, prosody), whereby dysfunction is hypothesized to mediate social withdrawal behaviors in autism; and regulates maladaptive defense strategies (e.g., fight-or-flight or immobilization and shutdown) and self-soothing (e.g., repetitive)

behaviors, also characteristic behavioral patterns of ASD (Porges, 2003). The vagus controls heart rhythms through inhibitory (parasympathetic) slowing of the heart, and disinhibitory (sympathetic) speeding up of the heart. These beat-to-beat fluctuations are referred to as heart rate variability (HRV) and are used as a measure of self-regulation and healthy ANS functioning (McCraty & Shaffer, 2015). Studies have shown that children with ASD have lower baseline HRV compared to controls (Bal et al., 2010; Van Hecke et al., 2009). Within the ASD population, those with higher HRV demonstrate superior emotion recognition, receptive language skills, social behavior, and caregiver-reported language and cognitive abilities (Bal et al., 2010; Patriquin, Lorenzi, & Scarpa, 2013; Patriquin, Scarpa, Friedman, & Porges, 2011). Therefore, there is incentive for researchers to investigate mechanisms that might enhance HRV in ASD.

HRV biofeedback (HRV-BFB) is a widely supported intervention for improving HRV and overall ANS functioning (Lehrer et al., 2006; Lin et al., 2012; Siepmann, Aykac, Unterdörfer, Petrowski, & Mueck-Weymann, 2008). While its clinical benefits have been demonstrated across a range of disorders, no known studies have examined HRV-BFB in the ASD population. HRV-BFB allows patients to see their fluctuating heart rhythms, in real-time, while practicing resonant frequency (RF) diaphragmatic breathing. RF refers to the unique breath rate, typically between 4.5 and 7.0 breaths per minute (bpm), where HRV is maximized due to "resonance" between ANS functions like the breath, baroreceptors, and vagal control of the heart (Lehrer, Vaschillo, & Vaschillo, 2000).

HRV may also be a reflection of social behavior based on the principle of neurovisceral integration (Thayer & Lane, 2000). Not only do CNS regions influence ANS activity through vagally mediated efferent pathways, but visceral regions also send afferent information back up to the brain. This bidirectional, integrated system is known as the Central Autonomic Network (CAN; Benarroch, 1993). Some regions in this network, such as the amygdala, insula, anterior cingulate, and orbitofrontal cortex, overlap with networks related to attentional, affective, and social processing that are thought to play a role ASD (Di Martino et al., 2009; Kana, Keller, Minshew, & Just, 2007; Sabbagh, 2004; Uddin & Menon, 2009). Through inhibitory, feedback, and feedforward loops, this system maintains homeostatic balance across the CNS and PNS; and disruption within these circuits leads to impairments in cognition and clinical symptoms (Thayer & Brosschot, 2005; Thayer, Hansen, Saus-Rose, & Johnsen, 2009). Therefore, interventions like HRV-BFB not only act on the PNS but may also influence CNS functioning as well.

Given evidence of both CNS and PNS dysfunction in ASD, interventions that target both "top–down" and "bottom–up" deficits might be more beneficial than either approach used alone. By improving global, underlying self-regulatory mechanisms, a broader range of behaviors beyond those targeted by standard behavioral interventions might be addressed, including self-stimulatory and repetitive behaviors, attention, and emotion regulation. Other comorbid diagnoses, such as anxiety, might also be impacted. The purpose of the current study was first, to evaluate the effect of HRV-BFB on symptoms of autism; and second, to evaluate whether a combination of HRV-BFB and MRS-NFB (HRV-BFB + MRS-NFB) is more effective than HRV-BFB alone. It was hypothesized that HRV-BFB would lead to improvements in autistic symptoms, social behavior, emotion regulation, anxiety, and HRV. Similarly, it was hypothesized that HRV-BFB + MRS-NFB would lead to improvements in autistic symptoms, social behavior, emotion regulation, anxiety, HRV, as well as mu suppression. Finally, it was speculated that HRV-BFB + MRS-NFB would lead to greater improvements in all of these domains than HRV-BFB alone.

Methods

Participants

A total of 15 children with ASD completed the study. Participants were recruited through Valerie's List (an online community providing autism-related support and resources), word of mouth, and a large metropolitan school district in southern California (approval was granted through the district's research review panel). The University of California, San Diego IRB approved this experiment. Informed consent was obtained from all individual participants included in the study.

Of the 15 subjects, 13 were male and 2 were female. Ages ranged from 9 to 18 years (M = 12.4, SD = 2.5). All subjects underwent diagnostic verification by a trained clinical psychologist using the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2; Lord et al., 2012), Wechsler Abbreviated Scale of Intelligence, 2nd Edition (WASI-II; McCrimmon & Smith, 2013), and Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994). See Table 1 and Table

2 for complete demographic and diagnostic information.

A minimum IQ score was not required for inclusion, and scores ranged from extremely low to superior. The inclusion/exclusion criteria were as follows: 1) children must be 6–18 years old; 2) participants must be able to perform the diaphragmatic breathing technique (see Preliminary HRV Biofeedback Training section), as it is an integral component of HRV-BFB. Participants who could not evidence this ability by the second session were excluded; and 3) children must be able to tolerate EEG procedures (e.g., electrodes and gel being placed on head), or they were otherwise excluded from the study.

Table 1
Demographic characteristics of HRV-BFB Only and HRV-BFB + MRS-NFB groups.

	Group 1 HRV-BFB Only (*n* = 7)	Group 2 HRV-BFB + MRS-NFB (*n* = 8)	Group 1 + Group 2 Combined (*N* = 15)
Gender (% Male)	85.7%	87.5%	86.7%
Age – Mean (*SD*)	12.1 (2.3)	12.8 (2.8)	12.5 (2.5)
Race/Ethnicity			
White/Caucasian	3	4	7
Asian/Asian-Pacific Islander	1	0	1
Hispanic/Latino	1	3	4
Mixed White/Asian/Hispanic	1	0	1
Mixed African-American/Asian	1	0	1
Mixed White/Hispanic	0	1	1
Medication (%)	42.9%	14.3%	26.7%

Table 2
Diagnostic data of HRV-BFB Only and HRV-BFB + MRS-NFB groups.

	ASD Cut-offs	Group 1 HRV-BFB Only (*n* = 7) Mean (*SD*)	Group 2 HRV-BFB + MRS-NFB (*n* = 8) Mean (*SD*)	Group 1 + Group 2 Combined (*N* = 15) Mean (*SD*)
WASI-II				
Full Scale IQ		94.4 (14.6)	87.3 (19.2)	90.6 (17.0)
Verbal Comprehension Index		92.1 (19.7)	79.6 (21.0)	85.5 (20.7)
Perceptual Reasoning Index		102.9 (13.9)	99.7 (18.3)	101.3 (15.7)
ADOS-II				
Communication	2	5.0 (1.8)	5.6 (2.3)	5.3 (2.0)
Reciprocal social interaction	4	9.3 (1.9)	10.9 (2.9)	10.1 (2.5)
Communication and social interaction	7	14.3 (3.4)	16.4 (5)	15.4 (4.3)
Imagination/Creativity	-	1.1 (0.7)	1.3 (0.8)	1.2 (.73)
Stereotyped behaviors and restricted interests	-	3.6 (1.5)	3.1 (1.8)	3.4 (1.6)

Table 2

Diagnostic data of HRV-BFB Only and HRV-BFB + MRS-NFB groups.

	ASD Cut-offs	Group 1 HRV-BFB Only (*n* = 7) Mean (*SD*)	Group 2 HRV-BFB + MRS-NFB (*n* = 8) Mean (*SD*)	Group 1 + Group 2 Combined (*N* = 15) Mean (*SD*)
ADI-R				
Qualitative abnormalities in reciprocal social interaction	10	15.3 (2.9)	18.1 (6.3)	16.7 (4.9)
Qualitative abnormalities in communication (verbal)	8	11.6 (2.1)	13.3 (6.3)	12.4 (4.6)
Qualitative abnormalities in communication (non-verbal)	7	8.0 (1.5)	10.6 (2.1)	9.3 (2.2)
Restricted, repetitive and stereotyped behaviors	3	5.7 (2.2)	5.0 (2)	5.4 (2.1)
Abnormality of develop evident before 36 months	1	3.1 (0.4)	3.6 (1.1)	3.4 (.84)

Procedure

Participants were assigned to either the HRV-BFB group (Group 1) or HRV-BFB + MRS-NFB group (Group 2) using stratified randomization according to age, gender, and IQ. All children underwent pretesting (T1; see Measures section), diagnostic testing, four preliminary sessions of HRV-BFB, 12 additional training hours of either HRV-BFB (Group 1) or HRV-BFB + MRS-NFB (Group 2) via "DVD Training Sessions" (see HRV-BFB and HRV-BFB + MRS-NFB ("DVD") Training section), and finally posttesting (T2; see Measures section). See Figure 1 for a complete study flow.

Preliminary HRV Biofeedback Training. Subjects in both Group 1 and Group 2 underwent four preliminary HRV-BFB training sessions utilizing Thought Technology Ltd. (Quebec, Canada) equipment and software (BioGraph Infiniti 6.0). A 5-min HRV baseline was recorded at the beginning of each session. HRV-BFB sessions were modeled after procedures outlined by Lehrer, Vaschillo, and Vaschillo (2000).

In the beginning of the first session, participants were taught a diaphragmatic breathing technique by a trained research associate. The research associate would first model "belly breathing" by placing one hand on their stomach and the other on their chest, breathing so that "only the hand on the stomach goes up and down." This behavior was then imitated by participants while being continuously shaped and positively reinforced through verbal praise, breaks, and preferred items (e.g., playing with their iPad).

In sessions 1–4, participants were connected to an electrocardiograph (EKG) and respiratory measurement devices, which displayed their heart rate (HR) and respiratory patterns on a computer screen. They were asked to breathe diaphragmatically along with a visual breathing pacer, while they received visual feedback of their HR going up and down, with each inhale and exhale, respectively (i.e., "variability" in HR). Children were verbally praised for following the breathing pacer and creating more variability in their HR. The goal was to find each child's unique resonant frequency (RF) breath rate (4.5–7.0 bpm; Lehrer et al., 2000); once this was found, children would continue to breathe at this rate (some children were slightly above the 4.5–7.0 bpm range as they could not breathe this slowly and were maintained at the slowest comfortable rate). Sessions lasted an hour each. Each session was broken down into 3 or 4 diaphragmatic breathing segments of 10 to 20 minutes. In between segments 5-min breaks were given in which participants were positively reinforced (e.g., verbal praise) and/or negatively reinforced (e.g., simply taking a break). Over the course of the four sessions, participants' breathing was shaped to improve the quality or speed, and/or find their RF rate.

HRV-BFB training in the lab was supplemented with RF diaphragmatic breathing practice at home. Parents were encouraged to practice with their child for 10 to 20 minutes per day, preferably before bedtime and/or in the morning. Apps for phones and iPads were suggested (e.g., MyCalmBeat, Breathe2Relax) to help simulate the breathing pacer utilized during lab sessions. From the first week to posttesting, parents completed a weekly breathing practice log that tracked the amount of time practiced each week. See Figure 2 for an illustration of HRV-BFB sessions.

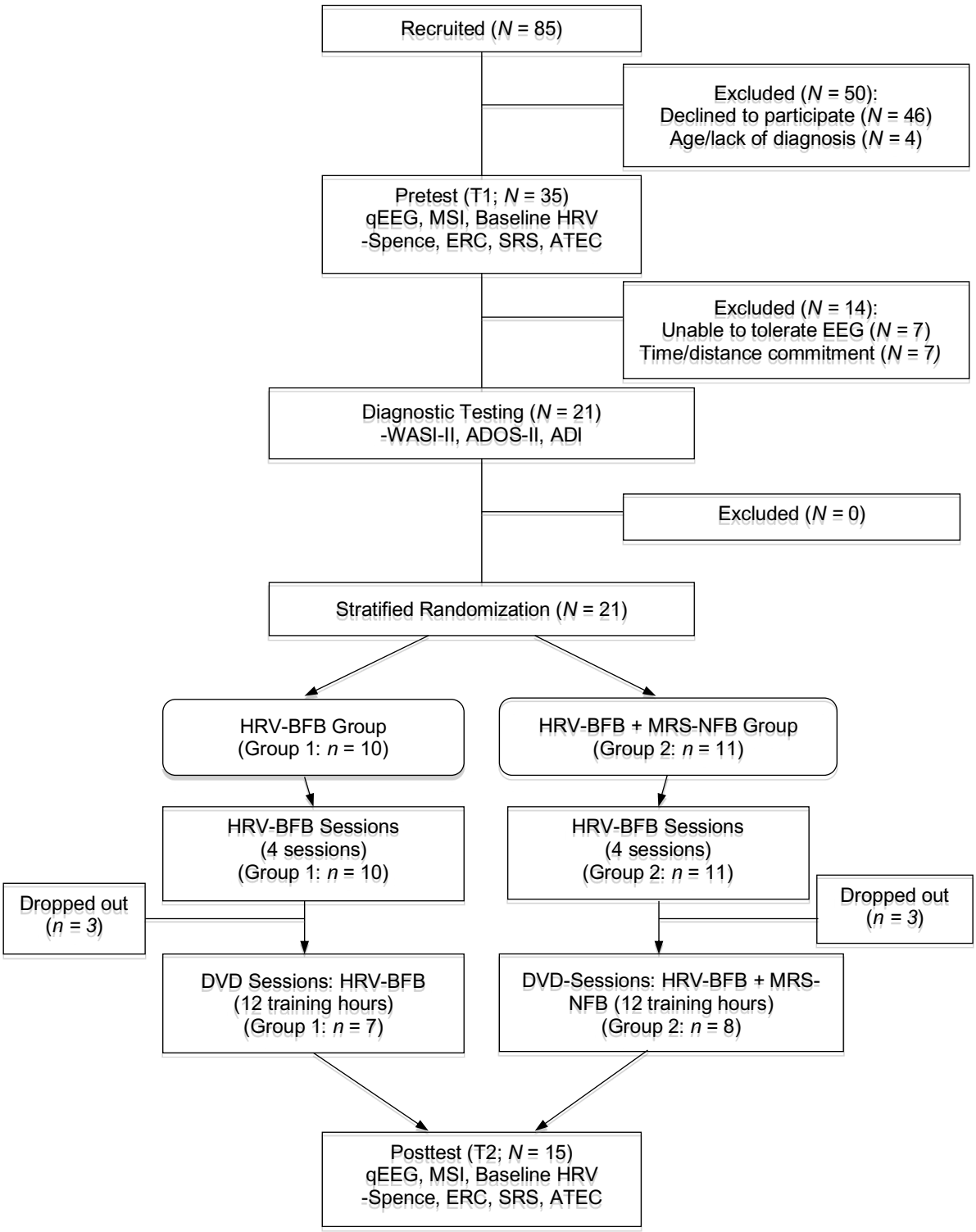

Figure 1. CONSORT Flow Diagram. Note: Pretesting was performed before diagnostic testing to ensure that children could tolerate the EEG procedure (e.g., gel, electrode placement) before using resources for diagnostic testing; stratified assignment was performed after diagnostic testing because IQ was used to match participants. *qEEG = Quantitative EEG; MSI = Mu Suppression Index; Spence = Spence Anxiety Scale; ERC = Emotion Regulation Checklist; SRS = Social Responsiveness Scale; ATEC = Autism Treatment Evaluation Checklist*.

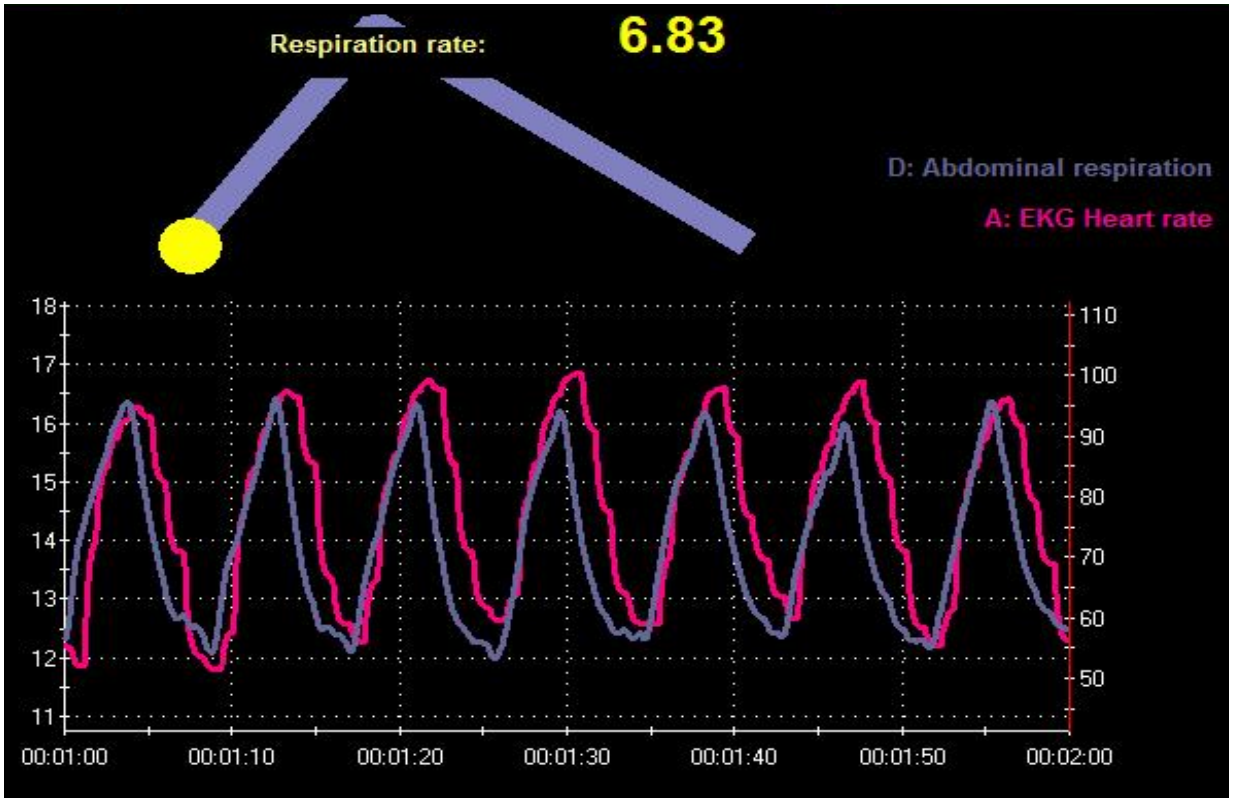

Figure 2. HRV Biofeedback Sessions. During HRV-BFB sessions, participants would breathe at their resonant frequency (RF) rate using a visual pacer (top) while receiving real-time visual feedback of their respiratory (blue) and cardiac (red) rhythms. Participants were verbally reinforced for producing large "peaks and valleys" (i.e., greater respiratory sinus arrhythmia [RSA]) and cardiorespiratory synchrony (i.e., overlapping blue and red lines). Resonant frequency (RF) breath rate was determined by calculating which breath rate (between 4.5 and 7.0 bpm) produced the largest RSA (i.e., peak-to-valley difference).

HRV Biofeedback Modifications. One participant (Group 2) required an additional (fifth) HRV-Biofeedback session due to experiencing nosebleeds and lightheadedness. With modifications, they still received the same 4 hr of HRV-Biofeedback training.

HRV-BFB and HRV-BFB + MRS-NFB ("DVD") Training.

Basic Design. Group 1 and Group 2 both completed 12 hr of "DVD" training using Thought Technology Ltd. (Quebec, Canada) equipment and software (BioGraph Infiniti 6.0). Participants brought a DVD movie from home or chose one in the lab, which served as the means for BFB and/or NFB reinforcement (see Group 1 Design and Group 2 Design sections). Prior to each DVD session, both groups underwent a 5-min HRV baseline recording. Additionally, a 1-min EEG baseline was taken from electrode C4 (sensorimotor cortex) to determine resting alpha mu (8–13 Hz) activity.

Group 1 Design (HRV-BFB "DVD" Training). For Group 1 the software was programmed to respond to the participant's RF diaphragmatic breathing threshold (determined during the four preliminary HRV Biofeedback training sessions). The DVD would play if the participant was breathing at or below the determined threshold. If their breath rate exceeded the threshold, the DVD would pause and not resume until the target rate was achieved again. Thus, participants were positively reinforced for RF breathing and negatively punished for faster breathing. Every 15 to 20 minutes, 5- to 10-min breaks were provided. See Figure 3 for a visual representation of the Group 1 training sessions.

Group 2 Design (HRV-BFB + MRS-NFB "DVD" Training). As with Group 1, RF diaphragmatic breathing thresholds determined whether the DVD would play (at or below RF rate) or pause (above RF rate). Additionally, participants in Group 2 were

reinforced for raising alpha mu (8–13 Hz) levels over C4. An initial alpha mu threshold was set according to the resting alpha mu values obtained during the one-minute EEG baseline. When alpha mu levels were below this threshold, the video on the screen would shrink in size, making the picture more difficult to see; when alpha mu levels exceeded this threshold, the video picture would grow in size. Thus, in addition to reinforcement and punishment for RF breathing, participants were positively reinforced for raising alpha levels and negatively punished for decreasing alpha mu levels. See Figure 3 for a visual representation of the Group 2 training sessions.

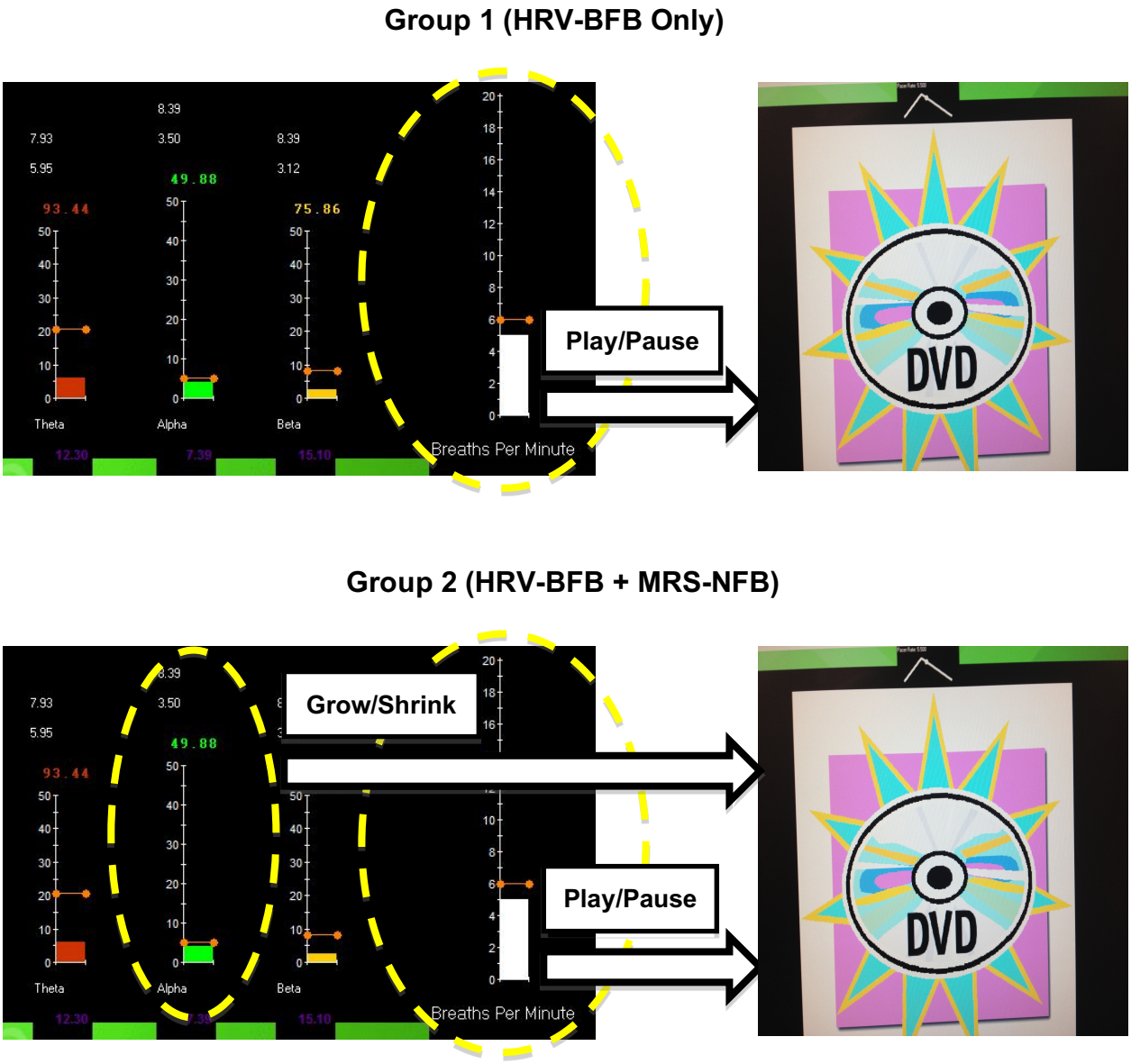

Figure 3. For participants in Group 1 (HRV-BFB Only), the movie on the screen would play *only* if they were breathing at or below the designated "breaths per minute" threshold, which was set at their resonant frequency (RF) pace. For participants in Group 2 (HRV-BFB + MRS-NFB), the same breathing conditions applied as in Group 1; however, for participants in Group 2, the movie screen would *also* grow or shrink depending on whether they exceeded or failed to meet alpha/mu (8–12 Hz) rhythm thresholds.

Modifications: Session Length and Mu Thresholds. The study began with six participants (Group 1: three participants; Group 2: three participants) undergoing DVD training in 1-hr sessions, twice a week, for 6 weeks. From this point, the remaining nine participants (Group 1: four participants; Group 2: five participants) underwent DVD training sessions in 2-hr sessions, once a week, for 6 weeks. This alteration was made in order to address the issue of participant retention, as many families found it difficult to attend the laboratory twice per week. Still, all participants in Group 1 and Group 2 received a total of 12 training hours over the course of 6 weeks. One participant (Group 2) struggled with the time length of the 2-hr sessions, so they were switched back to 1-hr sessions.

During DVD training sessions for Group 2, the first three participants utilized a fixed alpha mu threshold (i.e., the DVD shrank/grew in relation to a static threshold). For the additional five participants in Group 2, the alpha mu threshold was continuously modified over the course of the session to ensure that participants were being rewarded 70% to 80% of the time within the session. This adjustment was made to strengthen the learning curve due to concerns about within-session learning.

Measures

Quantitative EEG (qEEG). EEG recording was conducted using a Biosemi ActiveTwo 32-channel, 24-bit resolution EEG data acquisition system, with semiactive electrodes. Following the EEG capping procedure, participants were moved into an electrically shielded, sound-attenuating chamber where the various assessments took place. During both T1 (pretest) and T2 (posttest) assessments, participants were asked to sit quietly for 10 min with their eyes closed, then for another 10 min with their eyes open while EEG was recorded.

Mu Suppression Index (MSI). The MSI was developed and used in previous NFB experiments (Oberman et al., 2005; Pineda et al., 2008) to evaluate mu rhythm activity over the sensorimotor cortex. Subjects are shown five different types of motion videos and are also asked to perform one instance of self-movement. The five different types of motion include: (1) *Random motion*: dots of different colors moving across the computer screen, (2) *Non-biological human motion*: a point-light walker doing jumping jacks, (3) *Biological human motion:* a hand making a "duck" movement, (4) *Biological goal-directed motion:* a hand taking a crayon out of a box, and (5) *Socially-relevant biological motion:* three individuals passing around a ball, where the ball is periodically tossed towards the camera making it seem as if the subject were included in the activity. For the self-movement (6), subjects were prompted by a screen to make a "duck" movement with their hand, bringing digits 2 to 5 to the thumb and opening again, repeatedly.

The *random motion* condition (1) constitutes a baseline where little mu suppression is expected and is thus used as a baseline for resting mu activity. The remaining conditions (2–5) represent a continuum whereby mu suppression should increase, respectively, as motion becomes more biological and meaningful. The *self-movement* (6) condition is expected to produce the most mu suppression (given that the subject is producing a motor action) and is used as a reference for mu suppression. See Figure 4 for a visual representation of the MSI.

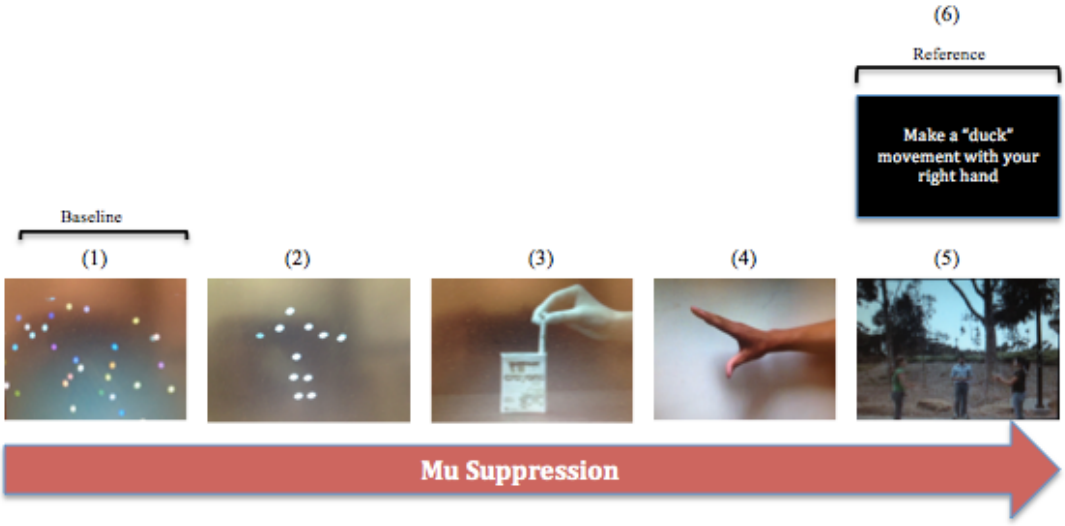

Figure 4. Mu Suppression Index. Subjects view six different stimuli, each lasting 1 min (repeated twice). As motion becomes more biological and meaningful, more mu suppression is expected.

Heart Rate Variability (HRV). HRV was recorded using Thought Technology Ltd. (Quebec, Canada) equipment and software (BioGraph Infiniti 6.0). During both T1 (pretest) and T2 (posttest), resting HRV was measured during the 20-min qEEG recording (see Quantitative EEG section). Resting HRV was also measured before each HRV-BFB (see Preliminary HRV Biofeedback Training section) and DVD training session (see HRV-BFB and HRV-BFB + MRS-NFB ("DVD") Training section) for 5 min. Specifically, data were extracted within the following domains: the standard deviation of NN ("normal-to-normal" wave) intervals (SDNN), the square root of the mean squared difference of successive NN intervals (RMSSD), and the high-frequency band. SDNN and RMSSD are overall indicators of HRV. The HF spectrum is the power (area under the curve) in each of the 5-min segments in the range from .15 to .40 Hz and reflects parasympathetic activity. The natural log of HF (lnHF) is a common index of vagal tone (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

Social Responsiveness Scale-2 (SRS-2; Constantino, 2012). The SRS-2 is a 65-item questionnaire used to identify social impairments often associated with ASD. For this study, all subjects were evaluated using the School-Age Form for ages 4–18, completed by the subject's parent. There are five subscales: Social Awareness (SA), Social Cognition (SCog), Social Communication (SCom), Social Motivation (SM), and Restricted Interests and Repetitive Behavior (RRB), plus the Total Score. Items are on a 4-point Likert scale (*1 = Not True*; *4 = Almost Always True*) and contain questions such as "expressions on his or her face don't match what he or she is saying" and "has an unusually narrow range of interests." *T*-scores of 59 and below are considered socially typical; 60–65 is considered mild social impairment; 66–76 is considered moderate social impairment; and 76 or higher is interpreted as severe social impairment. Research with large standardized samples has shown high internal consistency ($\propto$ = .95) and good reliability and validity (Bass, Duchowny, & Llabre, 2009; Constantino et al., 2003). In the current study, internal consistency using Cronbach's alpha was .89 and .69 for pre- and posttests, respectively.

Emotion Regulation Checklist (ERC; Shields & Cicchetti, 1997). The ERC Parent report measure is a 24-item measure of children's emotion regulation skills. The checklist includes both positively and negatively weighted items rated on a 4-point Likert scale (1 = *Rarely/Never*; 4 = *Almost always*). The ERC is divided into two scales: Emotion Regulation (ER; e.g., "is a cheerful child") and Emotional Lability/Negativity (LN; e.g., "exhibits wide mood swings"). Higher ER scores indicate superior emotion regulation; higher LN scores indicate higher emotional lability and negativity, or inferior emotion regulation. The ERC is a well-standardized inventory and shows strong convergence with other more established behavioral measures (e.g., Child Behavior Checklist; Shields & Cicchetti, 1997). In the current study, internal consistency using Cronbach's alpha was .54 and .45 for pre- and posttests, respectively.

Spence Children's Anxiety Scale (SCAS-Parent Report; Nauta et al., 2004; Spence, 1998). The SCAS is a 39-item parent-report questionnaire. It is used to assess anxiety symptoms across six subscales: Panic/Agoraphobia (PA), Separation Anxiety (SA), Physical Injury Fears (PIF), Social Phobia (SP), Obsessive-Compulsive symptoms (OC), and Generalized Anxiety (GA). Items are rated on a 4-point Likert scale (*1 = Never*; *4 = Always*). The SCAS yields a total score and individual subscale scores. Lower scores on all scales are indicative of less anxiety. Good internal consistency has been indicated with Spearman Brown coefficients for each subscale ranging from 0.80–0.92 (Nauta et al., 2004). In the current study, internal consistency using Cronbach's alpha was .85 and .91 for pre- and posttests, respectively.

Autism Treatment Evaluation Checklist (ATEC; Rimland & Edelson, 1999). The ATEC is a 77-item parent-report questionnaire consisting of four subscales: Speech/Language/Communication (SLC), Sociability (SOC), Sensory/Cognitive Awareness (SCA), and Health/Physical/Behavior (HPB). For the SLC section (e.g., "knows 10 or more words"), items are rated *N = Not true*, *S = somewhat true*, and *V = Very true*. Items on the SOC (e.g., "no eye contact") and SCA (e.g., "is aware of danger") subscales are rated *N = Not descriptive*, *S = Somewhat descriptive*, and *V = Very descriptive*. For the HPB subscale (e.g., "has an extremely limited diet"), items are rated *N = Not a problem*, *MI = Minor problem*, *MO = Moderate problem*, and *S = Serious problem*. Responses are entered via an online scoring form, which produces scores for each subscale as well as a total score. For the ATEC, a higher score is indicative of more autistic severity. Previous research had shown high reliability, validity, and internal consistency ($\propto$ = .94), and convergent validity with cognitive and behavioral functioning on other established scales such as the Wechsler Intelligence Scale for Children-IV (WISC-

IV; Geier, Kern, & Geier, 2013; Magiati, Moss, Yates, Charman, & Howlin, 2011).

Data Analysis

Data Entry and Cleaning. Behavioral questionnaires were scored and entered by two independent research associates. HRV data were analyzed using Kubios version 2.2 (Biosignal Analysis and Medical Imaging Group, University of Eastern Finland, Kuopio, Finland). Smooth priors trend analysis was applied to all HRV samples. Artifacts were manually inspected and cleaned using automatic artifact rejecting. SDNN, RMSSD, and HF (.15–.40 Hz) were extracted; HF was then normalized using the natural log (lnHF). For subjects whose HRV was measured twice per week, data were averaged to create a single value for that week. Thus, all participants had weekly baseline HRV values. To compile a score of how often participants practiced their breathing at home, total minutes practiced each day were added up into a weekly total, which was summed across weeks.

EEG Analysis. Resting baseline qEEG data were cut into 2-sec epochs, resampled at 512 Hz, and log transformed. Fast Fourier Transform (FFG) absolute power values (uV Sq) for delta (1–4 Hz), theta (4–8 Hz), low alpha/mu (8–10 Hz), high alpha/mu (10–12 Hz), beta (12–25 Hz), and gamma (30–40 Hz) were computed in channel space using NeuroGuide software (Applied Neuroscience).

Raw data were also analyzed to determine significant neural oscillations within the frequency band of interest, namely mu band (8–12 Hz). From this, a mu suppression index (MSI) was computed. The MSI data from the video conditions were appended, resampled to 256 Hz, and mu power extracted. To control for individual differences in scalp thickness and electrode impedance, a ratio was used: MSI = Log [Mu Power (experimental/baseline)].

EEG Independent Component Analysis. EEG data were analyzed using the EEGLAB toolbox (Delorme & Makeig, 2004) for MATLAB. These data were processed using a preprocessing pipeline that removed artifactual (non-brain) signals originating from head movements, muscle twitches, eye blinks, heart rate, and line noise. The pipeline used a standardized script of EEGLAB functions to automatically remove these artifacts from the EEG data. Each dataset was initially run through an impulse response filter (FIR filter) with low and high pass frequencies set to 0.5 and 40 Hz, respectively. The channel-space data was then re-referenced to a computed average reference of the entire set of electrodes being recorded and channels assigned to the locations based on a standardized head model. Afterwards, the continuous data were visually inspected and unsuitable portions rejected. The data were then separated into suitable short epochs (~1 sec). An ICA was performed on these epochs to derive their independent components. Semiautomated and visual inspection-based rejection of data epochs on the derived components was then performed. This involved the use of the tools/component option in EEGLAB and the use of absolute voltage to determine power density spectra above zero in low frequencies, which likely reflected eye movements (coupled with scalp distribution to make sure it is centered frontally). Similarly, low frequency plus beta (> 30 Hz) was used as an indicator of muscle activity (coupled with scalp distribution centered laterally near ears or posteriorly for neck muscle movement). We further computed two markers for every component to examine the kurtosis (high kurtosis is typical of artifacts), entropy (low values are typical of artifacts) so that those with higher kurtosis and local low entropy were marked for rejection. Following rejection of the selected data epochs, we performed ICA a second time on the pruned collection of short data epochs—this improved the quality of the ICA decomposition, revealing more independent components accounting for neural, as opposed to mixed artifactual activity. The ICA unmixing and sphere matrices were then applied to (longer) data epochs from the same continuous data. Longer data epochs were useful for time/frequency analysis and are desirable for tracking other slow dynamic features.

Missing Data and Outliers. All missing data (behavioral, HRV, and EEG) were handled by a mean imputation. One participant was missing data on the Spence Anxiety Scale (T1, Group 2). One participant's scores were replaced with the group total mean at both T1 and T2 on the ATEC due to an error in recording (Group 2). Means were imputed for HRV data for two participants at week 1 (both groups); one participant at week 3 (Group 1); one participant at week 5 (Group 1); and one participant at week 6 (Group 1) due to poor signal collection. Two participants (Group 2) were missing breathing practice time logs, and they were excluded from analyses involving breathing practice time. Outliers were assessed by calculating *z*-scores and windsorizing data beyond 2.50 standard deviations from the mean; no outliers, however, were found within this range.

Results

The assumption of normality was tested for all variables using the Kolmogorov-Smirnov test. A small minority of variables violated this assumption (p > .05). Data were not transformed due to the robust nature of the statistical tests performed, with the exception of MSI data, which were transformed into the log of the ratio to normalize it. Homogeneity of variance was assessed using Levene's test. A small minority of variables violated this assumption across behavioral measures (p > .05); and a large portion of variables violated this assumption across HRV indices (p > .05). To normalize HRV data, a log10 transformation was attempted; however, this corrected only a minority of variables. Thus, all data were left in their original form and relied on the robust nature of the statistical tests performed.

Baseline Group Differences. An independent samples t-test revealed no significant differences between groups on any diagnostic features (ADOS-2, ADI-R, and WASI-II) at baseline, except on the nonverbal communication subscale of the ADI-R, $F(12) = .912$, $p = .024$, such that Group 2 scored higher (i.e., less adaptive; see Table 2). There were also no significant differences between groups in age or baseline HRV. A chi-square analysis revealed no significant differences between groups in gender, ethnicity, or medication status.

Behavioral Outcomes. A between-group repeated-measures ANOVA was conducted to test the hypothesis that participants in Group 2 would show greater improvements on the ERC, Spence, SRS, and ATEC than those in Group 1 (see Table 3). A main effect for time was seen on the ERC Lability/Negativity scale, $F(1) = 7.30$, $p = .018$, $\eta^2 = .359$ and the SRS Total Score, $F(1) = 18.56$, $p = .001$, $\eta^2 = .588$, indicating improvements over time in emotional lability/negativity and social behavior when both groups were collapsed. There was also a trend towards a significant main effect of time on the ERC Emotion Regulation scale, $F(1) = 4.41$, $p = .056$, $\eta^2 = .253$ and a nearly significant main effect of time on the ATEC Total Score, $F(1) = 4.59$, $p = .052$, $\eta^2 = .261$. There were no significant group X time interactions on the ERC, Spence, SRS, or ATEC (p > .05), suggesting that Group 1 did not differ from Group 2 over time on any of these variables.

Given the initial hypothesis that both Groups 1 and 2 would show improvements in the ERC, Spence, SRS, and ATEC over time, a within-group repeated-measures ANOVA was conducted on each group (see Table 3). In Group 1, there was a significant increase on the ERC Emotion Regulation scale from T1 ($M = 21.57$, $SD = 1.81$) to T2 ($M = 24.29$, $SD = 2.22$), $F(1) = 6.26$, $p = .046$, $\eta^2 = .511$, indicating improvements in emotion regulation. Group 1 also showed a significant reduction in the SRS Total Score from T1 ($M = 80.57$, $SD = 8.48$) to T2 ($M = 71.57$, $SD = 8.06$), $F(1) = 16.20$, $p = .007$, $\eta^2 = .730$, indicating improvements in social behavior. There were no significant changes over time for Group 1 on the ERC Lability/Negativity scale, Spence, or ATEC (p > .05). In Group 2, a significant decrease was observed on the ERC Lability/Negativity scale from T1 ($M = 32.38$, $SD = 6.28$) to T2 ($M = 27.38$, $SD = 5.24$), $F(1) = 5.98$, $p = .044$, $\eta^2 = .461$, indicating improvements in emotional lability/negativity. Group 2 also showed a significant increase on the ATEC Total Score from T1 ($M = 40.86$, $SD = 19.74$) to T2 ($M = 36.14$, $SD = 20.62$), $F(1) = 6.97$, $p = .033$, $\eta^2 = .499$, indicating improvements in autistic symptoms. There were no significant changes over time for Group 2 on the ERC Emotion Regulation scale, Spence, or SRS.

Table 3
Behavioral Outcomes Within- and Between-Groups.

		T1	T2	Within group			Between Group		
Measure	Group	Mean (*SD*)	Mean (*SD*)	*F*	*p*	η^2	*F*	*p*	η^2
ERC	1	34.71 (8.64)	32.71 (7.34)	1.83	.225	.233	1.34	.268	.093
(*LN*)	2	32.37 (6.28)	27.38 (5.24)	5.98*	.044	.461			
ERC	1	21.57 (1.81)	24.29 (2.22)	6.26*	.046	.511	.366	.556	.027
(*ER*)	2	23.38 (5.34)	24.88 (5.64)	.863	.384	.110			
Spence	1	1.57 (2.37)	1.71 (2.06)	.023	.884	.004	.069	.797	.005
(*PA*)	2	3.29 (4.65)	3.13 (5.79)	.052	.827	.007			

Table 3

Behavioral Outcomes Within- and Between-Groups.

		T1	T2	Within group			Between Group		
Measure	Group	Mean (*SD*)	Mean (*SD*)	*F*	*p*	η^2	*F*	*p*	η^2
Spence (*SA*)	1	3.43 (2.15)	3.29 (3.45)	.034	.859	.006	.233	.638	.018
	2	3.57 (3.20)	3.00 (3.12)	1.31	.290	.158			
Spence (*PIF*)	1	6.29 (1.70)	5.71 (3.30)	.495	.508	.076	.030	.866	.002
	2	4.86 (3.18)	4.13 (2.53)	1.75	.228	.200			
Spence (*SP*)	1	4.29 (4.11)	4.00 (4.66)	.135	.726	.022	.394	.541	.029
	2	4.71 (3.61)	3.63 (2.20)	1.23	.304	.149			
Spence (*OC*)	1	1.29 (1.11)	1.71 (2.14)	.260	.629	.041	2.69	.125	.171
	2	4.86 (2.0)	3.50 (2.33)	3.69	.096	.345			
Spence (*GA*)	1	4.00 (1.83)	2.57 (2.15)	4.84	.070	.446	.535	.477	.040
	2	4.58 (2.61)	3.75 (2.25)	2.49	.159	.262			
Spence (*Total*)	1	20.86 (8.76)	19.00 (14.55)	.189	.679	.031	.369	.554	.028
	2	25.86 (12.81)	21.13 (14.78)	3.88	.090	.357			
SRS (*SA*)	1	73.00 (8.85)	67.86 (9.86)	1.72	.238	.223	.332	.574	.025
	2	70.12 (11.87)	67.63 (11.05)	.936	.366	.118			
SRS (*SCog*)	1	78.57 (7.96)	70.43 (6.35)	34.4†	.001	.852	2.65	.127	.170
	2	71.75 (11.37)	69.13 (7.12)	.811	.398	.104			
SRS (*SCom*)	1	79.57 (6.66)	71.14 (9.62)	8.16*	.029	.576	3.09	.102	.192
	2	71.25 (10.90)	69.25 (7.32)	.789	.404	.101			
SRS (*SM*)	1	68.86 (8.59)	64.29 (6.53)	5.64	.055	.484	.267	.614	.020
	2	68.38 (12.86)	62.25 (10.74)	7.43	.030	.515			
SRS (*RRB*)	1	80.71 (12.91)	70.14 (7.11)	8.76*	.025	.594	.677	.425	.050
	2	78.00 (7.33)	71.50 (10.65)	3.63	.098	.341			
SRS (*Total*)	1	80.57 (8.48)	71.57 (8.06)	16.2**	.007	.730	2.75	.121	.174
	2	74.38 (8.56)	70.38 (6.35)	3.86	.090	.356			
ATEC (*SLC*)	1	2.29 (2.63)	2.29 (2.75)	.000	1.00	.000	.579	.460	.043
	2	4.00 (3.67)	3.43 (2.77)	1.58	.249	.184			
ATEC (*Soc*)	1	12.57 (3.05)	11.00 (4.08)	1.37	.286	.186	.000	.996	.000
	2	10.14 (5.94)	8.58 (5.12)	2.55	.155	.267			
ATEC (*SCA*)	1	10.29 (5.22)	6.86 (4.10)	2.03	.205	.252	.702	.417	.051
	2	9.71 (5.55)	8.29 (5.42)	3.37	.109	.325			
ATEC (*HPB*)	1	14.71 (7.68)	13.00 (6.08)	.487	.511	.075	.041	.842	.003
	2	17.00 (7.48)	15.86 (9.70)	.522	.493	.069			

Table 3

Behavioral Outcomes Within- and Between-Groups.

		T1	T2	Within group			Between Group		
Measure	Group	Mean (*SD*)	Mean (*SD*)	*F*	*p*	η^2	*F*	*p*	η^2
ATEC	1	39.86 (11.14)	33.14 (11.87)	1.57	.256	.208	.139	.715	.011
(*Total*)	2	40.86 (19.7)	36.14 (20.60)	6.97*	.033	.499			

*p < .05, **p <. 01, † p < .003 (Bonferroni correction applied for all subscales [.05/15 = .003])
ERC = Emotion Regulation Checklist (ER = Emotion Regulation; LN = Lability/Negativity); Spence = Spence Anxiety Scale (PA = Panic/Agoraphobia; SA = Separation Anxiety; PIF = Physical Injury Fears; SP = Social Phobia; OC = Obsessive Compulsive); SRS = Social Responsiveness Scale (SA = Social Awareness; SCog = Social Cognition; SCom = Social Communication; SM = Social Motivation; RRB = Restricted Repetitive Behaviors); ATEC = Autism Treatment Evaluation Checklist (SLC = Speech/Language Communication; Soc = Sociability; SCA = Sensory/Cognitive Awareness; HPB = Health/Physical/Behavior).

HRV. A between-group repeated-measures ANOVA was conducted to test the hypothesis that Group 2 would show greater improvements in HRV over time compared to Group 1. There was no main effect of time for SDNN, RMSSD, or lnHF ($p > .05$), nor any significant group X time interactions for SDNN, RMSSD, or lnHF ($p > .05$).

Given the initial hypothesis that Groups 1 and 2 would both show improvements in HRV over time, a within-group repeated-measures ANOVA was conducted on each group. As shown in Figure 5, in Group 1, there were no significant changes over time for SDNN, RMSSD, or lnHF ($p > .05$). However, in Group 2, RMSSD showed significant improvements over time, $F(11) = 2.04$, $p = .035$, $\eta^2 = .226$, although SDNN did not. Also in Group 2, lnHF showed significant improvements over time $F(11) = 2.23$, $p = .021$, $\eta^2 = .241$.

HRV as a Function of Breathing Practice. To test whether the amount of time practicing one's breathing at home predicted changes in HRV over time, a repeated-measures ANOVA with breathing time (BT) as a covariate was run on the sample as a whole (both groups: $N = 15$). There was a significant time x BT interaction for SDNN, $F(11) = 2.55$, $p = .006$, $\eta^2 = .188$, suggesting that the amount of time spent practicing breathing at home predicted changes in HRV over time. There was also a time x BT interaction for RMSSD, $F(11) = 2.96$, $p = .005$, $\eta^2 = .212$. BT did not significantly predict changes in lnHF over time ($p > .05$). Groups 1 and 2 did not significantly differ in the average amount time spent practicing breathing at home.

Resting State EEG. There were no group differences in EEG power in delta, theta, and gamma bands, or any pre–post effects in the resting state conditions. However, group differences approached significance for the alpha band, $F(1,13) = 3.47$, $p = .085$, $\eta^2 = .211$ with Group 2 showing a larger mean (8.48 uV^2) compared to Group 1 (5.1 uV^2). For the beta band, there was an interaction that approached significance with pre–post measures, $F(3,39) = 2.41$, $p = .082$, $\eta^2 = .156$ such that posttraining measures were larger (3.93 uV^2) than pretraining measures (2.69 uV^2).

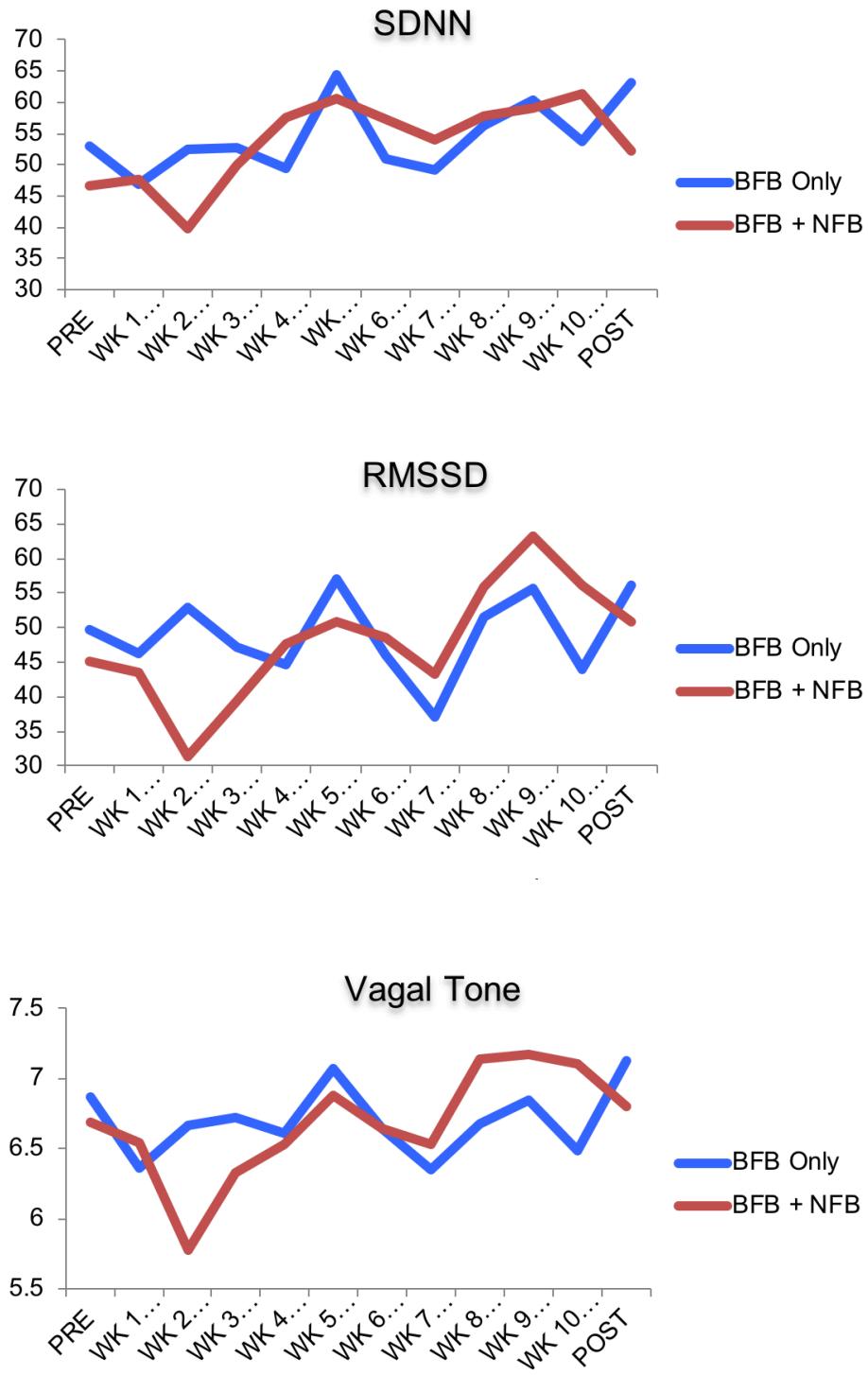

Figure 5. HRV Over the Course of Training for Groups 1 and 2. There were no significant differences between groups on SDNN, RMSSD, or vagal tone (lnHF) over time. Group 1 did not show any significant changes on SDNN, RMSSD, or vagal tone over time. However, Group 2 showed significant improvements in both RMSSD and vagal tone over time.

Mu Suppression. A mixed model ANOVA with pre–post (2), videos (hands, crayons, biomotion, social, self-movement), and electrode clusters (prefrontal, frontal, central, parietal, occipital) as within-subject factors and group (Group 1, Group 2) as a between subject factor was used to evaluate changes in mu rhythm suppression. There was a main effect of pre–post measures, $F(1,13) = 2.82$, $p = .023$, $\eta^2 = .340$ indicating a general reduction of mu suppression posttreatment (−.051 versus .072). As shown in Figure 6, a pre–post X group interaction, $F(1,13) = 3.14$, $p = .017$, $\eta^2 = .364$ showed that while Group 1 showed a small increase in mu suppression posttraining, Group 2 showed a marked reduction. As shown in Figure 7, a highly significant pre–post X clusters interaction, $F(4,52) = 4.40$, $p = .004$, $\eta^2 = .253$ showed that posttreatment measurement indicated large enhancements in mu synchrony (as opposed to suppression) over central and occipital cortices.

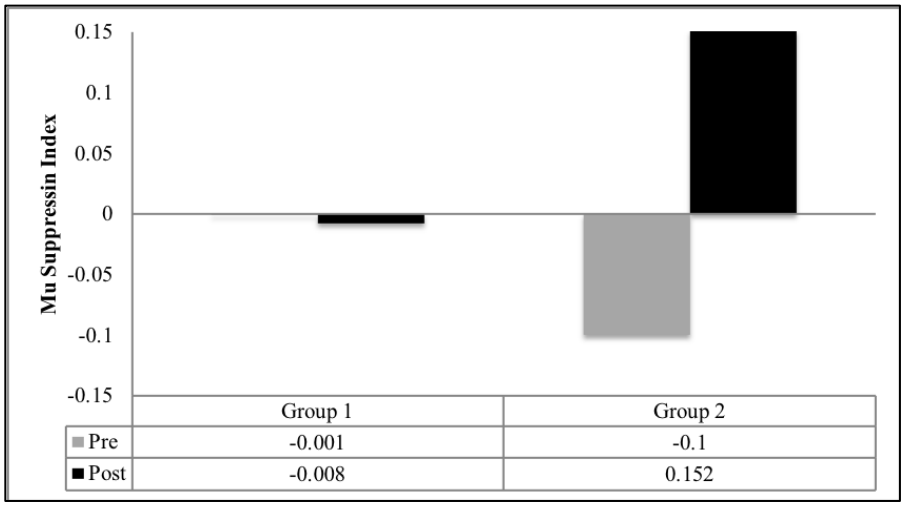

Figure 6. Effects of Training on Mu Suppression. Group 1 (HRV-BFB only) showed a small pre-post increase in mu suppression, while Group 2 (HRV-BFB + MRS-NFB) showed a marked pre–post reduction in mu suppression. Negative numbers represent more mu suppression.

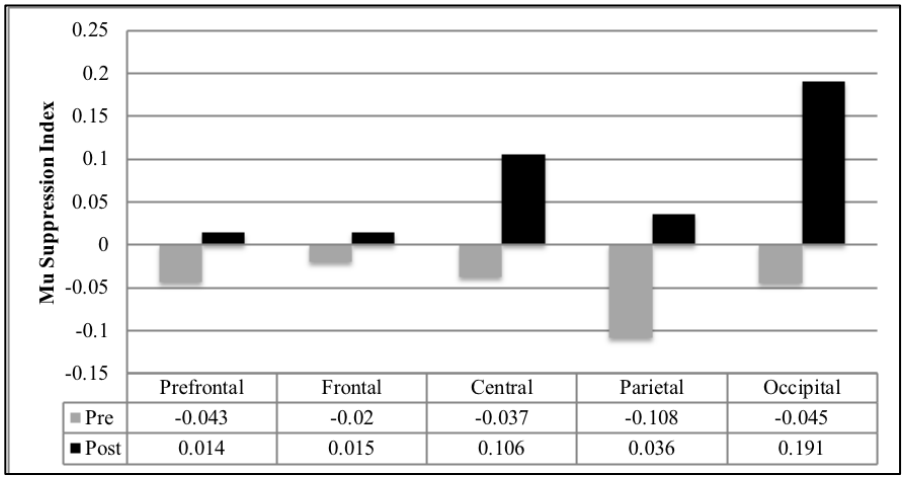

Figure 7. Training Effects on Mu Suppression Across Brain Clusters. Across both groups, the largest suppression effects were observed over frontal and parietal cortices, with posttreatment effects causing large enhancements in mu synchrony (as opposed to suppression) over the central and occipital cortices. Negative numbers represent more mu suppression.

Discussion

The current study evaluated whether HRV-BFB improved symptoms of ASD, and whether a combined HRV-BFB + MRS-NFB approach was more efficacious than HRV-BFB alone. It was hypothesized that HRV-BFB (Group 1) would lead to improvements in social behavior, autistic symptoms, emotion regulation, anxiety, and HRV; and that HRV-BFB + MRS-NFB (Group 2) would lead to greater improvements across each of these domains, in addition to increases in mu suppression. There were no differences between groups over time in social behavior, autistic symptoms, emotion regulation, anxiety, or HRV. However, Group 1 showed significant improvements in emotion regulation and social behavior, while Group 2 demonstrated significant improvements in emotional lability/negativity, autistic symptoms, and HRV. Significant time X group differences were found in mu suppression in a pattern contrary to our hypothesis: while Group 1 showed a small increase in mu suppression, Group 2 showed a large reduction in mu suppression (i.e., a less adaptive response).

The improvements observed in ASD behaviors following MRS-NFB are consistent with previous studies, including Friedrich et al. (2015) and Pineda et al. (2008), who found improvements on the ATEC and SRS using a similar training protocol. The effect of MRS-NFB on mu suppression in this study, however, stands in juxtaposition to previous literature. The decision to reward enhancements of alpha during NFB training was based on theoretical and experimental observations that learning to enhance alpha/mu power is a prerequisite for being able to suppress it (Pineda, 2005; Pineda et al., 2008; Pineda, Friedrich, & LaMarca, 2014). However, our results showed that rewarding alpha enhancements led to less mu suppression and greater resting alpha power. There are several possible explanations for why this may have occurred. First, it is certainly plausible that the outcomes were a direct result of the training protocol, and perhaps a reverse approach (i.e., training mu/alpha down) would be more appropriate. Friedrich et al. (2015) found that alpha enhancement training over C4 led to improvements in mu suppression over C4, but reductions in mu suppression over C3, in children with ASD during the socially-relevant biological motion task of the MSI (see EEG Analysis section); however, children who trained alpha both up and down over C4 showed an opposite pattern (i.e., decreases in mu suppression over C4, but increases in mu suppression over C3). In the current study, alpha enhancement training led to reductions in mu suppression over C4 during the socially-relevant biological motion task of the MSI. Thus, there is no clear pattern of outcomes with regard to an alpha enhancement protocol; or, it may be the case that distinct subgroups of ASD children may respond to different approaches. A second explanation is that the ability to suppress mu may require a longer period of training time than allotted in this study. While Friedrich et al. (2015) and Pineda et al. (2008) utilized 16 and 15 hr of MNS-BFB training, respectively, the current study utilized 12 hr of training. A third possibility is that a synergistic entrainment of alpha occurred in the HRV-BFB + MRS-NFB group, given that slow breathing may induce greater alpha due to relaxation. Previous studies have indicated a positive relationship between HRV and alpha (Casciaro et al., 2013). A fourth explanation is that the training protocol utilized was not inherently rewarding; in other words, the ability to control alpha based on DVD feedback (growing/shrinking of the screen) was not achieved, and pre–post differences were due to another variable unaccounted for. Finally, it is possible that results were skewed by poor EEG signals or the presence of artifacts during data collection. Many participants needed extensive artifact correcting due to excessive noise and signal overlap.

This is the first study to our knowledge to evaluate HRV-BFB as a potential intervention for autism. Study completion rates suggested that HRV-BFB is a feasible intervention to implement. However, there are also several barriers to using HRV-BFB in an ASD population. In the current study, several participants dropped out due to time commitment. Adjusting the frequency of laboratory visits from twice per week (1 hr each) to one per week (2 hr each) appeared to improve participant retention. Other potential obstacles to implementing HRV-BFB in children with ASD include age and level of functioning. Children in this study were at least nine years old and relatively high functioning; it was also anecdotally observed that younger participants, and participants lower on the spectrum, had more difficulty learning and executing the diaphragmatic breathing technique necessary for HRV-BFB. On the other hand, children who are lower functioning, and who present with lower baseline HRV, might benefit more from this intervention if they are able to learn the breathing technique: although there were no significant group differences at baseline, Group 2 had lower baseline HRV, lower IQ scores, and more severe autistic features, which might have raised

their ceiling for improvement and contributed to the significant increases observed in HRV.

In addition to suggesting that HRV-BFB and MRS-NFB are feasible interventions for ASD, this study has clinical implications beyond the use of BFB and NFB—which can be time and cost-intensive interventions. The positive effects observed in this study could potentially be due to diaphragmatic breathing practice versus BFB or NFB, per se. One finding was that children who practiced more diaphragmatic breathing at home had superior HRV outcomes. Diaphragmatic breathing teaches self-regulation of the ANS. Such changes not only influence comorbid features like emotion regulation, but also may impact social-emotional networks and improve core behavioral symptoms. For example, Uddin & Menon (2009) suggest that ASD characteristics may stem from multiple, overlapping networks including the SN, DMN, and ECN. The anterior insula, specifically, may be responsible for switching between the DMN and ECN and is thought to contribute to social-emotional dysfunction in ASD (Menon & Uddin, 2010; Uddin & Menon, 2009). The insula is also part of the CAN, thus pointing to a common node between autonomic, social-emotional, executive functioning networks. Other regions in the CAN, such as the amygdala, anterior cingulate, and orbitofrontal cortex, are also key players in social-emotional and executive networks that are known to contribute to ASD symptomology (Di Martino et al., 2009; Kana et al., 2007; Sabbagh, 2004).

There were several limitations to this study, and results should thus be contextualized within these limitations. The sample size was small which may have reduced power or contributed to differential outcomes across groups. For example, since HRV-BFB (Group 1) led to improvements in the SRS and emotion regulation subscale of the ERC, why didn't HRV-BFB + MRS-NFB (Group 2)—which contained the same HRV-BFB components of training—also lead to outcomes on the same scales? It is worth noting that Group 2 also showed improvements on the SRS; however, these changes were nonsignificant. Similarly, both Group 1 and Group 2 showed improvements on the ATEC; however, this effect was only significant for Group 2. A second limitation was the lack of a no-treatment control group. A comparison control group was not used in this study due to funding, resource, and recruitment limitations. It is possible that effects were simply due to time or nonspecific factors of the intervention. However, HRV tends to decrease with developmental age (Umetani, Singer, McCraty, & Atkinson, 1998), and even the flat slope observed in Group 1 (see Figure 5) may represent a health protective quality of HRV-BFB. Demand characteristics and parents' optimism about the intervention represent another important limitation. For parents of a child with ASD who are seeking treatment services, including "alternative" approaches such as the ones used in this study, there may be a strong bias towards positive clinical outcomes.

Although unlikely to significantly influence the results, another potential confound involved the modifications during the course of training. Six out of 15 participants completed twelve 1-hr training sessions, while the remaining nine participants completed six 2-hr sessions, with the time distribution being equal between groups. As noted earlier, this adjustment was made to enhance participant retention as it reduced the number of required lab visits. The decision to switch from a fixed reward threshold for alpha to a contingent reward threshold for Group 2 (see Modifications: Session Length and Mu Thresholds section) was made to enhance the NFB learning curve for Group 2. While this may have hindered or facilitated mu suppression/resting alpha power outcomes, this is unlikely to reverse trends or affect differences between groups, as both groups had the same HRV-BFB training.

This study was the first to suggest that HRV-BFB can positively affect symptoms of ASD. Similarly, MRS-NFB—either alone or in combination with HRV-BFB—can positively influence behavioral features of ASD; however, results from this study also raise further questions about how MRS-NFB affects mu suppression, at least when combined with HRV-BFB. Future studies might test alternative training protocols (e.g., inhibiting alpha) side-by-side with the current protocol (i.e., enhancing alpha). Further research should also include control conditions, including active or "sham" NFB/BFB control groups. Finally, future studies might examine whether daily diaphragmatic breathing (without the use of technology or complicated procedures) might positively impact ASD symptoms, given that this could be a simple, cost-effective method to improve behavioral regulation in autism.

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The authors declare that they have no conflict of interest.

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NeuroRegulation

Infra-Low Frequency Neurofeedback in Depression: Three Case Studies

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Abstract

Electroencephalographic (EEG) findings on depressive patients indicate theta and alpha activity higher than in normal controls. Extensive literature reports on the effectiveness of neurofeedback techniques in the treatment of cognitive and behavioral disorders by training the patients to modulate their brain activities, as reflected in their electroencephalogram. Three unmedicated, depressed individuals participated in this study of infra-low frequency neurofeedback (ILF NF) training. Along with the pre- and posttreatment Depression Rating Scales assessment, quantitative EEGs (qEEG) were recorded in eyes-open and eyes-closed resting states and during the visual cued Go/NoGo task before and after 20 sessions of training. Along with remission of the clinical symptoms of depression, significant decrease of theta power over frontal and central areas was observed in all three patients under all test conditions. These qEEG dynamics might be a correlate of ILF NF-related recovery of the appropriate level of frontal cortical activation.

Keywords: neurophysiology; neurofeedback; depression; qEEG; infra-low frequency

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Introduction

Depression is one of the most widespread mental health concerns, causing significant personal distress. The condition does not spontaneously remit in many individuals, and treatment is required for a return to an acceptable quality of life and ability to work. The clinical picture of depression is characterized by distinct emotional symptoms as well as by alterations of cognitive functions such as concentration, memory, and executive control (Austin, Mitchell, & Goodwin, 2001; Porter, Gallagher, Thompson, & Young, 2003).

Electrophysiological studies indicate abnormalities in spontaneous electroencephalogram (EEG) in depressed subjects as compared to healthy peers. The most consistent EEG findings are asymmetry in the alpha band expressed in the increased alpha power in the left frontal region (Davidson, 1995; Davidson & Henriques, 2000; Davidson et al., 2002; Tomarken & Keener, 1998) and/or in the right parieto-temporal region (Allen, Iacono, Depue, & Arbisi, 1993; Bruder et al., 1997; Henriques & Davidson, 1990), bilaterally increased frontal alpha (Brenner et al., 1986; John, Prichep, Fridman, & Easton, 1988; Lieber & Newbury, 1988; Pollock & Schneider, 1990). The inverse relation between alpha power in EEG and cortical activation (Cook, O'Hara, Uijtdehaage, Mandelkern, & Leuchter, 1998) can reflect cortical hypoactivation in these areas of the brain. Several studies reported an increase in slow-wave activity over the right (Kwon, Youn, & Jung, 1996; Volf & Passynkova, 2002) and left

(Roemer, Shagass, Dubin, Jaffe, & Siegal, 1992) hemispheres.

Elevated power in alpha, theta, and beta bands in posterior cortical areas was observed in our studies (Grin-Yatsenko, Baas, Ponomarev, & Kropotov, 2009, 2010). Increased theta power has been found in depressed patients in several studies (for review see Olbrich & Arns, 2013). A widespread scalp distribution of theta has been associated with decreased alertness and impaired information processing (Schacter, 1977). The few studies that have investigated theta in major depressive disorder (MDD) using source-localized theta have found this increased theta to be localized to the anterior cingulate cortex (ACC; Jaworska, Blier, Fusee, & Knott, 2012; Korb, Cook, Hunter, & Leuchter, 2008). The results of Pizzagalli, Oakes, and Davidson's study (2003) revealed a link between theta and cerebral metabolism in the ACC as well as disruption of functional connectivity within fronto-cingulate pathways in depression. Association of the increased widespread frontal theta with nonresponse to antidepressant treatment was reported in several studies (Arns, Drinkenburg, Fitzgerald, & Kenemans, 2012; Iosifescu et al., 2009; Knott, Telner, Lapierre, Browne, & Horn, 1996; Suffin & Emory, 1995). High frontal and rostral anterior cingulate theta was found in depressed patients in a study by Arns and colleagues (2016) and associated with treatment nonresponse.

EEG biofeedback (neurofeedback) has been found to be effective in modifying brain function and producing significant improvements in the clinical picture of depressive patients (Baehr, Rosenfeld, & Baehr, 2001; Hammond, 2000; Othmer, 1994; Rosenfeld, Baehr, Baehr, Gotlib, & Ranganath, 1996). The Othmer approach was an evolution of the original Sterman protocol for seizure management, which consisted of reinforcement of narrow-band EEG activity in the low beta band. Sterman had settled on 12–15 Hz as a standard approach (Sterman & Friar, 1972). This was referred to as the sensorimotor rhythm (SMR). Work with traumatic brain injury by Ayers (1987) led to the adoption of 15–18 Hz reinforcement (beta1) as a standard training band by Othmers as well, and recovery from the associated depression was routinely reported. Othmers then coupled left-hemisphere training in the beta1 band with SMR training of the right sensorimotor strip in order to address both the left and right hemisphere aspects of the depressive syndrome. By 1997 the training had moved off the sensorimotor strip to engage the prefrontal region with Fp1-C3 for improved activation, and the parietal region with C4-Pz for right-hemisphere overarousal (Othmer, Othmer, & Kaiser, 1999).

In the early years of this century the training frequencies started to be optimized for each client for improved training efficiency, and this led to a progression to ever lower target frequencies in order to meet the needs of the most challenging clients. Eventually this progression led to the adoption of training in the slow cortical potential (SCP) domain (i.e., below 0.1 Hz). This was referred to as infra-low frequency (ILF) training because it was still found to be highly frequency-specific. In this region one had direct access to a measure of cortical activation. That is to say, whereas the SCP reflects various physiological influences, the short-term dynamics of the signal appear to track the dynamics of cortical activation. By using bipolar montage, the measurement is sensitive to the differential cortical activation at the two sites.

The ILF training introduces some novelty into the standard training approach. The feedback to the client is based on a band-limited signal at frequencies below 0.1 Hz, the ILF region. Hence the signal is slowly varying, and thus potentially boring to the trainee. Moreover, the signal level on the screen is arbitrary; the sign of the signal is arbitrary; and the scale factor with which the signal is presented is arbitrary. In consequence, feedback options are provided in which the feedback signal is imbedded in visual imagery of greater visual interest. Thus, the feedback signal is likely to be covert in the perspective of the client. This means that the trainee is not able to volitionally follow the feedback signal. This in turn implies that feedback is contingent on detection of the relevance of the feedback signal to internal state. Trainees typically respond to the signal in a matter of minutes. This becomes apparent through the induction of state shifts—in arousal, vigilance, alertness, and in an emotional state.

This novel approach to training raises a number of questions that have been dealt with at length elsewhere. The question of the frequency-specificity was first treated theoretically in 2008 (Othmer, 2008). The question of how the brain engages with such slow signals is discussed at length in a more recent publication (Othmer & Othmer, 2017). The mechanisms of recovery are deemed to involve primarily induced alterations of both steady-state and dynamic functional connectivity (Othmer, Othmer, Kaiser, & Putnam, 2013). Evidence for this

proposition has recently been furnished through research performed at the Russian Ministry of Health in Moscow. Functional magnetic resonance imaging (fMRI) data were obtained on a number of trainees after single sessions of ILF neurofeedback using procedures identical to those at issue here. Some systematic changes in functional connectivity within the default mode were observed (Dobrushina, 2015).

The first publication on the new method was an observational study on the effect of the ILF training on chronic pain, in particular Complex Regional Pain Syndrome (CRPS1; Jensen, Grierson, Tracy-Smith, Bacigalupi, & Othmer, 2007). The second was a case series on combat-related PTSD (Othmer & Othmer, 2009). The third was a case series on pediatric epilepsy (Legarda, McMahon, Othmer, & Othmer, 2011). A fourth publication considered the application of the method to pediatric neurology generally (Othmer, Othmer, & Legarda, 2011). Finally, the method is placed in its historical context, and described in considerable detail, in a more recent publication (Othmer et al., 2013). Clinical data are shown for recovery from attentional deficits in a large cohort.

The goal of this study was to assess objectively the efficacy of infra-low frequency neurofeedback by comparing qEEG data before and after 20 sessions in depressed subjects, along with the assessment of the treatment results using three Depression Rating Scales. The working hypothesis is that the improvement of symptoms of depression correlates with decrease of alpha or theta power in EEG in the resting state and task conditions. The follow-up part of our study consisted of the assessment of the qEEG data and the Depression Rating Scales parameters in one year after the first, pretreatment examination.

Methods

Participants

Three depressed individuals participated in our study.

Case A. A 43-year-old male suffered from anxiety, depression, chronic fatigue, concentration and memory problems, chronic headache, and joint pain. He has a history of early childhood psychological trauma and difficulties with social communications. This could also be a case of high-functioning autism, but he was never examined to establish that diagnosis.

Case B. A 50-year-old male suffered from depression, loss of interest and motivation to engage in any activity, chronic fatigue, unexplained mood swings during the day, anxiety, tendency to hypercontrol, concentration and memory problems, learning difficulties, alcohol addiction, and sleep problems. He has a history of prenatal stress and childhood psychological trauma (he was brought up without a father).

Case C. A 35-year-old female with chronic fatigue and depression, problems with volitional regulation, the tendency of procrastination, and perfectionism. She also suffers from concentration and working memory problems for the last several years, as well as premenstrual syndrome (PMS). She has a history of early childhood psychological trauma and difficulties with social communication in childhood.

Patients A and B have suffered from depressive complaints for decades; patient C only for the last 6 months. None of the patients sought out doctors for their condition, nor had they ever taken antidepressants.

The baseline investigation consisted of symptom profiles, Depression Rating Scales: Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAMD), and Beck Depression Inventory (BDI); qEEG in eyes-closed, eyes-open conditions, and in visual cued Go/NoGo test. This took place 1–7 days before undertaking the course of NF training sessions. qEEG parameters were compared with the HBI normative Database. All the tests were repeated after 20 sessions in 1–7 days after the last session, and then again in one year after the first testing. The results of the second and third testing were compared with the pretreatment baseline.

The investigation was carried out in accordance with the declaration of Helsinki and has been approved by the ethics committee of the Institute of Human Brain of the Russian Academy of Sciences, Saint Petersburg. All participants gave written informed consent prior the experiments.

EEG Investigation

EEG was recorded using a Mitsar 21-channel EEG system (Mitsar, Ltd, St. Petersburg, Russia). Nineteen silver-chloride electrodes were applied according to the International 10-20 system. The input signals referenced to linked ears were filtered between 0.5 and 50 Hz and digitized at a rate of 250 Hz. The ground electrode was placed on the forehead. All electrode impedances were kept

below 5 kΩ. EEG was recorded in eyes-closed and eyes-open resting conditions, at least three minutes for every period, and during performance of the visual cued Go/NoGo task that uses pictures of 20 different animals, 20 different plants, and 20 different humans (together with a distracting beep tone) as stimuli (Kropotov, 2009). One trial consisted of the sequential presentation of two pictures (prime and target), presented for 100 ms each, with an ISI of 1000 ms (SOA = 1100 ms). Trials were separated by 1500 ms. Patients were instructed to press the left button of the computer mouse as quickly as possible when an animal was followed by an animal (Go condition), and not to respond when an animal was followed by a plant (NoGo condition), or when a plant was followed by a plant or a human (distractor condition). The response interval lasted from 100 to 1000 ms. The task consisted of 100 Go trials, 100 NoGo trials, and 200 distractor trials. Trials were presented pseudo-randomly with equal probability. All trials were presented to the subject on a computer screen 1.5 m in front of them using the PsyTask software (Mitsar Ltd., St. Petersburg, Russia). The centrally presented stimuli subtended an approximate visual angle of 3°. Trials with omission and commission errors were excluded from analysis. Quantitative data were obtained using WinEEG software. The epochs with excessive amplitude of nonfiltered EEG and/or excessive high and slow frequency activity were automatically marked and excluded from further analysis.

Neurofeedback

The instrument used for the clinical neurofeedback was the Cygnet system (BEE Medic), consisting of the NeuroAmp II and Cygnet software, integrated with Somatic Vision video feedback and run on a Windows 7 operating system using a standard personal computer (PC) with a high-resolution monitor. The optimal reinforcement frequency (ORF) was determined for each subject at the beginning of each neurofeedback session on the basis of subjective patient's report. Training was performed with bipolar placement of silver/silver chloride scalp electrodes applied using Ten20 Conductive electrode paste at T4-P4 and T4-Fp2 (according to standard 10-20 system) during the first several sessions, with subsequent adding of T4-T3 and T3-Fp1 locations. The "ground" electrode was placed at Fpz. Each patient received 20 separate 30- to 45-minute neurofeedback sessions over a period of 7–8 weeks. For each subject the frequency in the infra-slow band was selected individually with bipolar recordings at P4-T4, T4-Fp2, T3-T4, and T3-Fp1. The localization of electrodes was based on the neurofeedback approach developed by Susan Othmer (2017), which involves parameter optimization based on the clinical response.

Statistical Analysis

The Student criterion was used to estimate statistical significance of differences of EEG spectra values when comparing individual data with the HBI Normative Database and the dynamics of individual EEG spectral parameters after and before treatment. This analysis was performed for each condition (EO, EC, and the Go/NoGo task) separately and was carried out for total signal power in five frequency bands: δ (1.5–4.0 Hz), theta (4–8 Hz), α (8–12 Hz), β1 (12–20 Hz) and β2 (20–30 Hz), that was computed as a sum of power for corresponding frequencies.

Results

Assessment Before Initiating Neurofeedback

Case A. *Depression scales and inventory.* MADRS rating = 26. BDI rating = 16. HAMD rating = 21. In sum the Depression scales ratings indicated moderate degree of depression.

EEG investigation (as compared to the HBI Normative Database). Eyes-open state: elevated absolute theta activity of 6–8 Hz over midline frontal-central area (Fz, Cz) (t = 2.23, p < .05) and relative beta2 activity over the parietal and posterior temporal area (t = −2.94, p < .01); increased relative α power (8–9.5 Hz) over occipital, parietal, and posterior temporal cortical areas with maximal difference at P4 (t = 2.66, p < .01).

Eyes-closed state: increased relative slow α activity of 7.5–8.5 Hz over occipital, parietal, and posterior temporal areas (t = 2.58, p < .05) and relative beta2 activity over frontal-central area (t = 3.47, p < .001).

Go/NoGo task: increased absolute theta activity of 5.5–7 Hz over frontal area (t = 2.04, p < .05), and absolute beta2 activity of 25–28Hz over midline frontal area (Fz; t = 2.38, p < .05). Slow α rhythm spread over anterior cortical areas, relative slow α power (7.5–9.5 Hz) is increased over occipital, parietal, and posterior temporal cortical areas with maximum at P3 (t = 2.65, p < .01).

The increased level of theta and slow α activity over the frontal area might be a correlate of poor concentration, and with depressive symptoms. Enhanced high beta power over frontal-central region can be a sign of anxiety.

Case B. *Depression scales and inventory.* MADRS rating = 20. BDI rating = 26. HAMD rating = 16. In sum the Depression scales ratings indicated mild to moderate degree of depression.

EEG investigation (as compared to the HBI Normative Database). Eyes-open state: increased relative α power of 9.5–10.5Hz over parietal, central and frontal areas, maximal at Cz (t = 2.54, p < .05). Episodic groups of α and theta waves arise at temporal sites of both left and right hemispheres.

Eyes-closed state: α rhythm of 10 Hz spread over frontal cortical areas, episodes of α and theta waves at temporal sites of both left and right hemispheres.

Go/NoGo task: Increased relative α power of 9.5–11Hz over temporal, central and frontal areas, maximal at Cz (t = −2.46, p < .05).

The increased level of α activity over frontal area, and increased α and theta activity over temporal areas might be a marker of chronic stress, depression, fatigue, and poor concentration.

Case C. *Depression scales and inventory*. MADRS rating = 17. BDI rating = 18. HAMD rating = 15. In sum the Depression scales ratings indicated mild to moderate degree of depression.

EEG investigation (as compared to the HBI Normative Database). Eyes-open state: episodes of spreading of α rhythm over frontal cortical areas. Increased absolute beta2 (t = −3.70, p < .001) and increased relative theta (t = −5.63, p < .0001), α (t = −3.82, p < .001) and beta2 (t = −3.44, p < .001) activity over frontal areas.

Eyes-closed state: increased relative theta power over parietal (t = −4.78, p < .0001) and left posterior temporal area (t = −2.99, p < .001); prevalence of α rhythm of 11 Hz over the left parietal-occipital area, spreading of α rhythm over frontal cortical areas.

Go/NoGo task: Increasing of both absolute (t = −2.79, p < .01) and relative (t = −2.91, p < .01) beta2 activity over frontal and central area.

The spreading of α activity over the frontal area might be a correlate of poor concentration, volitional regulation and working memory, and also with depressive complaints. Increased beta activity and high-frequency basic rhythm can be the signs of high vigilance and perfectionism.

Posttreatment Assessment

Case A. After completion of 20 neurofeedback (NFB) sessions, the patient indicated disappearance of tension in his body and an increase of energy level. He has improved the perception of his body and the surrounding space. His headaches became less intense and arose more seldom. He reported on improvement of concentration and stable positive mood from the middle of the training course.

Control assessment. The Depression profile score during the second testing was: MADRS rating = 2 (improvement of 92.3%). BDI rating = 1 (improvement of 93.75%). HAMD rating = 2 (improvement of 90.5%). After NFB course the Depression scales ratings indicated no signs of depression.

EEG in eyes-open condition (Figure 1) showed significant decrease of both theta (t = 12.80, p < .0001) and beta2 (t = 5.88, p < .0001) activity at frontal and central sites; during Go/NoGo task performance decreasing of absolute theta (t = 5.68, p < .0001), and beta2 (t = 288.71, p < .001) power was also most prominent over frontal and central cortical areas (Figure 3). The absolute α rhythm power decreased significantly at all sites mostly in eyes-open condition with maximal differences at P4 (t = −6.60, p < .0001), which reflects the higher cortical activation. In eyes-closed state α power increased in parietal cortical areas (Figure 2), which might relate to a better ability to relax.

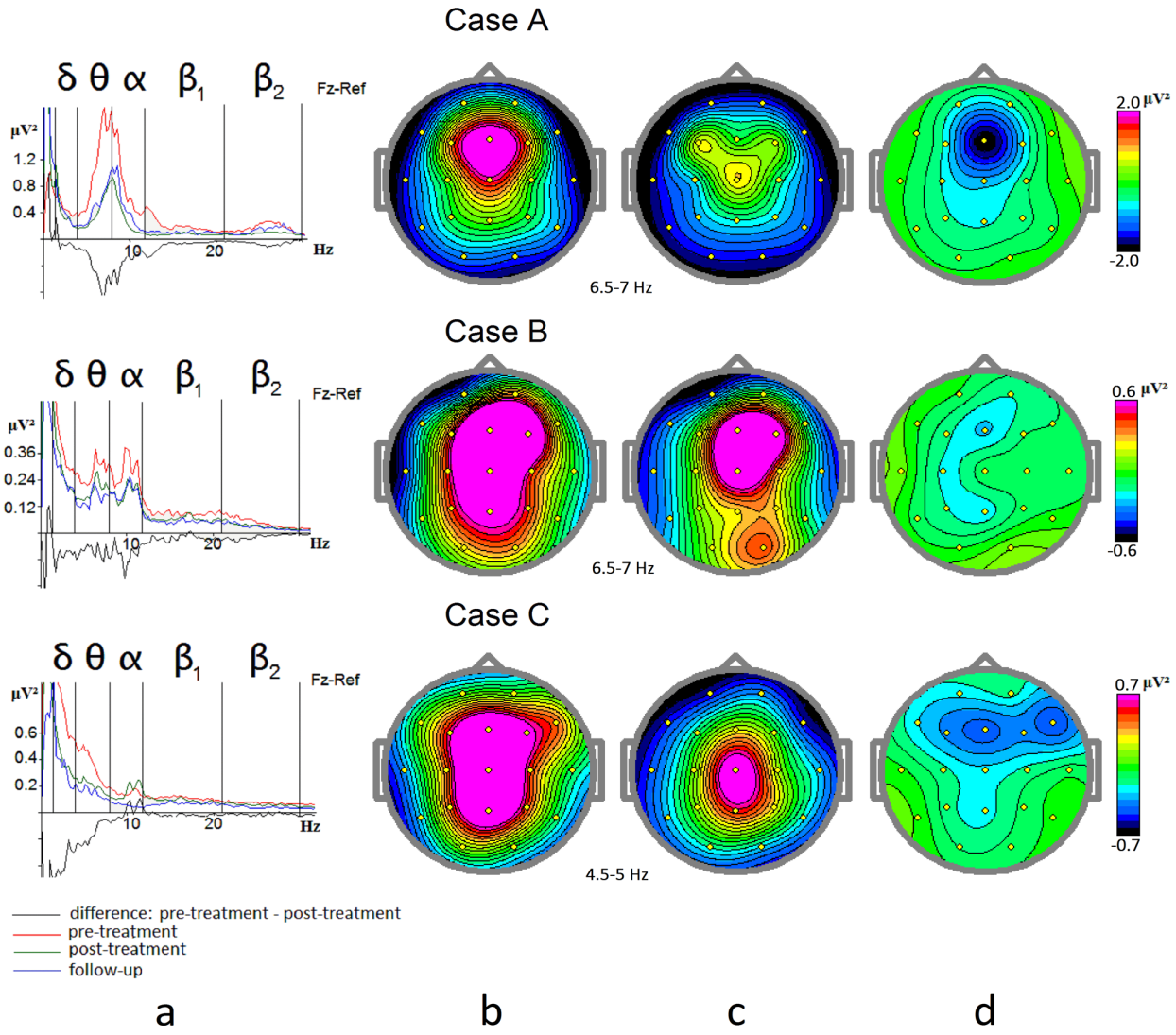

Figure 1. Dynamics of EEG spectra after ILF NF course in depressed patients in eyes-open condition. Grand average power spectra of the raw EEG in patients A, B, and C are presented in (a). X-axis = frequency in Hz, Y axis = power in μV². Maps of theta power in the selected frequency band (indicated below the maps) in pretreatment and posttreatment EEGs are represented in (b) and (c) correspondingly. Maps of difference of theta power in the selected frequency between posttreatment and pretreatment EEGs are shown in (d). Scale is presented at right of the maps.

Case B.

After completion of 20 NFB sessions, the patient reported a dramatic decrease of inner tension and reactivity to stressful situations. His emotional stability increased, and the level of anxiety diminished. Relationship with other people improved; he began to understand them better. He has significantly reduced the use of alcohol. He reported that confidence, calmness, and a sense of power had returned to him. The depressive mood disappeared, and he felt clarity in his mind and had constructive ideas on the organization of his future life.

Control assessment. The Depression profile score during the second testing was: MADRS rating = 6 (improvement of 70%). BDI rating = 2 (improvement of 92.3%). HAMD rating = 5 (improvement of 68.75%). After NFB course the Depression scales ratings indicated no signs of depression.

EEG showed a significant decreasing of power of both alpha (t = 7.97, p < .0001) and theta (t = 48.74, p < .0001) activity over frontal area in eyes-open state (Figure 1), and decreasing of theta power over frontal, central and parietal area during Go/NoGo task performance (Figure 3) with maximal changes at Fz (t = 2.39, p < .05), which might be a result of better activation of frontal cortex. In eyes-closed state the maximum of alpha rhythm power shifted from the parietal to the occipital area (Figure 2), which is a normal distribution of the alpha rhythm with eyes closed.

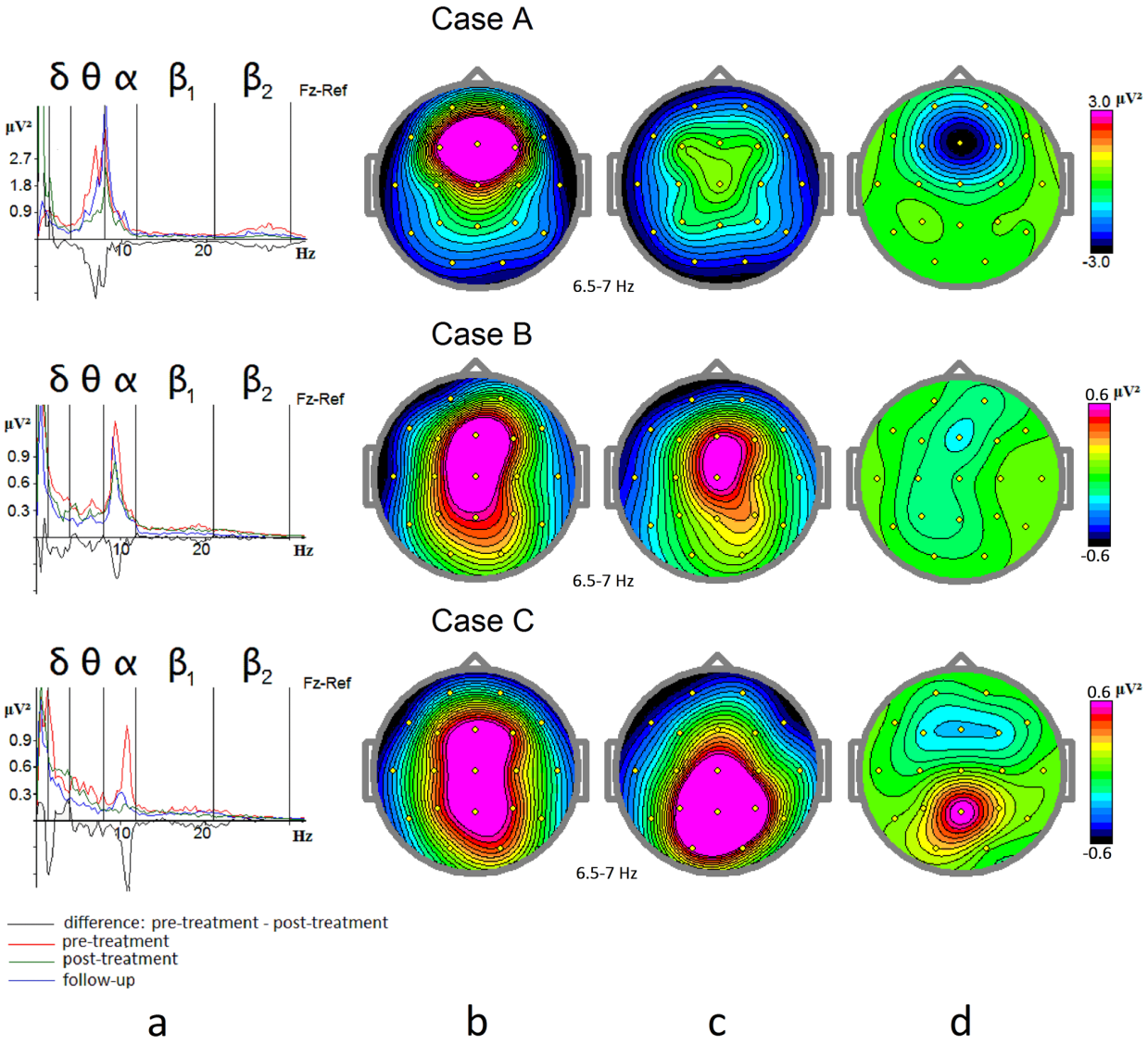

Figure 2. Dynamics of EEG spectra after ILF NF course in depressed patients in eyes-closed condition. Grand average power spectra of the raw EEG in patients A, B, and C are presented in (a). X-axis = frequency in Hz, Y axis = power in μV². Maps of theta power in the selected frequency band (indicated below the maps) in pretreatment and posttreatment EEGs are represented in (b) and (c) correspondingly. Maps of difference of theta power in the selected frequency between posttreatment and pretreatment EEGs are shown in (d). Scale is presented at right of the maps.

Case C. After completion of 20 NFB sessions, the patient reported remarkable improvement of her mood and decrease of anxiety level. She became calmer, more able to deal with sudden unplanned and stressful events. She developed the intention to act to achieve new goals and a clear understanding of what activities are necessary and valuable, and which are not. She started to exercise regularly; her mental performance and success at work increased remarkably.

Control assessment. The Depression profile score during the second testing was: MADRS rating = 4 (improvement of 76.5%). BDI rating = 3 (improvement of 83.3%). HAMD rating = 3 (improvement of 81.4%). After NFB course the Depression scales ratings indicated no signs of depression.

EEG showed a significant decreasing of power of theta activity (t = 3.82, p < .001) at frontal and central sites in eyes-open condition (Figure 1), and decreasing of theta power over frontal and central sites during Go/NoGo task (t = 11.45, p < .0001), which might be a correlate of the higher cortical functional activity in this region (Figure 3).

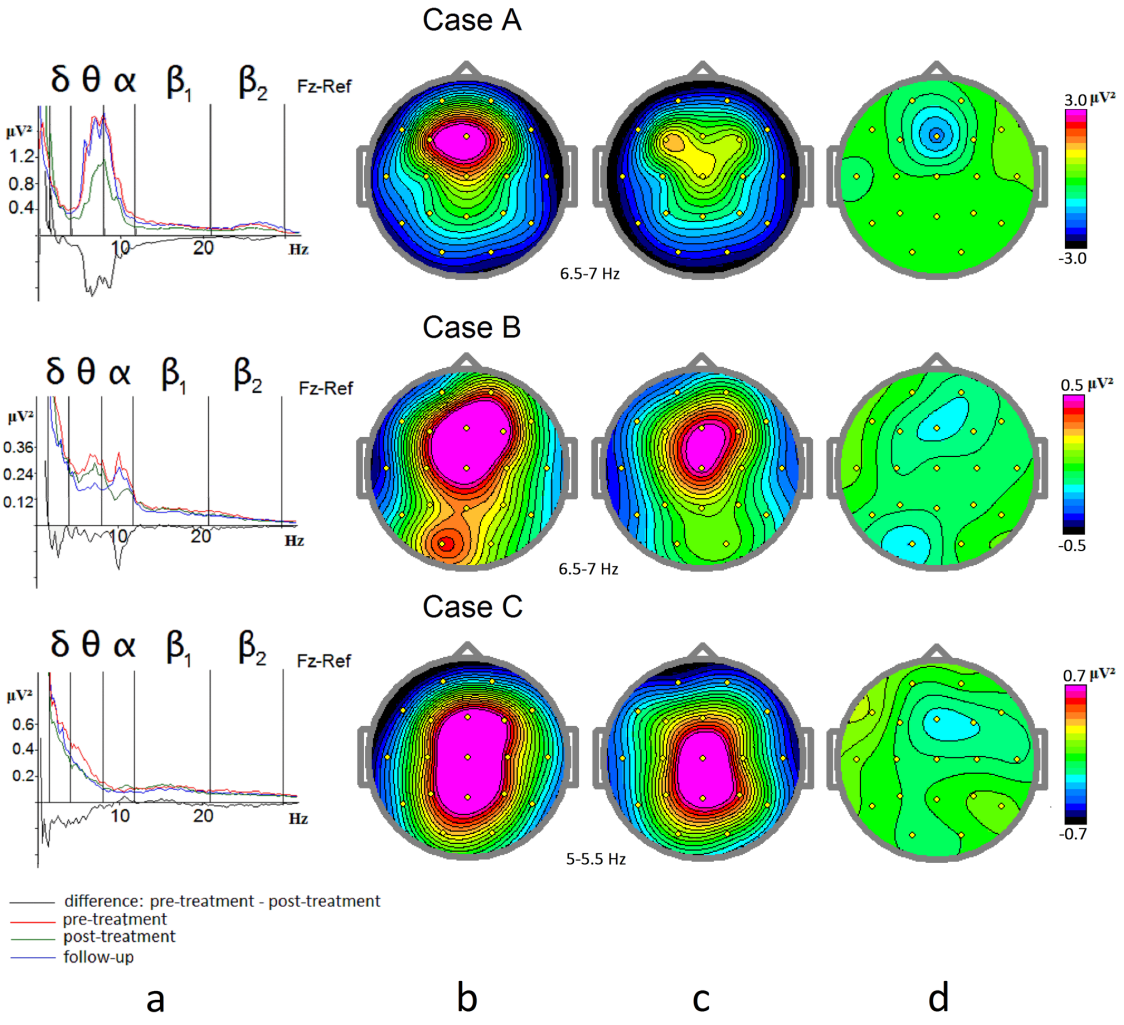

Figure 3. Dynamics of EEG spectra after ILF NF course in depressed patients during Go/NoGo task performance. Grand average power spectra of the raw EEG in patients A, B, and C are presented in (a). X-axis = frequency in Hz, Y axis = power in μV². Maps of theta power in the selected frequency band (indicated below the maps) in pretreatment and posttreatment EEGs are represented in (b) and (c) correspondingly. Maps of difference of theta power in the selected frequency between posttreatment and pretreatment EEGs are shown in (d). Scale is presented at right of the maps.

Follow-up Assessment

Case A. One year after the start of the ILF NF course, the patient reported that all positive changes in his state remained despite the fact that he has been overloaded by work. He perceives his thoughts, emotions, and moods mindfully, and he is able to manage them. The headaches arise very seldom, and his improved concentration has maintained.

Control assessment (as compared to the pretreatment assessment). The Depression profile score during the second testing was: MADRS rating = 0 (improvement of 100%). BDI rating = 1 (improvement of 94%). HAMD rating = 0 (improvement of 100%). The Depression scales ratings indicated no signs of depression, and the scores improved as compared to in posttreatment assessment.

EEG. Decrease of theta activity at frontal and central sites observed after treatment remains in the third EEG in eyes-open (Figure 1) and eyes-closed (Figure 2) state. However, during Go/NoGo task performance theta power at anterior sites returned to the pretreatment level (Figure 3). Alpha power decreased at central and parietal sites in all states, and increased at occipital sites in the last EEG, which corresponds to the normal alpha rhythm distribution.

Case B. One year after the pretreatment investigation, the patient reported that improvement of his mood after ILF NF remained steady. He does not suffer from the mood swings any more, and depressive and unsettling thoughts arise quite rarely. He seldom uses alcohol, sleeps well, his emotional stability and level of energy are high, and he experiences “lust for life.” Yet there remain the concentration problems, and his memory is still poor.

Control assessment (as compared to the pretreatment assessment). The Depression profile score during the second testing was: MADRS rating = 5 (improvement of 75%). BDI rating = 9 (improvement of 69.3%). HAMD rating = 3 (improvement of 81.4%). The Depression scales ratings indicated no signs of depression, and the scores even improved as compared to the posttreatment assessment for two of the three scales.

EEG. Decreasing of theta and alpha activity at frontal sites observed after treatment remains in the third EEG in eyes-open (Figure 1) and eyes-closed (Figure 2) states, and during Go/NoGo test (Figure 3). Frontal theta power during Go/NoGo task is lower than in posttreatment EEG. There remains a decrease of alpha power (as compared to the pretreatment EEG) in parietal region and alpha prevalence in occipital area in eyes-closed state.

Case C. One year after the first (pretreatment) investigation, the patient reports that the positive shift in her mood obtained after the course of treatment remains stable. She does not suffer from depression or fatigue since the training finished. At the same time, she sometimes experiences procrastination and insufficient concentration.

Control assessment (as compared to the pretreatment assessment). The Depression profile score during the second testing was: MADRS rating = 4 (improvement of 76.5%). BDI rating = 5 (improvement of 72.2%). HAMD rating = 3 (improvement of 80%). The Depression scales ratings indicated no signs of depression, and the scores are about the same level as in posttreatment assessment.

EEG. The decrease of theta activity at frontal and central sites in eyes-open condition (Figure 1) and during Go/NoGo test performance (Figure 3) observed after treatment remains in the third EEG. Alpha power decreased at all sites in eyes-open state and during Go/NoGo test. In eyes-closed state (Figure 2) the initially excessive alpha power decreased all over the scalp, but predominantly in parietal and occipital cortical areas of the left hemisphere.

Discussion

In our study, we selected a protocol that implemented infra-slow EEG frequencies (below 0.1 Hz) as a biofeedback parameter in three depressed individuals. The time course of the signal at these very slow frequencies reflects variations in cortical excitability (Vanhatalo et al., 2004; van Putten, Tjepkema-Cloostermans, & Hofmeijer, 2014). This suggests that the most direct effect of the neurofeedback challenge is on the regulation of tonic central arousal. The within-session effects of perceived calming are consistent with this hypothesis.

The choice of principal electrode placements was driven originally by considerations of functional neuroanatomy and was then refined on the basis of empirical observation over the course of many years (Othmer, 2017). The principal sites correspond with the multimodal association areas in cortex, which

reflect cortical activity at its most integrative stage. These are also the regions most readily subject to dysregulation. Further, these sites correspond to those regions in which the principal hubs of the default mode are accessible to us at the cortical surface (Buckner, Andrews-Hanna, & Schacter, 2008). Since engagement with the outside world constitutes at most a modest perturbation on baseline activity, as demonstrated by cortical hemodynamics, the burden of functionality is carried mainly by our task-negative network, the default mode, and the training addresses itself to that as a first priority (Raichle, 2011). A secondary objective is to train the salience network, which mediates between the task-negative and the task-positive network, the Central Executive. Menon (2011) has made the case that a number of major psychopathologies can be traced to deficits in the functional connectivities within and among our intrinsic connectivity networks. Broyd et al. (2009) have evaluated the role of the default mode in mental disorders more inclusively.

On the basis of the Menon model, the favorable outcomes in this study may be attributed at least partly to the renormalization of functional connectivity within the default mode, and to altered relationship between the default mode, the Salience Network, and the Central Executive. That in turn would imply improved functionally specific activation, which could also account for the remediation of the depressive state. This hypothesis remains to be proved through independent measurement.

For the above reasons, our approach differs from the conventional protocols for the treatment of depression that are based on models of altered hemispheric asymmetry, and use either an alpha asymmetry protocol (Baehr & Baehr, 1997; Baehr et al., 2001; Baehr, Rosefeld, Baehr, & Earnest, 1998, 1999; Choi et al., 2011; Dias & Van Deusen, 2011; Earnest, 1999; Rosenfeld, 2000; Rosenfeld et al., 1996) or a relative left frontal beta enhancement with concomitant theta suppression (Othmer et al., 1999), or a theta/beta ratio reduction (Dias & Van Deusen, 2011). However, as the results of the present study indicate, the application of our protocol turns out to be as effective as conventional protocols.

In each of three patients 20 sessions of this type of neurofeedback considerably improved mood and self-organization skills, decreased anxiety and inner tension, and increased emotional stability and stress tolerance. Their clinical symptoms, as assessed with the Depression Rating Scales: MADRS, HAMD and BDI, improved significantly and did not indicate depression any more. Moreover, the improvements of the Depression profile scores obtained after ILF NF training remained stable over one year after the beginning of ILF NF course in all three patients.

Pretreatment qEEG investigation in two participants of our study revealed absolute and/or relative theta, alpha, and beta2 elevation, as compared to the normative database, in passive conditions and during Go/NoGo task performance. The differences were observed mostly in frontal and central areas of the brain. These findings are in agreement with studies that found abnormally large theta (Jaworska et al., 2012; Korb et al., 2008; Strijkstra at al., 2003) and alpha (Lieber & Newbury, 1988; Pollock & Schneider, 1990) power in depressed patients in anterior regions, which may relate to diminished frontal cortical activation (Cook et al. 1998; Strijkstra at al., 2003). Enhanced beta activity is also reported in depressed patients (Fingelkurts et al., 2006; Grin-Yatsenko et al., 2009, 2010; Shankman & Klein, 2003; Yamada, Kimura, Mori, & Endo, 1995). This phenomenon was observed in the EEG when anxiety symptoms were part of the clinical picture. In one patient, pretreatment theta and beta were borderline normal, but relative frontal and central alpha activity was elevated.

Our study showed that ILF NF sessions led to a significant decrease of theta power over frontal and central areas in all three patients in passive states and during Go/NoGo task performance. Besides, frontal alpha and beta decreased in those patients in whom the pretreatment powers in these bands were enhanced. These EEG spectral dynamics might be a correlate of ILF NF related recovery of the level of frontal cortical activation.

The results of this research are comparable to the data of previously reported studies (Baehr, Rosefeld, & Baehr, 1998; Dias & Van Deusen, 2011; Earnest, 1999; Rosenfeld et al., 1996), which used neurofeedback based on EEG spectra in depression. Recent studies report on the role of infra-slow cortical potential oscillations in the modulation of conventional frequency bands (Lörincz, Geall, Bao, Crunelli, & Hughes, 2009; van Putten et al., 2015). Therefore, modulation of these infra-slow oscillations during ILF NF sessions could exert a modulating and normalizing influence on EEG bands in depressed individuals participated in our study. Conversely, conventional band training could derive its effectiveness at least partially from the correlation with infra-low frequency activity. Both methods appear successful in mobilizing a system response that gradually allows functional

renormalization to occur. This may explain the similarity of positive results in treatment of depression in our study and in the works of researchers who used the conventional EEG spectra neurofeedback in treatment of this disorder.

The follow-up qEEG data showed that decreased frontal theta power remained stable in two patients. Still in one patient theta went up almost to the pretreatment level during the Go/NoGo task challenge, despite the fact that his clinical achievements were sustained, and baseline EEG measures were maintained in their posttraining status. This observation could indicate some ambiguity in the relationship of changes in the level of theta activity and the efficiency of functioning of the affective network. The elevated theta activity could simply be the result of increased cognitive demand. Probably the interrelation of these characteristics is more complex than a direct relationship.

The present study reveals qEEG correlates of ILF NF in depression. It shows that not only psychophysical parameters of affective network functioning improve by the neurotherapy, but also objective neurophysiological parameters change, reflecting improvement of emotional stability and control in depressed individuals after ILF NF.

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Conflict of Interest

The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article. The second author (SO) was only involved in a critical review of the manuscript but had no ability to influence the research design, the conduct of the research, or the analysis and presentation of the data.

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NeuroRegulation

Biofeedback and Anger Management: A Literature Review

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Abstract

The purpose of this article was to systematically review the literature on the effects of biofeedback therapy on anger. Biofeedback methods are shown to be effective in the treatment of a number of health conditions; however, a systematic review of biofeedback therapies on anger management has yet to be conducted. Results of the literature review show that little attention was given to anger over the years in comparison to other health and emotional conditions. Research is needed to determine whether biofeedback is an efficacious treatment for emotional regulation.

Keywords: biofeedback; anger; emotion regulation

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Anger is an internal state involving various degrees of, and interactions between, physiological, affective, cognitive, and verbal components (Sharkin, 1988). Anger is a naturally occurring emotion expressed on a continuum; however, over time pent up anger can become expressed in ways that become problematic such as assault, violence, and property damage (e.g., Levey, 1990; Maiuro, Cahn, Vitaliano, Wagner, & Zegree, 1988). Because anger is often accompanied by other negative behaviors—such as aggression, hostility, and health issues—it is important to explore anger as an independent outcome. Del Vecchio and O'Leary (2004) point out that the concept of anger is considered distinct from the concepts of hostility, aggression, and violence and therefore merits separate analysis. Patients with anger issues often display problems with self-regulation that interfere with adaptive functioning (Berenbaum, Raghavan, Le, Vernon, & Gomez, 2003). One way to teach individuals how to effectively manage their anger is through biofeedback.

Biofeedback—a term for any intervention that uses medical equipment to monitor body function that is otherwise outside of our awareness—is a mind–body technique to help people learn to better control involuntary physiological responses. However, biofeedback is not a passive "treatment," such as electrotherapy or ultrasound; instead, it is a noninvasive method where a person actively learns how to control bodily processes. The feedback helps a person focus on making subtle bodily changes such as recognizing when muscles are tense and relaxing those muscles or focusing on heart rate and breathing patterns.

In 2008, the Association for Applied Psychophysiology and Biofeedback (AAPB), the Biofeedback Certification International Alliance (BCIA), and the International Society for Neurofeedback and Research (ISNR) agreed upon a working definition for biofeedback:

> Biofeedback is a process enabling an individual to learn how to change physiological activity for the purposes of improving health and performance. Precise instruments measure physiological activity such as brain waves, heart function, breathing, muscle activity, and skin temperature. These instruments rapidly and accurately provide 'feedback' information to the

user. The presentation of this information—often in conjunction with changes in thinking, emotion, and behavior—supports desired physiological changes. Over time, these changes can endure without the use of an instrument.

In the years since 1990, as shown in Figure 1, the popularity of biofeedback has exploded, both in the literature and in practice. Biofeedback training is offered in physical therapy clinics, medical centers, universities, and hospitals (AskMayoExpert, 2015). In addition, a growing number of biofeedback devices are being marketed for home use (Mayo Clinic, 2016). Only a few articles were published between 1960 and 1989 (e.g., Baglis-Smith, Smith, Rose, & Newman, 1989; Corder, Whiteside, & Haizlip, 1986; Fishbain et al., 1988; Maiuro & Eberle, 1989). In the 1990s, 122 articles were published (e.g., Carlson, Singelis, & Chemtob, 1997; Engel & Rapoff, 1990; Lundervold & Poppen, 1995; Nicholson & Blanchard, 1993), and between 2000 and 2009, 744 articles were published (e.g., Hawkins & Hart, 2003; McLay & Spira, 2009; Sarafino & Goehring, 2000; Vaschillo, Vaschillo, & Lehrer, 2006). From 2010 to April 2017, 473 articles on biofeedback were published (e.g., Faedda et al., 2016; Glombiewski, Hartwich-Tersek, & Rief, 2010; Prinsloo, Derman, Lambert, & Rauch, 2013).

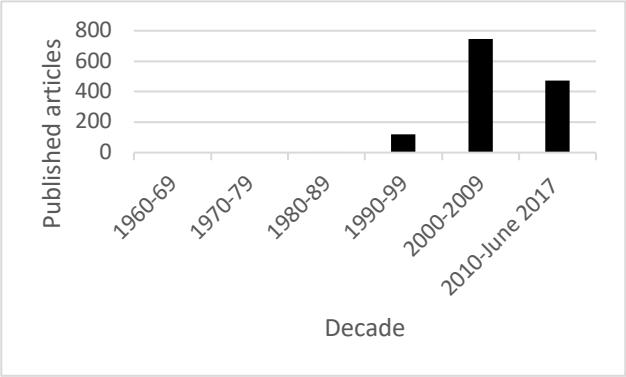

Figure 1. Number of published biofeedback articles by decade, between years of 1960–2017.

Over the years, biofeedback has been shown to have various levels of efficacy for over 40 health conditions including, but not limited to, anxiety, ADHD, headache, insomnia, and chronic pain (e.g., Frank, Khorshid, Kiffer, Moravec, & McKee, 2010). Frank et al. (2010) conducted a literature review of the effectiveness of biofeedback on various health conditions, and they found that the majority of the published studies were effective and modifying the target behavior. See Table 1 for the list of the health conditions. However, after reading Frank et al. (2010) the authors of this article questioned whether biofeedback had been used to increase emotional regulation, specifically decreasing anger. The purpose of this article was to conduct a review of the biofeedback literature examining whether biofeedback was used in reducing feelings of anger.

Table 1
Health conditions addressed with biofeedback.

Condition	Number of Articles	Effectiveness
Alcoholism	47	Probably efficacious
Anxiety	667	Efficacious
Attention Deficit Hyperactivity Disorder/ADHD	258	Efficacious
Chronic Pain	454	Efficacious
Constipation (adult)	12	Efficacious
Diabetes Mellitus	64	Probably efficacious
Epilepsy	112	Efficacious
Fecal Incontinence	29	Probably efficacious
Headache (adult)	92	Efficacious
Headache (pediatric)	78	Probably efficacious
Hypertension	182	Efficacious
Insomnia	115	Probably efficacious
Motion Sickness	16	Efficacious
Raynaud's Disease	4	Efficacious
Substance Abuse	100	Probably efficacious
Temporomandibular Disorder	41	Efficacious
Traumatic Brain Injury	79	Probably efficacious
Urinary Incontinence (female)	41	Efficacious
Urinary Incontinence (male)	24	Probably efficacious
Vulvar Vestibulitis	16	Probably efficacious

Method

The information retrieval strategy included a search of Psychology journals between 1900 and September 2017, using the Educational Resources Information Center (ERIC) and PsychINFO databases. Search parameters included using a combination of the following descriptors: *biofeedback*, *biofeedback and anger*, and *biofeedback and anger management*. From the initial search 7,347 articles were found. Studies were eligible for inclusion in the review if the words *biofeedback and anger* were in the title or the abstract of the paper. Of the 7,347 articles, only 48 met these criteria. Two reviewers independently reviewed each of the 48 articles to determine inclusion eligibility based on the following criteria: (1) the words *biofeedback*, *anger*, or *anger management* had to be in the abstract; (2) the study used biofeedback as a treatment; and (3) the study assessed the effectiveness of biofeedback on anger or anger management. Five articles were identified as meeting the criteria of using biofeedback as a treatment protocol specifically focusing on anger.

Results

Brief Overview of Studies

A breakdown of the five articles can be seen in Table 2. The five studies included in the analysis were published between 1982 and 2017, with two of the five studies published in 1982 and 1986 and three articles published after 2012. Two of the studies used a pre–post intervention design, and three studies used a variation of the case study design. Experimental control was demonstrated in one study (Kahn, Ducharme, Rotenberg, & Gonzalez-Heydrich, 2013) through the use of an experimental and control group. Social validity was measured in one study (Kahn et al., 2013). Length of intervention ranged from 5 days to 5 weeks for four of the articles and 56 sessions over the course of one year for one of the articles (Golden & Consorte, 1982).

Table 2

Characteristics of the five articles that used biofeedback with emotional regulation.

	Chapman (2017)	Corder, Whteside, & Haizlip (1986)	Ducharme et al. (2012)	Golden & Consorte (1982)	Kahn, Ducharme, Rotenberg, & Gonzalez-Heydrich (2013)
Design	Case study	Pilot study	Pre–post intervention test	Case studies	Pre–post intervention
Participants	1 Adult	13 adolescents (range 13–18 years old)	16 years old	4 mildly retarded adults (19, 30, 36, and 54 years old)	38 (range 9–17 years old)
Setting	Two settings: Home Public	State hospital, adolescence inpatient ward	Inpatient psychiatric unit	Not stated	Inpatient psychiatric unit
Treatment	Biofeedback, using the emWave2 portable biofeedback unit	Biofeedback, cognitive skills, and relaxation training program	RAGE-Control videogame, loosely based on an arcade game. Players control their physiological arousal while responding to the stress presented by the challenges of the game.	Rational emotive therapy, biofeedback assisted relaxation, behavioral treatment. Biofeedback apparatus was used.	RAGE-Control videogame, a biofeedback strategy
Duration	5 weeks; two interventions/day	9 weeks, weekly training sessions of 1 hour	5 days, 1 hour each day	56 sessions over 1 year for 30-year-old	5 days, 1 hour each day
Target behavior	Anger and temper	Temper and impulsive behavior	Anger regulation	Self-control of anger	Anger regulation

Table 2
Characteristics of the five articles that used biofeedback with emotional regulation.

	Chapman (2017)	Corder, Whteside, & Haizlip (1986)	Ducharme et al. (2012)	Golden & Consorte (1982)	Kahn, Ducharme, Rotenberg, & Gonzalez-Heydrich (2013)
Results	Behavior measured in frequency (a decrease from a high of 13 anger events each of the second and third weeks to 2 during the fifth week) and intensity (dropping from 3 each of the first 2 weeks to 0.6667 during the last week).	No data, anecdotal reports from aides and teachers saying that impulsive behavior of participants decreased.	Client's anger decreased from baseline score of 59 out of a possible score of 60 (indicates very high levels of anger) to post treatment score of 11. These data indicate a large drop in her reported level of anger and aggression.	Only one participant used biofeedback. His results showed his anger outbursts decreased to two minor outbursts by the end of his treatment. However, authors do not state what his baseline level was.	Treatment group had statistically significant reduction in anger intensity

Review of Included Studies

Chapman (2017) used a case study design to study the effects of biofeedback therapy on a 54-year-old male who indicated lifelong high-intensity anger issues and extreme difficulty controlling his temper. Prior to the study the participant attended individual counseling. During the study the participant attended counseling along with biofeedback intervention using a portable biofeedback unit. Biofeedback treatments consisted of participant putting on the biofeedback unit and controlling physiological responses based on feedback from biofeedback apparatus. Each treatment was approximately three minutes long and conducted twice daily. During a 12-day baseline the participant experienced 32 anger events. During a 29-day biofeedback intervention, the participant's number of anger events decreased to 10 during the first 7 days and two anger events during the last 7 days of the intervention.

Corder, Whiteside, and Haizlip (1986) conducted a pilot study to study the effects of a multimodal treatment approach consisting of biofeedback, cognitive skills, relaxation training, and individual therapy on temper and impulsive behavior of 13 adolescents residing in a state hospital adolescent treatment unit. The intervention consisted of 1-hour weekly training sessions over a 9-week period. Each session included practice in cognitive training, recognizing behavioral cues leading to aggression and relaxation techniques using biofeedback. Each session ended with the assignment of homework that consisted of practicing the tasks introduced in the session. Results were gathered through anecdotal reports from hospital unit aides and teachers working with the adolescents. Unit staff and teachers reported positive changes in increased impulse control of the participants and a decrease in the number of time-outs participants received during the pilot study. A number of teachers reported the ability to diffuse crisis situations in the participants by simply reminding the participants to use their relaxation techniques. Even though Corder et al. (1986) reported the multimodal treatment approach was successful at reducing temper and impulsive behavior, they did not report any pre- and posttreatment data. Hence, it is impossible for the authors of this article to arrive at their own conclusions about whether the treatment was, in fact, efficacious.

Ducharme et al. (2012) described the treatment of a 16-year-old girl who received anger control therapy (ACT) with an active biofeedback video game "RAGE-Control" intervention. The intervention was delivered as daily counseling sessions and ended with playing RAGE-Control over 5 consecutive days. Using the State Trait Anger Expression Inventory for Children and Adolescents (STAXI-CA) where the maximum possible score is 60, the participant's feelings of anger decreased from a baseline score of 30 to a posttreatment score of 11. Likewise, the participant's anger intensity reduced from a baseline score of 29 to posttreatment score of 19.

Golden and Consorte (1982) studied the effects of a cognitive-behavioral approach on reducing chronic anger behaviors of four adults with an intellectual disability. The treatment consisted of cognitive-

behavioral therapy and biofeedback-relaxation techniques. However, the treatment components varied for each of the four participants; only two participants received biofeedback. Since the treatment was not identical in all four cases and only two participants received biofeedback as part of their treatment, we are only discussing the data on those two participants. One participant was a 30-year-old male whose treatment consisted of biofeedback-assisted relaxation—using a portable biofeedback device, relaxation training, coping statements and imagery, assertiveness training, Rational Emotive Behavior Therapy (REBT), and behavioral rehearsal. The participant received 56 sessions over the course of 1 year, and during this time had two minor angry outbursts. The second participant was a 36-year-old woman whose treatment consisted of biofeedback-assisted relaxation, a stress-inoculation training, and behavioral rehearsal. The participant received 24 sessions; however, Golden and Consorte (1982) do not state the length of time the sessions occurred. The results demonstrate that at least some individuals with limited intellectual capacity can learn to regulate anger outbursts.

Kahn, Ducharme, Rotenberg, and Gonzalez-Heydrich (2013) compared an experimental group (18 children ranging between 9 and 17 years of age) to a control group (19 children ranging between 9 and 17 years of age) to evaluate the effects of a treatment consisting of anger control therapy (ACT) with an active biofeedback video game called "RAGE-Control" on increasing emotional regulation skills and reducing feelings of anger. Treatment consisted of therapy and game playing for 5 consecutive days. The authors measured pre- and postintervention levels of anger using the State and Trait Anger Expression Inventory for Children and Adolescents (STAXI-CA). Compared with the control group, children in the experimental group showed statistically significant decreases in frequency of feeling angry and a decline in anger intensity. However, Kahn et al. (2013) did not report baseline or treatment data. Hence, it is impossible for the authors of this article to make their own conclusions on whether there really was a significant decrease in anger and intensity among the participants. In addition to measuring feelings of anger and anger intensity, Kahn et al. (2013) also compared the amount of time each participant stayed below a specific heart rate threshold. Those children in the experimental group had a statistically significant improvement in controlling their heart rate during game play. The authors inferred lower heart rate to higher emotional regulation.

Discussion

While these five articles demonstrate the potential effectiveness of biofeedback in anger management, there are important limitations to consider. First, all but two articles outlined the effectiveness of a biofeedback intervention with only one participant. For example, Golden and Consorte (1982) used four participants in their study but only one participant used biofeedback as a treatment. It is difficult to generalize results to the wider population of people with anger issues. More research is needed focusing on more participants before stating biofeedback is an effective way to regulate emotions.

Second, all five studies used biofeedback in addition to other treatments—such as relaxation, group or individual therapy, and cognitive-behavioral therapy. When biofeedback treatments contain several treatment components, it is difficult to determine which treatments resulted in reduction in anger episodes. More research isolating biofeedback components is needed to evaluate the effectiveness of biofeedback on reducing anger in people. Conducting research where biofeedback is the only treatment variable may allow researchers to tease out effective components contributing to anger reduction.

Third, only one study (Kahn et al., 2013) demonstrated experimental control through the use of a control and experimental group. The other four articles used a variation of case study research, which is not a strong experimental design when considering effectiveness of a treatment. More research using stronger experimental methods is needed to demonstrate that biofeedback is in fact the variable—and not other confounding variables—causing changes in emotional regulation.

Fourth, anger management is not a behavior that only occurs in a treatment setting, hence researchers need to assess generalization effects of biofeedback treatments in reducing anger across various settings. Success of a biofeedback treatment needs to be judged based on the ability of the person to reduce anger in multiple settings. Chapman (2017) was the only study that evaluated the effects of the biofeedback treatment in two different environments—home and public settings. In the home setting, the participant's anger events decreased from three anger events during baseline to zero anger events during the last week of intervention. In the public setting the participant's anger events decreased from 29 events during

baseline to 8 events during the first week of intervention to 2 events during the last week of intervention. When conducting research—especially with anger management—an important factor to focus on is whether the treatment that was effective in the treatment setting is effective in other, diverse settings. Even though Chapman (2017) evaluated the effects of a biofeedback treatment across two settings, more studies are needed to demonstrate generalizability of biofeedback treatments. More research collecting generalization data is needed to close the gap that exists between demonstrating biofeedback effectively reduces anger in treatment settings and demonstrating that biofeedback generalizes to other environments.

Lastly, none of the five articles provided follow-up data after completion of the treatment. Completing follow-up data collection adds validity to the findings reported during the study. The five articles in our review reported how biofeedback reduced anger, but can the treatment gains maintain over time and, if so, for how long? Collecting data after the completion of the research is as important as collecting data during treatment implementation. More research collecting follow-up data points on anger management is needed to demonstrate not just the effectiveness of biofeedback interventions but also how long the treatment gains last.

While more evidence is needed to support the effectiveness of biofeedback on anger management, the preliminary data and anecdotal reports gathered in the five studies appear to show that biofeedback treatments are promising in reducing anger among adolescents and adults. Despite the limitations discussed above, we highly recommend continued research in the area of anger and using biofeedback to improve patients' quality of life. Biofeedback is less invasive, does not involve drugs, and is potentially less expensive and more effective than other counseling or anger management alternatives (Nordqvist, 2017; Schwartz, 1995). For example, Chapman (2017) reported the participant—after a few hours of training—administered biofeedback by himself. However, there is a need for high-quality studies examining the efficacy of biofeedback on anger specifically.

There are dozens of studies discussing biofeedback and its effect on stress relief, and thousands that address many other health conditions (e.g., Greenspoon & Olson, 1986, Shellenberger, Turner, Green, & Cooney, 1986; Wyner, 2015). Only a very few appear to focus on addressing the effects of biofeedback on anger as its own construct. While biofeedback has been used successfully in conjunction with other therapies, it has yet to be determined whether or not it is a viable tool in and of itself. With both the frequency and intensity of anger on the rise in today's society—and given that there is little in the way of published research—further research on the effects of biofeedback on anger management not only seems necessary but is strongly encouraged.

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