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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).

NeuroRegulation

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Contents

EDITORIALS

Editorial – Volume 4, Number 2 64
Rex L. Cannon

RESEARCH PAPERS

Neuromodulation Based on rTMS Affects Behavioral Measures and Autonomic Nervous System Activity in Children with Autism 65
Guela E. Sokhadze, Manuel F. Casanova, Desmond P. Kelly, Emily L. Casanova, Brook Russell, and Estate M. Sokhadze

REVIEW ARTICLES

Neurotherapies and Alzheimer's: A Protocol-oriented Review 79
Javier Vigil and Lisa Tataryn

CLINICAL CORNER

Biofeedback Intervention for Anger Management: A Case Study 95
Charles J. Chapman

ERRATA

Erratum to: Combined Neurofeedback and Heart Rate Variability Training for Individuals with Symptoms of Anxiety and Depression: A Retrospective Study 99
Elyse K. White, Kayleah M. Groeneveld, Rachel K. Tittle, Nicholas A. Bolhuis, Rachel E. Martin, Timothy G. Royer, and Majid Fotuhi

NeuroRegulation

Editorial – Volume 4, Number 2

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Welcome to *NeuroRegulation* Volume 4, Issue 2.

As neurofeedback continues to draw attention for its unique focus on neuroscience and the brain, so does the criticism and its lack of rigor in conclusions. It is somewhat interesting when one examines the number of meta-analyses and critiques devoted to one process over the course of its development and its advancement in technological superiority. Recently, neurofeedback was drawn into the murky water of politics of late by more than one news media outlet which have been, in my opinion, reckless and irresponsible. Clearly, the authors have not researched the topics of the article with any rigor or competency. Neurofeedback has been studied extensively over the past 60 years and enough data exists to support its benefits and limitations. Our novel understanding of the brain and its enigmatic properties will continue to evolve at an exponential rate over the next decade and we would do well to adjust our dogma to accommodate this process.

In this issue, Guela Sokhadze, Manuel Casanova, Desmond Kelly, Emily Casanova, Brook Russell, and Estate Sokhadze provide data demonstrating the effects of repetitive transcranial magnetic stimulation (rTMS) on behavioral and autonomic measures in children with Autism. Charles Chapman examines data in a case study of neurofeedback for anger management. Elyse Kemmerer White, Kayleah Michelle Groeneveld, Rachel Kelly Tittle, Nicholas Abram Bolhuis, Rachel E. Martin, Timothy G. Royer, and Majid Fotuhi submit an addendum with correction to a recent article evaluating retrospective data demonstrating the effects of neurofeedback and heart rate variability training with symptoms of anxiety and depression. The authors concluded that the typographical error did not impact the conclusions. Finally, Javier Vigil and Lisa Tataryn present a review of neurotherapeutic protocols and Alzheimer's Disease. We would like to thank the authors for their contribution to the scientific literature and for choosing *NeuroRegulation* to publish their work.

NeuroRegulation is encouraging submissions of case studies utilizing neurofeedback and other neurotherapeutic techniques as well as review articles of neurotherapeutic processes in specific populations of clients (e.g., depression, anxiety, ADHD). These are exciting times in neuroscience and stiff resistance to change is always a bit cumbersome. We will be also incorporating a student spotlight section in which we will welcome students to publish data from research projects in our journal. Bright, young brains are needed to shift the current paradigm and spur enlightenment. Thanks for choosing *NeuroRegulation* as your source of information regarding neurofeedback and applied neuroscience.

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Neuromodulation Based on rTMS Affects Behavioral Measures and Autonomic Nervous System Activity in Children with Autism

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Abstract

Many children with autism spectrum disorder (ASD) exhibit symptoms associated with autonomic nervous system (ANS) dysfunction indicative of low psychophysiological flexibility. It is suggested that ASD symptoms are associated with generalized abnormalities in the central nervous system, including structures and networks involved in the top-down regulation of the ANS. Repetitive transcranial magnetic stimulation (rTMS) has been suggested as a possible therapy to target ANS regulation deficits in ASD. In the current study we used neuromodulation based on rTMS over the dorsolateral prefrontal cortex (DLPFC) to reduce sympathetic arousal and increase parasympathetic activity in children with ASD. In a study on 27 children with autism we administered weekly 0.5 Hz rTMS bilaterally over the DLPFC with concurrent recording of autonomic activity. Statistical analysis of time and frequency domain heart rate variability (HRV) indices and skin conductance level (SCL) revealed a strong linear regression of most HRV and SCL measures. Several parental behavioral rating scores improved post-TMS and showed a correlation with autonomic outcomes; in particular, parasympathetic indices of HRV negatively correlated with repetitive and stereotyped behaviors, while sympathetic arousal indices showed positive correlation with the same behaviors. The paper discusses potential neurobiological mechanisms involved in post-TMS autonomic balance and aberrant behavior improvements.

Keywords: autism; rTMS; autonomic activity; repetitive and stereotype behaviors; prefrontal cortex

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Introduction

Autism spectrum disorder (ASD) is characterized by deficits in social interaction and communication as well as restricted, repetitive, and stereotyped behavioral patterns (APA, 2013). A frequently reported symptom of ASD is autonomic nervous system (ANS) dysfunction observed during exposure to sensory stimuli, engagement in social interaction, and resting state. Children and adolescents with ASD have been reported to have high sympathetic tone and low parasympathetic tone compared to controls (Benevides & Lane, 2015; Kushki, Brian, Dupuis, & Anagnostou, 2014; Ming et al., 2011; Ming, Julu, Brimacombe, Connor, & Daniels, 2005). This abnormal autonomic balance is indicative of low psychophysiological flexibility and rigid social communication ability (Thayer & Lane, 2000). An extensive body of literature suggests that ASD symptoms are associated with generalized abnormalities in the central nervous system, including structures and networks involved in "top-down" control of the ANS. For example, ASD has been associated with pathological findings in

structures that play a crucial role in modulating the ANS response, including the amygdala, anterior cingulate cortex, and insula (Loveland, Bachevalier, Pearson, & Lane, 2008). According to recent studies, ASD may be associated with autonomic arousal typical for anxiety that is most consistent with sympathetic overarousal and parasympathetic underarousal (Kushki et al., 2013). According to some authors, anxiety in people diagnosed with autism should be recognized for its direct links with atypical autonomic control and excessive sympathetic arousal (Gillott, Furniss, & Walter, 2001; Helverschou & Martinsen, 2011). The ANS is responsible for multiple physiological responses, and dysfunction of this system is often hypothesized as contributing to abnormal cognitive, affective, and behavioral responses in children with autism (Benevides & Lane, 2015; Smeekens, Didden, & Verhoeven, 2015). Exploring the relationship between ANS function and social competence is important to gaining an understanding of how dysregulation of autonomic activity may adversely affect social functioning in individuals with ASD.

Transcranial magnetic stimulation (TMS)-based neuromodulation

Repetitive transcranial magnetic stimulation (rTMS) has been suggested by our group as a therapeutic attempt at overcoming ANS regulation deficits typically observed in individuals with ASD (Casanova et al., 2014; Hensley, El-Baz, Casanova, & Sokhadze, 2013; Hensley et al., 2012). In the current study we propose using low-frequency rTMS over the dorsolateral prefrontal cortex (DLPFC) to reduce sympathetic arousal and increase parasympathetic activity, thus improving autonomic balance in children with ASD. The approach uses rTMS to induce changes in ANS activity (shown in our preliminary results, Casanova et al., 2014; Wang et al., 2016) to lower aberrant behavior, stereotyped and repetitive behaviors, and anxiety symptoms as well as to improve social awareness and social cognition children with ASD.

TMS operates based on Faraday's law of electromagnetic induction, which describes the process by which a changing magnetic field induces the flow of electric current in a nearby conductor, preferentially one standing at a 90º angle to the magnetic field. Studies have indicated that low-frequency or ''slow'' rTMS (< 1 Hz) increases inhibition of the stimulated cortex through activation of inhibitory cortical circuits (Pascual-Leone, Walsh, & Rothwell, 2000). The proposed mechanism of post-TMS effects on autonomic arousal may include improved normative tonic frontolimbic inhibitory influences known to be deficient in autism (Bachevalier & Loveland, 2006; Loveland et al., 2008). We hypothesized that slow rTMS stimulation applied to the DLPFC will lower sympathetic arousal and normalize autonomic balance.

Theoretical rationale for the proposed intervention was based on a "minicolumnar" neuropathological model of autism (reviewed in Casanova, Sokhadze, Opris, Wang, & Li, 2015). Prior studies from our group suggest that supernumerary minicolumns and reduced cell size of pyramidal cells biases cortico-cortical connections in favor of short (i.e., arcuate) projections at the expense of longer ones (i.e., long association fibers). Furthermore, the abnormal width of minicolumns in autism reflects primarily a loss of the inhibitory tone of anatomical elements surrounding this modular structure, resulting in a reduced lateral inhibition effect (Casanova, 2005, 2006; Casanova, Buxhoeveden, & Brown, 2002; Casanova et al., 2006). The minicolumnar abnormalities are even more pronounced in the prefrontal cortex (PFC), resulting in weakened frontal control of other cortical and subcortical networks, including those involved in regulating ANS arousal (Casanova et al., 2014, 2015). We theorize that contrary to other inhibitory cells (such as basket cells and chandelier cells whose projections keep no constant relation to the surface of the cortex), the geometrically exact orientation of double-bouquet cells and their location at the periphery of the minicolumn (inhibitory surround) make them an appropriate candidate for induction by a magnetic field applied parallel to the PFC. Over a course of treatment, slow rTMS may selectively depotentiate enhanced synaptic weights associated with pathological conditions, and in the case of ASD it may lower the cortical excitation/inhibition ratio.

Review of autonomic dysfunctions in autism

Cardiac activity. In autism, ANS dysfunction includes blunted cardiac responses to visual and auditory social stimuli (Hirstein, Iversen, & Ramachandran, 2001; Palkovitz & Wiesenfeld, 1980). These responses are important for understanding social situations and awareness of social context during communication (Jansen et al., 2000). Developmental deficits in autonomic regulation of the cardiac activity in children with autism may result in a lower ability to engage in social communication (Porges, 2003; Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996). In addition to increased sympathetic tone, a decrease in cardiac parasympathetic tone has been often reported in ASD (Kushki et al., 2013, 2014; Ming et al., 2005, 2011; Ming, Julu, Wark,

Apartopoulos, & Hansen, 2004). Julu et al. (2001) reported reduced cardiac vagal tone, decreased baroreflex sensitivity, and unstable respiratory rhythm in individuals diagnosed with autism. The respiratory dysrhythmia in children with ASD, according to Ming, Patel, Kang, Chokroverty, and Julu (2016), is a phenomenon associated with lower cardiac vagal activity. Both respiratory and cardiac vagal control hypofunction in ASD may suggest a brainstem dysfunction or diminished top-down control of the PFC over limbic and subcortical structures (Bachevalier & Loveland, 2006; Loveland et al., 2008). Low parasympathetic activity can help explain chronic sensory hyperarousal and some of the social communication difficulties in children with ASD. This hypothesis is concordant with Porges' "polyvagal theory" (Porges, 2003, 2011) that emphasizes the important role of both efferents and afferents of the vagus nerve in support of social engagement and communication. The inhibitory parasympathetic vagus nerve acts as a vagal "brake" that slows heart rate (HR). Such modulation of HR enables rapid engagement and disengagement with objects and people, a skill important for promoting social behaviors (Porges, 1995, 2003).

Time and frequency domain-based analysis of heart rate variability (i.e., HRV) represents a measure commonly used in psychopathology research for assessment of cardiac autonomic control (Berntson et al., 1997; Cohen, 2000; Thayer & Friedman, 2002). Attenuated spectral power of high frequency (HF) component of HRV, frequently used as an index of parasympathetic control, is an indicator of limited psychophysiological flexibility (Berntson et al., 1997; Cohen et al., 2000; Movius & Allen, 2005; Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012). Children diagnosed with ASD have been found to have deficits in suppression of HF component of HRV during social tasks, compared to controls (Althaus, Mulder, Mulder, Aarnoudse, & Minderaa, 1999; Hutt, Forrest, & Richer, 1975). Furthermore, children with ASD demonstrate dampened HR reactivity, unusually small deceleratory HR responses, and generally low cardiac reactions to auditory stimulation including socially relevant speech, phrases, and tones (Corona, Dissanayake, Arbelle, Wellington, & Sigman, 1998; Palkovitz & Wiesenfeld, 1980; Zahn, Rumsey, & Van Kammen, 1987). Kleberg (2015) emphasized that atypical autonomic arousal has been used to explain some of the core symptoms of ASD. In effect, it has been hypothesized that either elevated or attenuated tonic arousal was a causal factor behind some of the core autism symptoms, such as repetitive behaviors (Hirstein et al., 2001; Toichi & Kamio, 2003; Toichi et al., 1999) and avoidance of social interaction (Rogers & Ozonoff, 2005). According to other current theories, atypical regulation of arousal could cause impairment in attention, another symptom commonly associated with ASD (Orekhova & Stroganova, 2014). A series of current studies of autonomic dysfunctions in ASD were reported in the literature showing drastically increased interest in the investigation of autonomic system functioning abnormalities in children with autism (Benevides & Lane, 2015; Cohen, Masyn, Mastergeorge, & Hessl, 2015; Kleberg, 2015; Kushki et al., 2013, 2014; Patriquin, Lorenzi, & Scarpa, 2013; Smeekens et al., 2015). As noted by Rees (2014), there is an urgent need to recognize the importance of the ANS in pediatrics, not limited to neurodevelopmental disorders.

Electrodermal activity. Electrodermal activity is a commonly used measure in psychophysiology and cognitive neuroscience research as it reflects sympathetic neural responses independent of direct parasympathetic control, or as its activity may reflect effects of adrenaline (Boucsein, 2012; Williams et al., 2004). Studies of skin conductance level (SCL) in autism have demonstrated several manifestations of abnormal sympathetic function (Ming et al., 2004, 2005, 2011, 2016). Classical psychophysiological studies of skin conductance response (SCR) in children with autism have shown a lack of the normal habituation in the magnitudes of SCR to the same stimulus presented over time, and they demonstrate poor adaptation to a repeated stimulus (Barry & James, 1988; van Engeland, 1984). Furthermore, higher tonic electrodermal activity, as well as larger SCRs to sounds, was observed in autistic children compared to controls (Barry & James, 1988). Palkovitz and Wiesenfeld (1980) did not find differences in electrodermal reactivity to auditory stimulation compared to controls, but reported that the autistic group had a higher baseline SCL. In addition, it has been reported that children with autism had blunted autonomic arousal to visual and auditory social stimuli (Hirstein et al., 2001; Ming et al., 2016; Zahn et al., 1987). Several of our own pilot studies reported excessive but less differentiated SCR to affective sounds, visual, and audio-visual stimuli in various affective stimulation tests (Dombroski et al., 2014; Sokhadze et al., 2012). Since SCL is controlled solely by sympathetic inputs, the above effects are indications of high sympathetic tone and at the same time relatively low selectivity of ANS responses to sensory stimuli in autism. High sympathetic reactivity to sound may underlie the atypical

behavioral responses to sound often demonstrated by children with ASD (Chang et al., 2012).

Liss, Saulnier, Fein, and Kinsbourne (2006) suggested that the overfocused attentional style in ASD may be the result of hyperarousal, while Keehn, Müller, and Townsend (2013) hypothesized that atypical behavioral arousal regulation in persons with ASD results from early deficits in disengaging attention. The term "arousal" was originally used to describe both behavior and physiological activity, including its cortical and autonomic components (Lacey & Lacey, 1970). The most widely used measures of autonomic arousal are the tonic SCL and spontaneous and stimulus–related fluctuations in electrodermal activity along with reduced HRV. Schoen, Miller, Brett-Green, and Nielsen (2009) have found that most children with autism had high SCL (high tonic arousal) associated with higher than normal SCR magnitudes, faster latencies, and slower habituation.

Goals of the study

The aim of this case series study was to investigate the effects of 18 weekly sessions of low-frequency (0.5 Hz) rTMS over DLPFC on autonomic function measures and on behavioral symptoms (based on parental behavioral reports) in children with ASD. We predicted that the course of rTMS would have positive effects on behavioral rating scores similar to those reported in our prior studies (Casanova et al., 2014; Hensley et al., 2012, 2013; Wang et al., 2016). In particular, based on our pilot studies, we expected that the proposed rTMS therapy would provide for improvements in irritability, hyperactivity, and repetitive stereotyped behavior rating scales on the Aberrant Behavior Checklist (ABC; Aman & Singh, 1994) and Repetitive Behavior Scale (RBS-R; Bodfish, Symons, & Lewis, 1999). In addition, we used the Social Responsiveness Scale (SRS-2, Constantino & Gruber, 2005) to assess changes in social awareness, social cognition, and social motivation. We hypothesized that the behavioral improvement would also be manifested in autonomic measures indicative of lower sympathetic arousal, increased parasympathetic tone, and normalized cardiac autonomic balance.

Methods

Subjects

In this study, we investigated the activity of the ANS during rTMS treatment course in 27 children with ASD (21 boys and 6 girls, mean age 12.52 ± 2.85 years). Participants with ASD were recruited through the University of Louisville Weisskopf Child Evaluation Center (WCEC). Diagnosis was made according to the DSM-IV-TR and further ascertained with the Autism Diagnostic Interview–Revised (ADI-R; LeCouteur, Lord, & Rutter, 2003) by a clinical psychologist, who also did pre- and post-TMS behavioral evaluations using ABC, RBS-R, and SRS-2. Children with a history of a seizure disorder, significant hearing or visual impairment, identified brain abnormality, identified genetic disorder, or comorbid severe psychopathology were excluded. Subjects were excluded at the intake stage if they were unable to tolerate TMS or autonomic monitoring procedures such as placement of adhesive electrodes and sensors on their skin. Medication of enrolled subjects was monitored, but subjects were not taken off prescribed medications.

All participants were high-functioning children with ASD and with full-scale IQs > 80 assessed using the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; Wechsler, 2004). Twenty-nine ASD subjects out of 32 enrolled in the study completed all 18 sessions of rTMS. Two subjects had excessive gross movements and artifacts affecting autonomic activity recording and their data were not entered into final analysis.

The study complied with all relevant national regulations and institutional policies and has been approved by the local Institutional Review Board (IRB). Participating subjects and their parents were provided with full information about the study including the purpose, requirements, responsibilities, reimbursement, risks, benefits, alternatives, and the role of the local IRB. The consent and assent forms approved by the IRB were reviewed and explained to all subjects who expressed interest in participating. All questions were answered before consent/assent signature was requested. If the individual agreed to participate, both the child and parent/guardian signed and dated the informed consent/assent forms and received a copy countersigned by the investigator who obtained consent.

Low-frequency rTMS procedure

A trained electrophysiologist delivered rTMS using a Magstim Rapid system (Magstim Co, Whitland, UK). Participants were seated in a reclining chair and fitted with a swimming cap. Motor threshold at the first session was detected by mild supra-threshold stimulations administered over the left motor cortex to determine the optimal area for stimulation of the abductor pollicis brevis muscle of the right hand. The output of the machine was increased by 7% each time until the least amount of machine power that induced a 50-μV deflection or a visible twitch was identified in four out of five trials over the cortical area controlling the contralateral abductor pollicis brevis muscle. Surface electrodes were attached over the abductor pollicis brevis and first dorsal interossei areas. Electromyographic (EMG) responses (motor-evoked potentials) were recorded using the C2 J&J Engineering Inc. (Poulsbo, WA) physiological data acquisition system with USE software interfaced with Magstim TMS device. Similar procedure was applied to determine motor threshold for the right hemisphere. The TMS treatment course was administered once per week for 18 weeks over the DLPFC (six over the left, six over right, and the last six sessions equally distributed the number of pulses over the both left and right hemispheres). The site for stimulation was placed 5 cm anterior to and in a parasagittal plane to the site of maximal abductor pollicis brevis stimulation. The figure-eight coil, with a 70-mm wing diameter, was kept flat over the scalp. Stimulation was performed at 0.5 Hz and 90% of resting motor threshold, with a total of 160 pulses per day (eight trains of 20 pulses, with a 20-s interval between trains; for additional details, see Casanova et al., 2012, 2014; E. Sokhadze et al., 2009, 2016; G. Sokhadze et al., 2012).

ANS monitoring

Physiological activity was monitored and recorded from subjects during each rTMS session. Additionally, several minutes of baseline and postbaseline activity was recorded before and after each TMS session. However, for data analysis in this particular study we included only data recorded during the administration of TMS. HRV measures were calculated from 10-min segments derived from an artifact-free electrocardiogram (ECG) recording and mean SCL. Integrated EMG was used to detect movement-related artifacts. ECG, EMG, pneumogram, and electrodermal activity were acquired (1024-Hz sampling rate for EMG and ECG, 128 Hz for pneumogram and electrodermal activity) by a C-2 J&J Engineering Inc. physiological monitoring system with USE-3 software (Physiodata, Poulsbo, WA). Three Ag/AgCl electrodes (EI-503, Biopac Systems, Inc., CA) were attached for measurement of Lead II ECG, three Ag/AgCl electrodes (EL-501 from Biopac) for EMG recording from the right hand, and pneumogram was recorded with a strain gauge transducer (J&J Engineering). Electrodermal activity was recorded by Ag/AgCl electrodes (EL-507 by Biopac with Unibase isotonic gel) attached to the distal phalanx of index and middle fingers to measure SCL. Average R-R intervals in ECG (RR), standard deviation of all normal R-R intervals (SDNN), square root of the mean of the squares of successive RR interval differences (RMSSD, or the average change in interval between beats); frequency domain HRV measures such as power of high-frequency (HF), low-frequency (LF), very low-frequency (VLF) components, and the ratio of the LF over the HF (LF/HF ratio is used as an indirect autonomic balance index) of HRV were calculated as time domain and frequency domain cardiac activity measures (Kleiger, Stein, & Bigger, 2005). Artifact-corrected ≥ 5-min-long recording epochs were analyzed with fast Fourier transform (FFT) to assess HRV. Integrals of the spectrum in 0.003–0.040 Hz (VLF of HRV), 0.04–0.15 Hz (LF of HRV), and 0.15–0.40 Hz (HF of HRV) bands were measured (in ms^2). All HRV data was analyzed offline using Kubios HRV software version 2.0 (University of Kuopio, Finland).

HRV interpretation was based on the following concepts: (1) the HF component of HRV is often referred to as respiratory sinus arrhythmia and is assumed to be the noninvasive index of parasympathetic influences on the heart (Berntson et al., 1997; Sohn, Sokhadze, & Watanuki, 2001); (2) the LF component of HRV has been linked to sympathetic nervous system activity and sympatho-vagal balance by numerous studies (Malliani, Pagani, & Lombardi, 1994; Pagani et al., 1986). Other studies have shown that the LF variability is rather a reflection of both sympathetic and vagal influences related to baroreflex mechanisms (Berntson et al., 1997). It is thought that changes in blood pressure amplitude may cause vagally-mediated baroreflex responses as well as changes in LF variability. Respiration rate on a per minute basis and peak respiration frequency were calculated. These measures were used to control HF peak in HRV related to respiratory frequencies in HRV and were not used as dependent measures.

Statistical analysis

The primary statistical analyses included linear regression plot estimation of each autonomic dependent variable (RR, SDNN, RMSS; VLF, LF, and HF of HRV; LF/HF index) over 18 sessions of rTMS course as well as paired sample student's *t*-test of pre- and post-TMS behavioral measures (ABC, RBS-R, SRS-2). For each behavioral rating score analyzed using paired sample student's *t*-test, normality of distribution test was performed to ensure appropriateness for the *t*-test. To estimate the power of the test for the linear regression analysis, statistical results also included values of observed power at α = 0.05 and, when appropriate, their comparisons to the desired power of 0.80. Actual *R*, R^2, and adjusted R^2 values are reported for each dependent variable in regression analysis. In addition, we analyzed mean changes of autonomic measures from the first to the last session of the rTMS course. The changes of physiological variables (time and frequency indices of HRV and SCL) were entered in a correlation analysis (Pearson correlation) with changes of behavioral evaluation scores of ABC, RBS-R, and SRS-2. SPSS and SigmaStat statistical software packages were used for analysis.

Results

Behavioral evaluations post-TMS

As expected based on our prior studies, the ABC, RBS-R, and SRS-2 parental behavioral checklists' rating changes showed statistically significant improvements in several domains. *Lethargy/Social Withdrawal* subscale of the ABC (Aman & Singh, 1994) showed a significant score reduction, mean decrease -2.21 ± 3.58, $t(26) = -2.69$, $p = .015$. *Hyperactivity* score of the ABC also showed reduction, -4.79 ± 7.34, $t(26) = -2.84$, $p = .011$. *Inappropriate Speech* score decreased as well, -1.63 ± 2.92, $t(26) = 2.49$, $p = .028$. *Stereotypy* behavior scores had a marginal decrease that did not reach a significant level, -2.26 ± 4.78, $t(26) = -2.06$, $p = .054$.

We found a significant decrease in stereotypic, repetitive, and restricted behavior patterns following 18 sessions of bilateral rTMS as measured by the RBS-R (Bodfish et al., 1999). *Total RBS-R* score decreased, -4.21 ± 5.59, $t(26) = -3.28$, $p = .015$. *Stereotypic Behavior* subscale showed a significant decrease, -0.95 ± 1.26, $t(26) = -3.25$, $p = .004$; and *Ritualistic/Sameness Behavior* subscale scores showed a decrease, -0.94 ± 1.74, $t(26) = 2.36$, $p = .03$. *Compulsive Behavior* subscale also demonstrated a significant decrease, -1.26 ± 2.46, $t(26) = -2.23$, $p = .039$. Analysis of Social Responsiveness Scale (SRS-2; Constantino & Gruber, 2005) revealed changes in several subscale rating scores. *Social Awareness* score of the SRS-2 improved post-TMS, -7.03 ± 7.96, $t(26) = -4.51$, $p < .001$; along with *Social Cognition,* -8.19 ±7.22, $t(26) = -5.47$, $p = .001$; and *Social Motivation* rating scores, -6.73 ± 9.42, $t(26) = -3.64$, $p = .001$.

Autonomic activity measures

Time domain measures of HRV (RR intervals, standard deviation of RR [SDNN], HR RMSSD). Cardiointervals in ECG (RR intervals) showed a statistically significant linear regression over sessions of rTMS, $R = .70$, $R^2 = .50$, adjusted $R^2 = .47$, $F = 15.11$, $p = .001$, power of performed test (hereafter referred as *power*) = 0.88 at $\alpha = 0.05$ (Figure 1). Standard deviation of RR (SDNN) intervals showed a statistically significant linear increase over rTMS course, $R = .74$, $R^2 = .54$, adjusted $R^2 = .52$, $F = 19.38$, $p < .001$, power = 0.95 at $\alpha = 0.05$ (Figure 2). Paired sample *t*-test showed that increase of SDNN from the first to the last session of rTMS course was significant, 29.3 ± 56.4 ms, $t(26) = 2.26$, $p = .036$. Root mean square standard deviation of RR (RMSSD) also showed linear increase, $R = .66$, $R^2 = .44$, $F = 12.52$, $p = .003$, power = 0.87 at $\alpha = 0.05$. The *t*-test yielded a significant increase of RMSSD, 27.78 ± 48.84 bpm, $t(26) = 2.48$, $p = .023$.

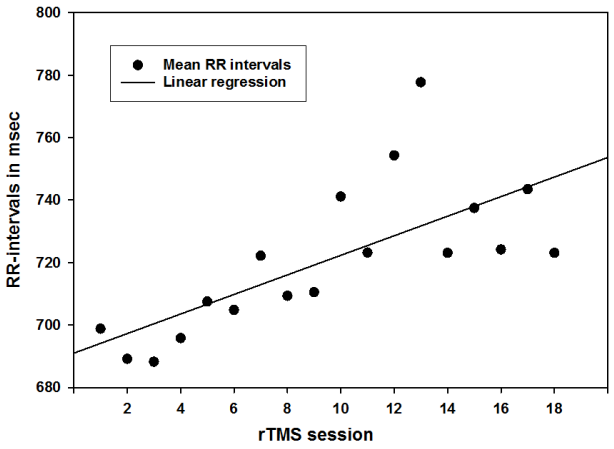

Figure 1. Mean RR intervals over 18 sessions of rTMS in children with autism spectrum disorder.
$R = .70$, $R^2 = .49$, $F = 15.1$, $p < .001$, power = 0.92.

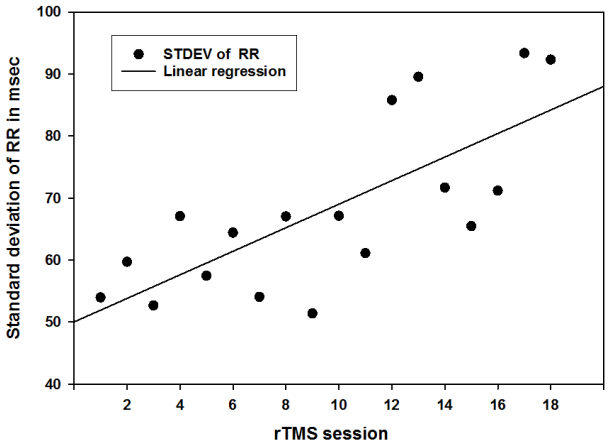

Figure 2. Standard deviation of RR intervals over 18 sessions of rTMS in children with autism spectrum disorder.
R = .74, R^2 = .55, F = 19.3, p < .001, power = 0.95.

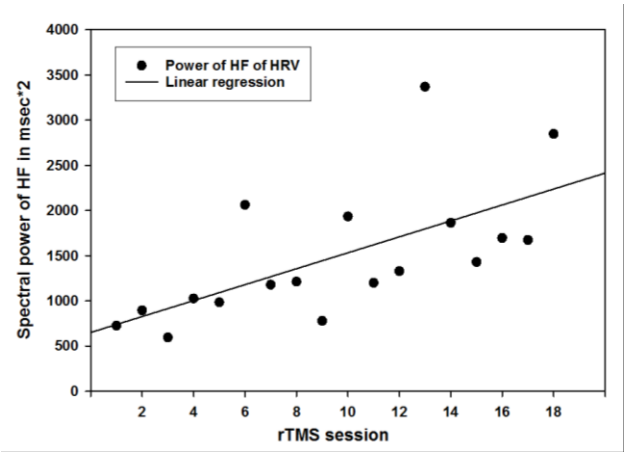

Figure 4. Power of high frequency (HF) of heart rate variability (HRV) over 18 sessions of rTMS in children with autism spectrum disorder.
R = .64, R^2 = .41, F = 11.2, p = .004, power = 0.84.

Frequency domain measures of HRV (VLF, LF and HF of HRV, LF/HF ratio). The power of the VLF component of HRV did not show any linear regression trend, F = 0.14, p = .71. The power of the LF component of HRV showed a marginal trend towards linear regression, R = .50, R^2 = .25, adjusted R^2 = .21, F = 5.43, p = .033, power = 0.57 at α = 0.05, below desired power level of 0.80 (Figure 3). The HF component of HRV showed a statistically significant linear increase in power, R = .64, R^2 = .41, adjusted R^2 = .37, F = 11.25, p = .004, power = 0.84 at α = 0.05 (Figure 4). Increase of the HF power was confirmed by paired sample t-test, 865 ± 1418 ms^2, t(26) = 2.66, p = .016.

The LF/HF ratio of HRV (cardiac autonomic balance index) showed a linear regression that was statistically significant, R = .79, R^2 = .62, adjusted R^2 = .59, observed power = 0.97 at α = 0.05 (Figure 5). The LF/HR ratio of HRV tended to decrease from the first to the last session of rTMS but failed to reach statistical significance, -0.42 ± 1.07, t(26) = -1.72, p = .103.

Skin conductance level (SCL). SCL showed statistically significant linear regression over 18 sessions of rTMS, R = .63, R^2 = .40, adjusted R^2 = .36, F = 10.70, p = .004, power = 0.94 at α = 0.05 (Figure 6).

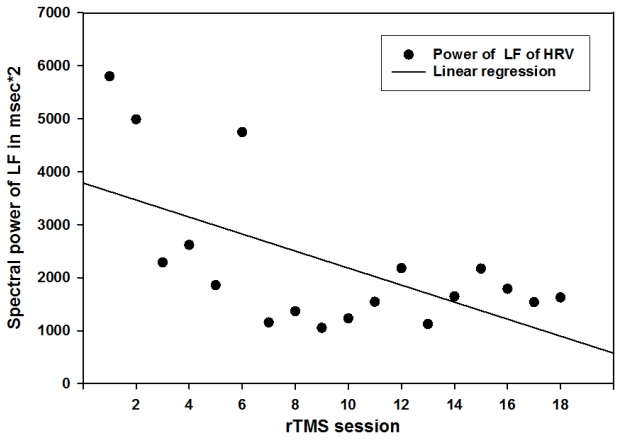

Figure 3. Power of low frequency (LF) of heart rate variability (HRV) over 18 sessions of rTMS in children with autism spectrum disorder.
R = .50, R^2 = .25, F = 5.44, p = .033, power = 0.57.

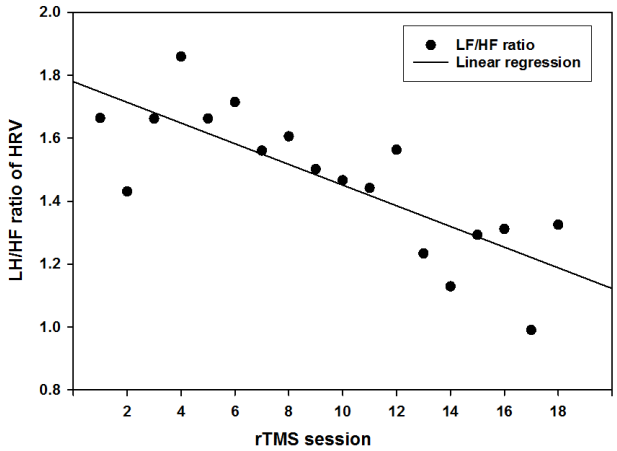

Figure 5. Mean low frequency/high frequency (LF/HF) ratio of heart rate variability (HRV) over 18 sessions of rTMS in children with autism spectrum disorder.
R = .79, R^2 = .62, F = 26.3, p < .001, power = 0.98.

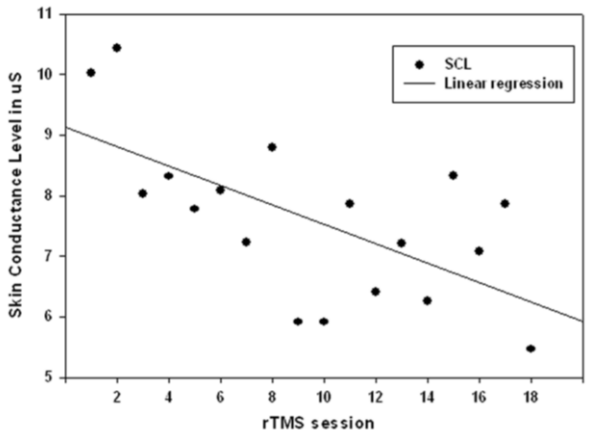

Figure 6. Skin conductance level (SCL) over 18 sessions of rTMS in children with autism spectrum disorder.
R = .63, R^2 = .40, F = 10.7, p = .005, power = 0.93.

Correlation of changes in HRV and SCL measures with behavioral score changes

Several time domain measures of HRV associated with increased HRV showed significant negative correlation with *Stereotypy* rating of the ABC (SDNN, r = -0.73, p = < .001; RMSSD, r = -0.69, p = .001). The LF component of HRV showed positive correlation with *Stereotypy* rating changes (r = 0.76, p < .001). In a similar manner, correlation of *Total Repetitive and Stereotyped Behaviors* score changes on the RBS-R questionnaire showed negative correlation with time domain measure (RMSSD of HR) changes (r = -0.51, p = .028), but positive correlation with LF/HF ratio (r = 0.58, p = .008). Skin conductance changes showed positive correlation with the *Total Repetitive and Stereotyped Behavior* of RBS-R (r = 0.56, p = .017). There were no significant correlations found between individual HRV and SCL measures and SRS-2 rating score changes.

Discussion

The most notable result of the study is a replication of the findings in our prior case series studies (Casanova et al., 2014; Wang et al., 2016) reporting improvements in aberrant, stereotyped, and repetitive behaviors. In addition, we found improvements in social awareness, social cognition, and social motivation ratings of the SRS-2 questionnaire. Furthermore, there was a linear increase of HR, as well as both time and frequency domain measures of HRV. Our post-TMS HRV and SCL outcomes point to a decrease of sympathetic arousal and to an increase of parasympathetic activity resulting in a trend of normalization of the autonomic balance. The demonstration of decreased sympathetic arousal, as indexed by decrease of LF and LF/HF of HRV and decreased electrodermal activity posttreatment, is also an important finding. Considering that sympathetic activation is often associated with autonomic arousal, abnormalities of arousal regulation should become one of the main aims of autism research and treatment.

In a study by Hirstein et al. (2001) children with autism mainly had higher than normal baseline SCL and high-amplitude SCRs. In the majority of the children, however, SCL and SCR magnitude dropped below the values observed in normal control groups as soon as they became involved in self-stimulatory activities (such as putting their hands in a bowl of dry beans). Stereotyped and repetitive motor behaviors, one of the core features of autism, has been proposed to be a coping response to reduce hyperresponsive sympathetic activity (Hirstein et al., 2001; Toichi & Kamio, 2003; Toichi et al., 1999). Arousal dysregulation in autism may manifest in two distinct modes of functioning. The first mode is characterized by elevated tonic arousal, anxiety, and difficulties in focusing attention. The second mode is reflected in reduced tonic arousal, self-stimulatory activities, and decreased awareness of the surroundings. Our results showed a positive correlation of LF of HRV with *Stereotypy* ratings on ABC and a positive correlation of LF/HF index with *Total Repetitive and Stereotyped Behaviors* scores on RBS-R. At the same time we found negative correlations of *Stereotyped Behavior* scores on both ABC and RBS-R with such HRV measures as SDNN, RMSSD, and standard deviation of HR. These finding are supportive of hypotheses proposing that stereotyped repetitive behaviors can be considered as a coping mechanism for reducing sympathetic overactivation and alleviating anxiety in children with ASD.

How does prefrontal rTMS affect autonomic functions? Only a few studies have looked at the effects of rTMS on the autonomic system, despite the fact that many frontal cortical areas are directly implicated in ANS control (Czéh et al., 2002; Filippi, Oliveri, Vernieri, Pasqualetti, & Rossini, 2000). It has been reported that there might be neurohumoral changes after treatment with rTMS (Beh-Shachar, Belmaker, Grisaru, & Klein, 1997). There is also a hypothesis suggesting that the anxiolytic effects of rTMS may act through normalization of hypothalamic-pituitary-adrenocortical (HPA) axis (Holsboer, 2000). Chronic rTMS-induced changes in

stress-related corticotropin and corticosterone levels have been found in animal models providing support for the suggestion that frontal brain exposure to rTMS may attenuate the activity of the HPA system (Hedges et al., 2002). It was shown that low-frequency rTMS can influence autonomic balance assessed using HRV (Yoshida et al., 2001). Udupa et al. (2007) reported HRV measures indicating that rTMS produced significant reduction in the cardiac sympathetic/vagal ratio, suggesting improvement in sympatho-vagal cardiac balance, an effect similar to our findings. Lower post-TMS sympathetic activity was reported in the study of Jenkins, Shajahan, Lappin, and Ebmeier (2002).

We propose that it is possible that rTMS effects are mediated through frontolimbic connections. The limbic system is a complex network of structures central to anxiety and mood regulation (Seminowicz et al., 2004). Originally rTMS was investigated as a potential antidepressant therapeutic device under the assumption that magnetic stimulation of the PFC would engage the connected limbic regions involved in mood and anxiety regulation (George, Lisanby, & Sackeim, 1999). The hypothesis is consistent with PFC rTMS modulating the function of frontolimbic circuits and subcortical structures controlling autonomic activity.

The effects of rTMS on the ANS may also result from a change of cortical excitation/inhibition balance. Several studies outlined a disruption in the cortical excitation/inhibition ratio in individuals with autism (Casanova, 2006; Casanova et al., 2002; Casanova, Buxhoeveden, & Gomez, 2003; Rubenstein & Merzernich, 2003). One possible explanation for an increase in the cortical excitation/inhibition bias in ASD is the finding of abnormalities in cortical minicolumns (Casanova, 2005). Double-bouquet cells in the peripheral neuropil space of minicolumns impose a strong vertically directed stream of inhibition surrounding the minicolumnar core (Mountcastle, 2003). In ASD, our preliminary studies indicate that cortical minicolumns are reduced in size and increased in number, especially within the PFC (Casanova, 2005, 2006; Casanova et al., 2002, 2006, 2012). Disturbances in the ratio of cortical excitation to inhibition may lead to an increase in cortical “noise” which may influence functional cortical connectivity and may hinder the binding of associated cortical areas. It has been proposed that the effect of low-frequency rTMS arises from increases in the activation of inhibitory circuits (Casanova et al., 2015; Sokhadze et al., 2014). Over a course of treatment rTMS may selectively lower the ratio of cortical excitation to cortical inhibition. Low-frequency rTMS over DLPFC may therefore lead to improvement in executive functions due to stronger lateral inhibition and enhanced functional connectivity that may lead to improvement in frontolimbic functions, leading to restoration of the normative inhibitory top-down control exerted by the frontal structures.

In previous studies we have reported on the positive effects of rTMS in autism using a large variety of outcome measures (Baruth et al., 2010, 2011; Casanova et al., 2012, 2015; Sokhadze et al., 2009, 2012, 2014, 2016; Wang et al., 2016). For better understanding of potential mechanisms of TMS neuromodulation effects on autonomic activity, it is necessary to consider the interaction between the central and autonomic nervous systems. The Central autonomic network (CAN) model proposed by Thayer and Lane (2000) describes how neural structures involved in cognitive, affective, and autonomic regulation are related to HRV and cognitive performance. In this model, the anatomical details of a CAN are described, linking the nucleus of the solitary tract in the brainstem with forebrain structures including the anterior cingulate cortex, insula, ventromedial PFC, amygdala, and hypothalamus through feedback and feed-forward loops. Thayer et al. (2012) outlined connections between the amygdala and medial prefrontal cortex (mPFC), which evaluate stimuli in the context of threat and safety and which regulate HRV through their connections with the nucleus of the solitary tract. Furthermore, the CAN model proposes that vagally-mediated HRV is linked to prefrontal executive functions and that HRV reflects the functional capacity of the PFC to support emotional and physiological self-regulation. It was hypothesized that parasympathetically mediated HRV is positively correlated with prefrontal cortical performance; thus, when prefrontal cortical functioning is decreased, HR increases and HRV decreases. Prolonged prefrontal cortical inactivity can lead to hypervigilance, defensiveness, and social isolation (Thayer, Hansen, Saus-Rose, & Johnsen, 2009). The CAN model predicts reduced HRV and hypofunctional vagal activity in anxiety, as it might be associated with abnormal ANS cardiac control (Friedman, 2007). This approach challenges the sympathetic overarousal model of anxiety that overlooks the role of a hypofunctional parasympathetic system. From this perspective, disorders presenting with anxiety and dysregulated autonomic control can involve varying degrees of sympathetic overactivation and parasympathetic underactivation. The main point is to account for

both autonomic branches' activation status in research aimed at understanding the nature of autonomic dysfunction.

The strategy for the selected intervention, considering the CAN model, is that neuromodulation of the DLPFC using low-frequency rTMS can increase the PFC's ability to exercise top-down control of emotional responses. Due to a cascading effect caused by the anatomical and functional connectivity of this integrative prefrontal brain region, we expected the TMS-based intervention not to be limited to the site of magnetic stimulation but rather to generalize to other cortical and subcortical areas including those directly involved in autonomic arousal control. Biophysical foundations underlying TMS effects are reviewed in Wagner, Rushmore, Eden, and Valero-Cabre (2009), while effects of TMS on connectivity of the cortical structures are reviewed in Paus et al. (1997). Results of our pilot studies (Sokhadze et al., 2009, 2016) showed changes of event-related potentials and induced electroencephalographic (EEG) gamma oscillations that occurred not only in the frontal lobe but also in distal cortical areas (e.g., parietal, parieto-occipital). Effects of rTMS over DLPFC are possibly extended to paralimbic and limbic structures as well and may manifest themselves in ANS activity changes.

Brain functions involved in the generation and representation of arousal state have been linked to social cognition in typical development (Critchley, 2005), suggesting that they may be important to disorders of social interaction such as ASD. According to Critchley (2005), emotional and cognitive processes evoke patterned changes in profiles of physiological measures that may signal a particular emotional state. The modulation of the visceral state is mediated by the sympathetic and parasympathetic divisions of the ANS. Moreover, neural afferents support and convey representations of the internal state of the body to the brain to further influence emotion and cognition. Feedback from the viscera is mapped in the brain to influence efferent neural signals and, at the cortical level, to reinforce affective responses and emotional states. The discrete cortical substrates for these representations include the anterior regions of the insula and orbitofrontal cortex, areas that have direct connections with the DLPFC. The misperception of heightened arousal level (either over- or underestimation of actual autonomic arousal level status) may readily evoke significant changes in emotional behavior. Cognitive processes such as decision-making are guided by central feedback of bodily arousal responses (Damasio, Everitt, & Bishop, 1996). The influence of transient arousal responses on aspects of affect and cognition is embodied within Damasio's "Somatic Marker Hypothesis" which proposes that emotional feelings originate in mental representations within the somatosensory cortices (Damasio et al., 1996). Empirical studies have implicated the insular cortex as the substrate for emotional states, supported by activity within the amygdala, anterior cingulate cortex, and orbital prefrontal regions—structures which communicate directly with the DLPFC. The anterior insula and ventromedial prefrontal cortex contribute to the integration of visceral afferent information. These observations also map into the insula theory of anxiety of Paulus and Stein (2006), who propose that feelings of anxiety emerge through mismatched representation of anticipated and perceived bodily states within the insular cortex. The role of the heightened sympathetic arousal and reduced vagal afferent activity biasing normal autonomic/visceral state representations therefore may negatively affect emotional reactivity in individuals with ASD.

There are several limitations of this study that need to be noted. The study was not controlled, as it was not randomized and did not use a sham rTMS group, and as such represents a continuation of our case series studies. Furthermore, we measured only tonic resting state autonomic activity during rTMS procedure. Considering that the differences between children with ASD and typically developing children are reported not only in tonic basal autonomic arousal level but also in phasic autonomic responses to various stimuli, it would be important to have a comparison in autonomic reactivity as well. The age range in our cohort was quite wide, even though our statistical analysis of age-related factor yielded age differences only in peaks of VLF and LF of HRV. Medication status of all subjects was monitored but not included as a confounding factor in statistical analysis. Ratio of boys vs. girls was 3.5:1, which was probably the reason why we could not find any gender-related factor effects on rTMS course outcomes. Our future studies will address limitations listed above by adding sham-TMS group, stratified blinded randomization of children with ASD into active and sham-TMS groups, and a battery of psychophysiological tests pre- and posttreatment. We plan also to recruit subjects with more restricted age eligibility range to rule out age-related factor influences.

Conclusion

In general, complementing rTMS treatment with concurrent monitoring of autonomic functions may advance neuromodulation approaches in other psychiatric and neurological disorders as well, especially in those where rTMS treatment has been shown to be effective (e.g., major depression, obsessive compulsive disorder, schizophrenia, Parkinson disease).

The current theory-guided pilot study was based on a hypothesis proposing that rTMS over the DLPFC improves cortical excitation/inhibition ratio in autism and enhances prefrontal functioning, including enhancing normative prefrontal inhibitory influences on the limbic system and subcortical centers controlling level of autonomic arousal. We propose that the application of rTMS has potential to be considered as a novel, customizable neurotherapeutic tool targeting autonomic balance that may positively affect the social and behavior deficits as well as the hyperactivity and anxiety problems experienced by children and adolescents with autism. In addition, this tool could serve as a platform for the development of treatments of other childhood anxiety disorders.

We believe that the application of neuromodulation techniques to increase parasympathetic activity and lower sympathetic activity is a potentially powerful approach to treating some symptoms of autism. Our underlying rationale for using rTMS in children with autism links cardiac underreactivity in socially engaging situations to dysfunctions in cardiac autonomic regulation in autism which results in a reduced attentional capacity to attend socially relevant stimuli critical for effective communication with peers. This hypothesis outlines an important role of the ANS in emotional reactivity and social behavior. Poor control of HR and vulnerability to tachycardia is an important consequence of chronic increased sympathetic activity and decreased vagal tone (Berntson et al., 1997; Corona et al., 1998; Friedman & Thayer, 1998; Thayer et al., 2012). The baseline sympathetic arousal found in autism may be a condition of disinhibition, resulting from compromised baseline parasympathetic inhibition. Reduced frontolimbic connectivity and poor prefrontal tonic inhibitory control over the limbic system might be one of the reasons for excessive excitation of the sympathetic system in ASD. TMS could be an effective technique for restoring regulation of parasympathetic activity and for improving sympatho-vagal cardiac balance in autism. It may also result in restoration of normative visceral representations thought to be distorted in autism due to chronic sympathetic overarousal.

Future randomized clinical trials with blinding and sham TMS control conditions may help in establishing rTMS as a neuromodulatory treatment aimed to regulate autonomic balance in children with ASD. The current study is an early step aimed at demonstrating the feasibility of this approach and a call for further exploration and rigorous, controlled clinical trials.

Author Notes

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NeuroRegulation

Neurotherapies and Alzheimer's: A Protocol-oriented Review

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Abstract

Due to recent findings in animal models of Alzheimer's disease (AD), neurotherapy studies are reviewed with a focus on brainwave studies, neurofeedback, and audiovisual stimulation techniques with a goal of finding improvement of cognitive impairment from aging and Alzheimer's disease as well as the possible diagnostic, preventative, and therapeutic use in humans. Some protocols which might offer significant improvements in attention, executive functions, and mood states are identified, specifically for the first stages of the disease. The recent advances in microglia stimulation are also reviewed. In general, the analyzed data of the classical protocols match with the result of the last 15 years of investigation of Alzheimer's disease EEG characteristics.

Keywords: Alzheimer's; AVE; 40 Hz; neurofeedback; binaural beats; gamma; MCI; microglia

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Methods

From January 1 to May 31, 2017, a search was conducted on PubMed and Scholar Google for papers or publications containing the terms *Alzheimer*, *Alpha*, *Gamma*, *Neurofeedback*, and *Binaural beats*.

Alzheimer's Disease and Societal Burden

Alzheimer's disease (AD) is one of the biggest social and health problems, with probably the largest economic cost due to the high incidence rate in aging societies. In a European country such as Spain, it is calculated that about 1 million people will be suffering from the disease by 2050. As a neurodegenerative process, it slowly turns into a disease which impairs the person, causing loss of independence and, finally, death by immobility, drug complications, and/or cardiovascular problems (Prieto Jurczynska, Eimil Ortiz, López de Silanes de Miguel, & Llanero Luque, 2011). The advancement of the disease causes problems such as memory loss, insomnia, and dementia. Rodrigues, Castro, and Spanish Red Cross (2014) find that personality changes in patients with AD, especially in neuroticism and openness. Some notable psychological findings are anosognosia and the lack of immediate memory. The latter is the consequence of the dysfunction of episodic memory (temporal left medial area), while anosognosia is in relation with hypoperfusion of the right dorsolateral prefrontal cortex (DLPFC) and inferior Mini-Mental State Examination (MMSE) scoring (Gil et al., 2001).

The psychological impact of the diagnosis on family members is also important; in fact, depression can have a significant impact on the family. Depression and anxiety are burdensome for the family and their environment. Notification of the diagnosis might cause a greater impact on the caregiver and the family than on the subject himself (Lladó, Antón-Aguirre, Villar, Rami, & Molinuevo, 2008). The Handbook of Dementia (Lichtenberg, Murman, & Mellow, 2003) says that AD causes two victims: the

caregiver and the subject. Caregivers tend to be women (wife or daughter) suffering from anxiety, depression, and burnout; three studies on different continents sampled caregivers and reported respondents had similar burnout and mean ages: 52.5 in Japan, 55 in Spain, and 50 in Colombia (Gupta, Stankus, Fukuda, & Okumura, 2015; Peinado Portero, 1998; Zambrano Cruz & Ceballos Cardona, 2007).

One of the factors leading to caregiver burnout is the lack of handling and coping strategies. Caregiver burnout could improve with mindfulness-based programs, though the efficacy seems to be only short term (Franco, Sola, & Justo, 2010). Effects in executive function (EF) are found; Stroop and anxiety and depression scores are impacted (Bromberg et al., 2015). Correa et al. (2015) find that cognitive impairments in caregivers are linked to decreased BDNF levels and increased cortisol/DHEA ratios.

Pharmacological treatment

Drug treatment has been based on cholinesterase inhibitors and the N-methyl-D-aspartate (NMDA) receptors such as memantine. Memantine seems to avoid the neurotoxic effect of the excessive level of glutamate present in AD. The goal of memantine is to avoid the development of the disease and increase the general cognitive capacity. However, the drug, as a single treatment or together with anticholinesterase, does not seem to work in the very first stages of the disease. Its efficacy on the last stage of impairment seems to also be limited (Schneider, Dagerman, Higgins, & McShane, 2011). On top of this, extreme overdose could lead to a lack of consciousness (Kitagawa & Sakurai, 2016). The meta-analysis of Matsunaga, Kishi, and Iwata (2015) finds that a memantine monotherapy produces a small improvement in cognition, behavior, and daily activities in studies with patients with an average age of 76 years old. Recently, some companies have had to abandon anti-amyloidal drugs due to failures in efficacy and issues with toxicity, such as in solanezumab and verubecestat trials (Hardy & De Strooper, 2017), which is very bad news for the advancement of the pharmacological treatment of the disease.

Cognitive rehabilitation

Cognitive rehabilitation (e.g., brain training platforms, memory exercises, cognitive treatment, and psychomotor exercise via Kinect-based platforms) seems to be the option proposed from the field of Cognitive and Health Psychology in order to keep maximum self-autonomy for daily activities. These treatments have been evaluated because they are the most common option of treatment in day centers and nursing homes, where it is very easy to keep optimum experimental follow-up. Gates and Sachdev (2014) found that cognitive training in preclinical people produces effects which can be transferred to other domains of daily activity. However, in meta-analysis Bahar-Fuchs, Hampstead, and Clare (2014) didn't find significant data that supports any option of cognitive training or rehabilitation. Clare and Woods (2004) analyzed several techniques of stimulation, rehabilitation, and training and did not find any significant effect.

The analysis of Frank and Konta (2005) is especially critical of the lack of outcome evaluation standards in this field, despite one third of the studies showing an improvement in the life of the subjects. Olazarán et al. (2010), on the other hand, analyze cognitive and educational treatments oriented to the life of the patient and the caregiver and find some evidence that nonpharmalogical therapies can improve the quality of life for both persons; for example, through a delay in the institutionalization of the patient by stressing training of daily life activities and behavior management. The FEEN study also shows that any strategy to delay the institutionalization of the patient is a positive benefit versus cost and merits attention and investment (Prieto Jurczynska et al., 2011, p. 29, 34). Recently, Orrell et al. (2017) found in an analysis that a structured and individualized stimulation therapy versus "treatment as usual" has no differential effect for people with dementia. Nonetheless, one of the conclusions is interesting: the caregivers believed that the experimental condition was "the best of things," such that the quality of the relationship between caregiver and the subject appeared enhanced after participation, but, on the other hand, the quality of life of the subject did not improve significantly.

AD: Models of the Disconnection Syndrome

The amyloidal hypothesis of AD by Hardy and Selkoe (2002) keeps an increase in β-amyloidal "production versus clearance" as the main scientific explanation for the disease's cause. The beginning of the disease is hypothesized as an alteration of production of amyloid β-peptide (Aβ), probably by genetic causes, which produces the accumulation of Aβ and toxic plaque deposits. This mechanism could be initiated by a decrease in production of cholinergic inhibition.

The mechanism release damages in synapses, microglia activation, and astrocytes in M1 state and

causes neuronal damage, oxidative load (NOx also helps Aβ to accumulate in plaques), and inflammation. Later, tau neurofibrillary accumulation within neurons, apoptosis, and destruction of functional connective structures occurs. Microglia is "primed." The production of amyloidal plaques is believed to originate in the entorhinal medial temporal lobe (MTL) zone (Heneka et al., 2015), which is involved with episodic memory. Therefore, the most common concerns, which are a lack of recent memory in mild cognitive impairment (MCI) and subjective memory complaints (SMC), could be a symptom of the advance of the disease in this area.

To this model, the addition of activity-dependent degeneration (ADD) connectivity and activity impairment (de Haan, Mott, van Straaten, Scheltens, & Stam, 2012) is based on the extension of the disease via functional networks from the MCI status to the final phase. Parietal lobe and default mode network would suffer from the spread of the disease from subcortical areas, and then, finally, the frontal lobes would be affected. Loss of connectivity could mean an increment of activity due to the lack of inhibition, and the chronic neuronal damage would result in symptoms such as epilepsy.

Jack's (2013) model contributes that Aβ is not enough for AD to show, but we need to also have biomarkers of neurodegeneration such as cortical atrophy and hypometabolism. The model additionally suggests the possibility that Aβ and tau are two distinct processes. The factors of cognitive reserve and brain resilience mediate the progression of the disease and the appearance of cognitive impairment (Jack, 2013, Point 4).

Hardy (2009) added vascular damage as a factor in relation to amyloidal accumulation that could explain cortical atrophy. The famous contribution of the Nun Study (Snowdon et al., 1997) highlights the preservation of the cardiovascular status as determinant to the appearance of the clinical symptoms. Aβ is produced by the simple sensorimotor neuronal activity, as shown in APP transgenic mice (Bero et al., 2011). Choi et al. (2014) realized an experiment in petri dishes with 3D human cells in a familiar Alzheimer's model called "Alzheimer's in a dish," which seems to confirm that the model begins with amyloidal deposition, extends to tau fibers, and finally causes a generalized neuroinflammation.

Brainwave studies in MCI and AD

Electroencephalography (EEG) analysis is a neuropsychological tool that allows measuring the brain activity through the analysis of the electrical activity registered with electrodes over the scalp. Improvement of systems, standardization of 10–20 placement system, and the existence of EEG databases allow us to register deviations (Collura, 2014, chapters 7–9; Kropotov, 2010). This enables us to elaborate on a hypothesis about the functionality of brain waves and centers according to psychological diseases and on protocols for the treatment of those.

The electrical activity is usually studied as delta δ (0.5–4.0 Hz), theta θ (4–8 Hz), alpha α (8–12 Hz), beta1 β1 (13–20 Hz), beta2 β2 (20–30 Hz), and gamma γ (30–100 Hz). Gamma is a name that covers a broad or narrow range (Chapin & Russell-Chapin, 2014). In γ neurofeedback papers, γ of 40 Hz is studied in the range of 36 to 44 Hz (Keizer, 2010). Tallon-Baudry and Bertrand (1999) consider that cognitive (poststimulus) operations fall in the range of 30 to 60 Hz. We will later study γ and AD.

Moretti et al. (2004, 2012, 2015), in various articles, use specific ranges for study of MCI: δ (2.9–4.9), θ (4.9–6.9), α1 (6.9–8.9), α2 (8.9–10.9), α3 (10.9–12.9), β1 (12.9–19.2), β2 (19.2–32.4), and γ (32.4–45), which must be considered in future references for this author. Individual α frequency for subjects with AD, for example, fall to 8.7 Hz in MMSE 20.5, within α1 (Moretti et al., 2004). We will list the main findings according to the chronological order of appearance in MCI and AD, according to findings with EEG, magnetoencephalography (MEG), and quantitative electroencephalography (qEEG).

Theta increase: Kropotov (2010) explains the beginning of the disease as a lack of cholinergic inhibition of septum to the hippocampal circuits, which produces θ hyperactivity. This causes a tonic θ rhythm, which can be measured not only in temporal but frontal areas. Theta increased is confirmed by Moretti (Moretti, Prestia, Binetti, Zanetti, & Frisoni, 2013) which finds a relation with hypoperfusion specifically in amnestic mild cognitive impairment (aMCI). Theta increase is, however, not a specific sign of AD, since it also appears in normal aging groups (NAG), women, and vascular dementia subjects (Jeong, 2004).

Beta1 decrease and spreading: Dauwels, in his review, finds that the range 7–17 Hz is severely decreased in retrieval operative memory tasks in AD (Dauwels, Vialatte, & Cichocki, 2010). Poil et al.

(2013) aim to show that there would be an abnormal distribution of the β-frequency range and β peak in AD (i.e., a faster, spread rhythm than no-AD).

Alpha decrease: α range is decreased in the range 8.0–10.5 Hz (Babiloni et al., 2009), specifically in central locations. Dauwels' review also confirms this reduction (Dauwels et al., 2010). Lack of α rhythm can be considered a lack of inhibition, cognitive flexibility, and behavior control (Sadaghiani & Kleinschmidt, 2016). In a longitudinal study, Kuskowski, Mortimer, Morley, Malone, and Okaya (1993) found that inferior qEEG power values of 8–12 Hz were associated with later MMSE score decline.

Delta increase: an excessive δ increase in the range of 2–4 Hz can be considered a sign of neuroinflammation (Dauwels et al., 2010), which can in turn be a sign of disconnection and the final stages of the disease as well as lack of white matter in the frontal lobes. In addition, Babiloni et al. (2006) find increases of frontal δ in cases of aMCI. Dauwels suggests that EEG diagnosis could allow us to establish the real damage level in the brain of the subject, in order to adopt the most adequate treatment in terms of cost and opportunity.

MCI diagnosis through EEG

There are some articles which study the EEG and MEG profile of MCI vs. NAG as a control in order to ascertain which could suffer a MCI and possibly later lead to AD.

Rodriguez, Copello, Vitali, Perego, and Nobili (1999) stress the difficulty of distinguishing between NAG and those with real cognitive problems, even with people showing early signs of AD. Some NAG may have an α of slightly over 8 Hz without any major cognitive symptoms. The most important signs are the so-called "shift to the left" or generalized increase in slow frequencies, increase of θ, global decrease of 8.0–9.5 Hz α and 10.0–11.5 Hz (α1 and α2), and, lastly, an increase of δ.

Kashefpoor, Rabbani, and Barekatain (2016) find the following possible MCI patterns in a group of patients who had cardiac catheterization with a MMSE of 27, determined through a fuzzy logic treatment of EEG: Increased ratio of slow and high frequencies (γ excluded); relative power of the α band (7.5–9.5 Hz), β2 (17.5–25 Hz) reduced power (and posteriorized) and posterior increase of γ. The most interesting finding is that peak α seems to not be a marker (even though the contributions of anterior and posterior zones might be different).

Garcés et al. (2013) found an extended α peak of 7–11 Hz with MEG, which correlates to the lack of posterior rhythm and hippocampal reduction. For subjects with MCI, these authors found an α peak of 9.05 ± 0.90 Hz. Van der Hiele et al. (2007) find that α reactivity (i.e., α EC vs. EO) is related to psychomotor and cognitive slowing and memory impairments.

Fauzan and Amran (2014) find a significant increase of *Z*-score of β2 in F4 (a potential marker of anxiety/depression) in six elderly persons with MCI (MMSE < 23) vs. 14 controls. In EC, the increase of θ is found in F8, P4, and T6. F8 shows also a significant increase in δ.

Finally, Babiloni et al. (2009), with Loreta, finds frontal increased δ (SMC and aMCI bigger than NAG), increased parieto-occipital amplitude in α1 and α2 (NAG and SMC bigger than MCI and aMCI) as two of the best EEG diagnostic markers (note the close MMSE scores: NAG 29, SMC 28.5, MCI 28, aMCI 26.82).

MCI converting to AD

We will now review which markers could indicate MCI converting to AD. The suggestion of some authors is to not use the diagnosis as an AD diagnosis but rather to keep specific care actions, since EEG markers have been linked to damages in hippocampal areas, or frontal or parietal atrophy. As precise EEG markers, the ratio of α3/α2 is linked to damage on the hippocampus (0.75) and the θ/γ ratio with damage in the amygdala.

Moretti (2015) studies the power ratio of α3/α2 as a diagnostic factor with SPECT neuroimaging help, showing cortical atrophy and temporo-parietal hypoperfusion. The α band is determined from the individual α frequency, but the author gives a power ratio bigger than 1.17 of α3 (10.9–12.9 Hz) vs. α2 (8.9–10.9 Hz) as a marker that links MCI conversion to AD and bilateral hypoperfusion in precuneus. The main explanation by the author is that the lack of inhibitory interneurons provokes a hypersynchronization in the neuronal network precisely because of the atrophy process. Moretti et al. (2004) also found as a significant marker the bigger relative power in α2 in NAG (MMSE 29.09) vs. AD (MMSE 20.58).

Poil et al. (2013) studied the diagnostic power of several EEG markers in advanced AD. The most significant seems to be the β (16–30 Hz) peak, with a difference of 17.6 Hz in controls vs. 19.6 Hz in MCI converters, that results in a mean posterior decrease

in MMSE from 28 to 24. The width of β peak seems to also be bigger in the AD group (3 Hz vs. < 1.5 Hz in MCI), and the α power ratio is also inferior (< 30% in AD vs. > 30% in MCI).

In the SMR/β1 range, sleep spindles, REM sleep time, and slow-wave production are shorter in AD (Tsolaki, Kazis, Kompatsiaris, Kosmidou, & Tsolaki, 2014). This could explain insomnia in AD and altered sleep/vigilance patterns. In general, β1 is one of the groups of frequencies with a larger decrease.

Hsiao, Wang, Yan, Chen, and Lin (2013) analyze a group of MCI with MMSE 22.7 vs. AD with 14.9, finding that the most important relation between MMSE and EEG scores can be found mostly in precuneus, posterior cingulate, and parietal and corresponds with increases in θ and decreases in α1 and α2. Rodriguez, Arnaldi, and Picco (2011) find a marker of AD to be the lack of α blocking and its anteriorization.

From the psychological point of view, the increase of β distribution suggests a neuronal background hyperexcitability, but an inefficient one. Sadaghiani and Kleinschmidt (2016) describe the need of α rhythms as "screen wipers" or slate cleaning, which allows the cyclic inhibition of signaling and control of information. Cognitive processes in α and β seem to be damaged in the AD conversion process. With reference to γ rhythm, the paradoxical increase in the rhythm could be on the local level, which means an adaptation to the disconnection and hypersynchronization syndrome. Van Deursen (2008) finds an increase in extended γ (30–100 Hz) in AD and MCI vs. NAG.

In the very last stage of the disease, Rodriguez et al. (1999) find an increase in the θ relative power in the right zone linked with incontinence. The authors also find an increase in relative δ power in the right zone, which correlates with the incapacity for activities of daily life, leading to the possibility of death.

Dynamic analysis

The reduced complexity term in other bands is identified in the review by Dauwels et al. (2010) as a finding of EEG characteristics in AD.

Jeong (2004) explains two factors that have been found through nonlinear mathematical analysis on AD with the use of a single EEG channel. The D_2 component (number of independent variants necessary to explain the complexity of a system, also explained as the dimensional complexity of the system in a geographic space) is one of them. The occipital measure of this component is reduced in AD. The author suggests that one of the explanations is the lack of connectivity that leads to local disconnected networks. In control subjects, D_2 is increased in the eyes-open condition, as response to desynchronization of α rhythm. In AD there is scarce difference between EO and EC (Pritchard, Duke, & Coburn, 1991). This suggests a disconnection from external stimulus and damage to α rhythm-related circuits. The second component is L_1, a dynamic component linked with flexibility of processing (also explained as the possibility of growth from an initial condition), which could be decreased in AD. Jeong (2004) suggests that these components appear in the middle and last stages of AD and show basic cognitive processes altered by the disease.

Lempel–Ziv (LZ) complexity has been used by Abásolo, Hornero, Gómez, García, and López (2006) and Gómez, Hornero, Abásolo, Fernández, and López (2006) in AD subjects vs. healthy age-matched controls. LZ is a measure of distinct substrings happening in any sequence of data, which analyzes the rate of occurrence and change along the sequence (also explained as the capability of temporal change of a frequency according to the number of new patterns of it). Sequences of data obtained from an electrode (EEG) or an MEG point are extracted and turned into binary (0,1) or 3-item (0,1,2) according to a threshold. An algorithm then calculates, left to right, when any given sequence is contained in the next sequence. Each new sequence makes a point, and the point is added to a counter C(n), or LZ. For those interested in the meaning of a "sequence" (such as is considered by the LZ algorithm), it can typically contain from one to six data bits (measures). At a supposed screening rate of 170 Hz for 3400 data in a 20-s epoch, this means about 1 bit = 0.006 s; therefore, sequences may last from 6 to 36 ms.

As any putative measure, the worth of LZ comes from the clinic and diagnostic power. LZ is lower in AD. The receiver-operating characteristic (ROC) for Abásolo et al. (EEG, AD MMSE 13.1/5.9) is 89.3, and for Gómez (MEG, AD MMSE 18/3.9) is 90.02. Abásolo finds 90.9% specificity on P3, 90.9% sensitivity on O1, and differences in P4, and, interestingly, also in T5 (the area of object naming and recognition memory) in the most damaged AD sample of both papers.

Neurotherapies

Neurotherapies can be explained as therapies that use the brain rhythms and their modulation (Chapin & Russell-Chapin, 2014, p. 3). This article will focus on neurofeedback (reinforcement) and audiovisual (stimulation). Other neurotherapies will also be mentioned.

Neurofeedback in NAG, SMC, MCI, and AD

Neurodegenerative diseases may be remediated with the help of neurofeedback. The example is Parkinsonism, which has been treated with neurofeedback (Azarpaikan, Torbati, & Sohrabi, 2014) showing success in balance improvement with reduction of θ in O1.

The number of scientific articles dealing with neurofeedback in MCI or AD is limited (a fact already noted by Kropotov in 2010), which could suggest that the disease is incurable or untreatable. One of the biggest problems is the difficulty of the treatment in seniors. In an fMRI neurofeedback mood treatment in NAG, Rana et al. (2016) mention motivation and attention as the factors most affected by fatigue or lack of stimuli novelty, or because of the logistics of the sessions. We will mention firstly neurofeedback articles with NAG and SMC and secondly the ones with MCI or AD subjects.

In elderly normal people, there are some interesting articles. Becerra et al. (2012) uses a protocol of reduction of θ rhythm (in the ROI where the ratio θ/α is bigger). This results in an increase of the α rhythm in amplitude power, reduction of θ in midline and left frontal, and an increase in verbal capacity and memory. Also in normal seniors without AD diagnosis, Angelakis et al. (2007) uses a protocol of elevation of peak α that increases processing speed and EF without significant improvement in memory.

Staufenbiel, Brouwer, Keizer, and van Wouwe (2014) use increases of β1 and γ frequencies in location Fz. The results of the eight sessions show an increase within sessions, but without any other significant findings nor transference in the behavior. An explanation for this, proposed by the authors themselves, could be the scarce number of sessions (eight) and that the brain of the seniors could not recognize properly the reinforcement signal (a sound). Improvement in sleep and reduction of appetite (linked to increase in β1 in F4) are noteworthy. Bird, Newton, Sheer, and Ford (1978) had already shown the feasibility of neurofeedback in the γ band (increase and decrease) in healthy people, from his first studies of α and γ range in cats.

We have to mention the classic protocol of "brain brightening," which basically is a reinforcement of the upper α range, a protocol similar to the work of Budzynski, Budzynski, and Tang (2007). Chapin and Russell-Chapin (2014, p. 187) find that this protocol is very possibly validated in children and adults. The work of Escolano, Navarro-Gil, Garcia-Campayo, Congedo, and Minguez (2014), about the individual upper α in children with ADHD and adults, adds evidence to this protocol. In adults, Zoefel, Huster, and Herrmann (2011) find the improvement of cognitive functions with similar protocols in Pz and Oz.

Now in subjects with AD, we have to mention the Luijmes, Pouwels, and Boonman (2016) paper. Using a qEEG and NeuroGuide database, the study uses a different protocol for each subject in 10 subjects on cholinesterase. The most common protocols are increases of median frequencies, α (spread in low and upper) in Pz, and decreases of θ and β2 in Fz. Using this procedure results in an increase of cognitive functions altered by AD. Lucas Koberda (2014) in his work with Loreta and *Z*-score mentions several cases of AD, but some of the specific cases (7, 9) do not show improvement with this technique.

In institutionalized resident subjects with mild AD (MMSE 27) a multimodal brain fitness program, which included neurofeedback via qEEG (BrainMaster Technologies, Inc., Bedford, OH) on a remarkable size (N = 127), showed a slight improvement in 84% of the subjects. A point of the treatment was psychological support (stimulation on sense of life). Reduction of excess β2 was one of the goals of the treatment. The most significant outcome is the maintenance or increase of the hippocampus via fMRI check in a subsample of 17, in 70% of the cases (note: physical exercise was fostered; Fotuhi et al., 2016).

Surmeli et al. (2016), with the help of qEEG neurofeedback, experience an important degree of success, due to the degree of impairment (MMSE 18.8) of the sample (N = 20) and the outcome after treatment (MMSE 24.5). A great number of subjects show brain atrophy and could leave medication after treatment and follow-up. Among the protocols used are suppression of slow waves and β2, increase of β1, and SMR increase in Cz-C4.

Table 1

Neurofeedback in Elderly: Protocols, ROI, and Results.

NAG Studies	Group (*N*)	Age (*M/SD*)	MMSE	Diagnostic? / EEG System	Protocol / ROI	Test / Process	Outcome
2007 Angelakis	NAG (3)	74 (70–78)	N/A	N/A	α IAF +2 Hz in POZ (3) vs. α amplitude (Control, 33 x 24')	Processing speed and EF memory improvement	Improves
2011 Lecomte Juhel	NAG (10)	75.25 (65–85)	N/A	Only 4 sessions	Inc. α, Inc. α/θ β1/θ in the same session. C3/C4	Memory, stress	Stress improves
2012 Becerra	NAG (7)	65.8 (60–84)	Test Exc.	θ Exp = Control	Decrease θ ROI > θ/α α↑ increase as EEG outcome (30 x 30')	EF, memory, and verbal	Verbal improves
2014 Staufenbiel	NAG (10+10)	67.8	N/A	N/A	Inc. γ and β1 in Fz (8 x 30')	Operative memory	WN, N/ signific.
2015 Gomez-Pilar*	NAG (11)	68 (60–80)	N/A	BCI Motor Imagery	Relative power in 12, 18, 21 Hz Zones C3, Cz, C4	Visospatial, verbal, memory	Improves
2016 Reis	NAG (9)	66 (59–72)	N/A	N/A	Feedback α (4d) θ (4d)	Rotation task (Operative memory)	Improves
MCI & AD Studies	**Group (*N*)**	**Age (*M/SD*)**	**MMSE**	**Diagnostic? / EEG System**	**Protocol / ROI**	**Test / Process**	**Outcome**
2009 Berman	AD (16)	N/S	N/S	qEEG	Inc. 10–18 Hz, 35 x 30' average	Verbal, orientation, behavioral, EF	All but EF
2011 Collura $ & Festa**	AD + NAG	74.8 (62–86)	AD 17	qEEG	Norm qEEG in C3, C4, P3, and P4 8 sessions x group	Speed in spatial orientation Attention in spatial orientation	Yes, in NAG Yes, in AD
2014 Koberda	AC, MCI, N/D	N/A		Loreta + *Z*-score	*Z*-score	Cognitive, mood, other	Improves 71%
2016 Fotuhi***	MCI (127)	70, 7 (10, 5)	27	qEEG BrainMaster	Dec. θ and δ Dec. β2	Cognitive, var. tests. Hippocampal atrophy	Improves Reduction
2016 Luijmes	AD (10)	71 (64–78)		Yes	Dec. θ (Cz, Fz), Dec. β2 (Fz) SMR Inc. in Cz, Inc. α Pz	Memory, cognitive tests	Improves
2016 Rana	AD (6)	66 (51–71)		fMRI NF	fMRI RT NF BOLD Insula	Cognitive flexibility	Improves
2016 Surmeli	AD (9) VD (11)	69 (58–79)	18, 8 (< 26)	qEEG	Dec. slow, Inc. β1 Inc. α, Inc. δ θ/β in C3, SMR in C4 Positions: Fp, F, C, O	Medication and MMSE (24, 5) Memory and EF Hippocampal atrophy	Improves Improves Reduction

* = Personal communication: power ratio as neurofeedback objective (threshold) during brain-computer interface (BCI) imagery; ** = Presentation by Festa, Heindel, Connors, Hirschberg, & Ott (2009); *** = Multimodal treatment included exercise, diet, and cognitive training; $ = Financial interest disclosed. Main protocols mentioned for MCI by Budzynski et al., 2007, pp. 246–247: α increase, peak α increase in Pz, slow frequencies decrease (2–8 Hz). Acronyms: POZ = parieto occipital zone; WM = working memory; VD = vascular dementia

Other Neurotherapies

We have to mention other therapies, such as music therapy, with a possible effect on memory maintenance and as a pleasant daily activity (Lichtenberg et al., 2003, p. 39). A Canadian musical therapist specializing in AD (Clements-Cortes, Ahonen, Evans, Freedman, & Bartel, 2016) has developed sing-along techniques (which stimulate memory and rhythm) and techniques of vibro-stimulation and stimulation with sounds at 40 Hz. Also remarkable is the slight improvement of AD with MMSE (0) in activity patterns and rest time in nursing homes with bright light therapies (Dowling, Graf, Hubbard, & Luxenberg, 2007; Skjerve et al., 2004). Hansen (2014) reviews other neurotherapies such as TMS, TDCS, and TENS. Some of them show promising data in memory improvement and cognition, increasing plasticity and neuronal connectivity, modulating α and θ rhythms. There are no major studies on CES.

The broad γ range

As we have seen before, γ range usually is defined as activity from 30 to 100 Hz. Gamma is defined as a mostly inhibiting activity, caused by interneurons on the body of pyramidal neurons. Gamma activity would be linked (phase and time) to other waves as α and θ, and would be the result of an excitation and inhibition game, or the result of mutual inhibitions (Buzsáki & Wang, 2012). Fast-spiking (FS), parvalbumin cells, a special interneuron type, seem to fire specifically at 25 ms, creating a range of frequencies of 35 to 40 Hz (Cardin et al., 2009).

The appearance of this rhythm would not happen spontaneously but due to inner processes which would be induced by a stimulus or evoked (not directly). The difference between induction and evocation could be defined as γ directly evoked and depending, on phase and amplitude, on another rhythm or evoking stimulus. 40 Hz, as an evoked rhythm, is temporarily linked to the appearance of a stimulus, meaning an "immediate" processing of the stimulus. Induced γ, on the contrary, has a bigger latency, is dependent from other cognitive processes (sensorial integration), and can be found on the wider 30–80 Hz range. The latter is subject to lateralization according to function: verbal stimulus induce γ on left hemisphere, image rotation induce right γ activity (Tallon-Baudry, Bertrand, Wienbruch, Ross, & Pantev, 1997).

Başar-Eroglu, Strüber, Schürmann, Stadler, and Başar (1996) call it a "Universal Operator," a kind of inner code that rules other brain oscillations. The authors summarize the range of 40–60 Hz with frontocentral attention processes, ambiguous image processing, and long-range brain synchronization. Ambiguous items would induce a bigger γ rhythm.

We have seen the role of γ in cognitive processes. Now we will see its relationship with AD. Gamma is produced by FS interneurons. Through optogenetic stimulation, Cardin et al. (2009) provoke FS cells to produce a rhythm of 35–40 Hz, which produces a suppression of sensorial stimuli. The inhibitor role of γ rhythm is demonstrated in a transgenic mouse model (hAPP) in which hypersynchronization is produced while γ rhythm is reduced, producing memory and learning deficits and epilepsy (Verret et al., 2012). This suggests that a reduction of γ 40-Hz range rhythm might produce similar symptoms as AD.

Audiovisual entrainment techniques

Audiovisual entrainment is a stimulation technique which uses acoustic and photic stimulus simultaneously. In the case of elderly people, the use of neurofeedback and audiovisual entrainment (AVE) was used by Budzynski (Grove, 2011), which can be reviewed in the book *Introduction to Quantitative EEG and Neurofeedback* (Collura & Siever, 2009). There are some AVE manuscripts (Siever, 2007) on ADHD, anxiety, depression, and PTSD. Teplan, Krakovská, and Štolc (2006a, 2006b) found short- and long-term effects of this audiovisual stimulation (AVS, 25 x 20', mixed median frequencies) therapy, which can be considered of linear and nonlinear effect.

Next, we will review studies on sound beats and photic stimulation in 10 Hz, 40 Hz, and other frequencies used in aging and cognitive function improvement in the elderly.

Click and monaural stimulation

Click stimulation has been realized with sounds of very short duration, which lack any psychological meaning (just "ticks"), used mostly in dichotic psychophysiologic studies. Some of these studies are monaural stimulus directed to an ear. Pastor, Artieda, Arbizu, Valencia, and Masdeu (2003) find that the stimulus at 40 Hz activates the pontocerebellum area, a zone implicated in timing and cortical inhibition. The maximum response is shown in F3 when the stimulus was presented in the right ear, and the maximum response amplitude was shown when the frequency was 37.75 Hz.

Ross, Picton, Herdman, and Pantev (2004) found that the ASSR (continuous stimuli response) is bigger when the listening is more active, not passive, with clicks at 40 Hz. An analysis by Chaieb, Wilpert, Reber, and Fell (2015) confirms the importance of binaural and monaural stimulation.

Monaural beats in 10 Hz and 40 Hz had an anxiety reduction effect (measured through STAI-test; Chaieb, Wilpert, Hoppe, Axmacher, & Fell, 2017). Monaural beats are beats which contain the same frequency in each ear, in this case a 40-Hz frequency.

Binaural beats in 10 and 40 Hz

Binaural beats are a technique which presents two different frequencies to left and right ears (fL and fR) that are felt and perceived as a single frequency (F) which corresponds to the subtraction of the frequencies, where F = fL – fR.

Binaural stimulation at 40 Hz created by 300/340 Hz provokes effects in the style of concentration, promoting a bigger attention to the task (Colzato,

Barone, Sellaro, & Hommel, 2017). It is noteworthy that the task used is a visual one. On the other hand, it was found that any binaural stimulation, even low frequencies, evoke a 40-Hz response (Ross, Miyazaki, Thompson, Jamali, & Fujioka, 2014). This is important to understand γ as a timing, selection, and control frequency; the author attributes the 40-Hz MEG response to interneuronal activation.

Referring to binaural stimulation in elderly people, their hearing capacity loss might have an influence in the response, especially due to loss of response in higher frequencies of sound processing structures. Grose and Mamo (2012) use a low frequency of 390/430 Hz and a high one of 810/850 Hz, finding that this last high one produced a very low-frequency generation response in the elderly group. In the low range, 36% of the subjects did not generate a measurable binaural γ response, but those who did had an amplitude similar to the young group. The critical binaural fusion frequency (Ross et al., 2014) is 60 Hz, where you cannot tell a pure tone from a vibrating one.

Photic stimulation at 10 and 40 Hz

The visual part of the AVE stimulation consists of photic stimulation, typically an LED fast-flicker stimulus corresponding to the frequency that is desired to be induced. The higher amplitude response zone is the occipital zone. Pastor et al. (2003) find that the photic stimulation on the 40-Hz range produces a lesser response than 10 (α), 15 (β1), or 35 Hz. Within the γ range, Herrmann (2001) finds an absolute peak of amplitude in the photic stimulation at 36 Hz, while at 39 Hz a subharmonic effect at 13.5 Hz would be noted. Tallon-Baudry et al. find two possible structures resonating: one occipital in 36 Hz, one central in 39 Hz (Tallon-Baudry et al., 1997, 1999).

A study on photic stimulation on elderly people on the α band (9.5–11.0 Hz) improved a memory task (Williams, Ramaswamy, & Oulhaj, 2006). The best results were obtained with frequencies between 10.0 and 10.5 Hz in the 67- to 92-year-old group. This band corresponds to the α "sink" happening in AD, as we have seen before.

Kikuchi et al. (2002) on photic stimulation at 5, 10, and 15 Hz, give two important outcomes: first, in NAG people, the effect of photic stimulation in principal and harmonics is important (there is a true stimulation) and, second, stimulation in relatively young AD subjects (mean age 59.4, MMSE 15.7) already shows damage in the 10-Hz and 20-Hz reverberating circuits, specifically showing the fourth harmonic of 5 Hz (20 Hz). This effect (loss of resonance at 10 Hz) had also been noted by Politoff, Monson, Hass, and Stadler (1992), who attributed this to the AD pathology in the rhythm-generating circuits.

As we have seen in the Grose and Mamo (2012) study, we might ask ourselves how aging influences the visual perception of continuous flickering stimuli, say, between a continuous light and a flickering one. The paradigm is called Critical Flicker Fusion (CFF). AD and NAG people show a 4-Hz difference in this threshold against young controls (Cronin-Golomb et al., 1991). In this study, it is detailed how cortical and associative deficits—and not neuro-ophthalmologic ones—would probably be the cause. Another study (Mewborn, Renzi, Hammond, & Miller, 2015) also finds a 3-Hz difference between young and old ones, in a higher education sample. The difference correlates with EF capacity. Herrmann (2001) finds the CFF point in about 30 Hz in a general sample where a flicker is perceived as a still light.

Regarding safety and risk of seizures, Gary Garcia (2008), it was considered that photic stimulation in the broad range of 40 Hz is safe enough for BCI applications.

AVS and AVE

We have previously mentioned the work of Budzynski et al. (2007), in which the protocol mentioned is a mixed-frequencies one (AVS), ranging from 9 to 22 Hz. Note there is a negative interaction in particular subjects with health pathologies (see p. 246, 248 for details). For improvements, see Table 2. In children, using 15- and 40-Hz alternating frequencies, there is a study in ADHD with 35 sessions, with outcomes in WISC improvement and concentration capacity (Olmstead, 2005). Gaspar et al. (2014) studied the effect of 20 AVE sessions of 30' in an AD group with MMSE 18–20 (MoCA adapted). In this level of impairment, Gaspar et al. find that brain brightening (α 12 Hz) produces a 50% increase in the α EEG rhythm and a good adherence. However, there is no finding in cognitive functions.

Table 2
Audiovisual Stimulation: Protocols, Frequencies, and Results.

Author	Exp. Group (*N*)	Age (*M/SD*)	MMSE	Type of Stimulation / Session	Protocol / Frequency / AVS/AVE	Test / Task / Trait	Outcome
2005 Olmstead $	24 + 6	ADHD Young	N/A	AVS (Freq. 15–40 Hz)	Protocol from 15 to 40 Hz & vice versa	WISC, concentration	Improves
2006 Williams	8 NAG vs. 8 Young	67/92	30	Photic	10 Hz (9, 5–11 Hz) Group 10–10, 5 Hz↑	Memory tasks	Improves
2007 Budzynski #	13 AVS/ 11 CTRL	NAG		AVE 20 sessions	Pseudoaleatory frequency from 9 to 22 Hz	Reaction time, spatial rot. memo, attention	Improves
2014 Gaspar	6 vs. 4 CTRL	AD 84	18/20	AVE 20 ss x 30'	AVE 12 Hz* vs. 0.1–0.2 CTRL	Cognitive function, memory	N/signific.
2015 Colzato	18 BB/ 18 CTRL	18/28	N/A	Binaural	40 Hz (300–340 Hz)	Reaction time, concentration on task	Improves
2017 Chaieb	25	24	N/A	Monoaural	10 Hz, 40 Hz (Variable freq. carrier)	Anxiety decrease: ES 0.61 10 Hz, 0.39 40 Hz	Improves

* = As from Abstract, 12 cps; $ = Financial interest disclosed; # = University of Washington study (Budzynski et al., 2007, pp. 252–256).

Microglia

Hortega, with the help of tincture method by silver carbonate, discovered the microglia cells. This fact surprised Cajal himself. In the first documents by Hortega, they are classified as "stick-looking cells" (Stabchenzell, a term coined by Nissi), which are supposed to mean microglia in chronified priming state by infections (Fariña González & Escalona Zapata, 2005). The sequence is studied as stick cells, amoeboid, and granuloadipose cells.

To understand the activity of microglia in relation with AD, we will briefly summarize the microglia activity as M1 (activated state, interleukin, and cytokine aggressive production) and M2 (true phagocytosis state, anti-inflammatory, or alternative activation). Microglia, in contact with Aβ, produces aggressive neuroinflammatory cytokines. A similar role is the one of astrocytes (Heneka et al., 2015). There would be a "true" microglia state (M2), which can correctly clean the milieu, and an "incorrect" activation state (M1) in AD, which, in fact, contributes to the spread of the pathology. Citing Heneka et al. (2015) again, microglia would be a "legitimate therapeutic target" in AD.

Microglia and γ frequency stimulation in mice

Leinenga and Götz (2015) stimulate the brains of transgenic mice with AD using an ultrasound cavitation technique with a 10-Hz frequency. The result in memory tasks is a 75% improvement. There are two effects in this kind of invasive technique: one of them is the opening of the hematoencephalic barrier. The second one is the activation of microglia itself (p. 5) with a more open structure and twice the amount of phagocytosis than the control group. The big problem of this technique in humans would be the temperature increase due to the cavitation procedure. Sommer (2015), later commenting on the Leinenga experiment, proposed that such results (increase of phagocytosis by microglia) could be obtained by laser stimulation, due to the effect on ATP.

Recently, Iaccarino and the Tsai lab group (Iaccarino et al., 2016) applied an optogenetic 40 Hz on interneurons type PV-FS, and later, a photic, exterior 40 Hz on mice, which improved the memory tasks, as in the case of Leinenga. The γ stimulation during a week (1 hour per day) modifies microglia to an alternative state, capable to reduce the amyloidal accumulation in occipital region in a mouse 5XFAD model (Aron & Yankner, 2016).

At the cell level, several wave longitudes are studied. Cheng, Kiernan, Eliceiri, Williams, and Watters (2016) add that the mere exposure to blue light to mice microglia (450 nm, commonly used in optogenetics) in several frequencies and powers produces a decrease of proinflammatory genetic activation in microglia exposed to LPS (activated). The pattern of stimulation used was a nonrhythmic and a classic 10-Hz optogenetic one. Both caused a decrease of proinflammatory factors activity (through increasing CoX2, a proinflammatory one).

Duggett and Chazot (2014) worked with in vitro transgenic mouse cells, exposing them to highly toxic doses of oligomeric and βA fiber. The ones radiated at 1068 nm could survive a larger amount (24% more). In another experiment, Grillo, Duggett, Ennaceur, and Chazot (2013) reduced the βA level in a transgenic mouse with exposition to 1072 nm.

Discussion: Neurotherapies

We have reviewed different techniques of neurotherapies applied with different success on aging people with MCI or AD.

1. Neurofeedback

A remarkable aspect is that neurofeedback has not produced any lateralized protocol on SMC/MCI with memory impairment, with evidence (Rusinek et al., 2004; Chan et al., 2001) of larger atrophy on the medial temporal lobe in the left temporal lobe which correlates with loss of episodic memory, atrophy, and MMSE rates. To check the importance of T3 and T5 (close to the hippocampus and amygdala), see Hammond (2005) for δ and θ findings in aging and dementia and suggested diagnostic montages.

Most of the protocols used in NAG or light MCI use α increase, θ decrease, or α/θ protocols. One of the neurofeedback protocols used for improvement of cognitive functions in elderly has been the brain brightening, which can be considered as an established protocol (Chapin & Russell-Chapin, 2014, p. 187) for elderly with mild cognitive problems. Keeping a healthy α rhythm in aging people and with MCI can be considered a goal, given the relationship of impairment in the rhythm with cognitive and memory problems. An advantage is that this protocol can work with few sessions. Position in POZ seems to help memory (for evidence, see Table 1).

Beta increase protocols in the β1, central positions, works in a BCI screen environment with cognitive, but not attention, improvement (Gomez-Pilar, Corralejo, Nicolas-Alonso, Álvarez, & Hornero, 2016). Surmeli et al. (2016) use two ADHD classic protocols in C3(θ/β) and C4(SMR). Gamma training seems to not have a significant outcome, and chances of activating frontal β2 seem to be an important negative point in the aging population.

With reference to AD patients, neurofeedback has shown that some patients still keep a fair neuroplasticity level. The outcomes are limited in memory issues, but interesting in orientation, EF, and verbal capacity. Most of the success cases in AD have used qEEG or *Z*-score-based neurofeedback and a standard number of sessions (20–30).

Protocols of frontal slow reduction, as suggested by Budzynski et al. (2007), do increase α amplitude and recover cognitive functions. Note that, in AD, only Luijmes et al. (2016) use a Pz α increase protocol.

Surmeli et al. (2016) uses two ADHD classic protocols in C3(θ/β) and C4(SMR). Increase of β1 in central positions and reduction of β2 are also used.

Berman used a neurofeedback reinforcement protocol in the median range, finding as most significant that the capacity of existing memory in the subject is, in fact, an independent variable which correlates with the result of the treatment. This suggests that treatment must adapt to the cognitive status of the subject, as well as outcome expectative from the treatment (Berman & Frederick, 2009).

2. Bianaural, Photic, and AVE

As we have seen, the different modalities of stimulation with clicks and waves in 10 and 40 Hz seem safe and in no case is there reference to problems of photosensitivity (epilepsy) caused by the stimulation. Anxiety is reduced in 40 Hz BB in audio stimulation alternatives (though a caveat of session duration should be set). It produces an improvement in attention, reaction time, and distraction-free style with a temporal effect.

Gaspar et al. (2014) AVE study in 12 Hz, of brain brightening, on the upper α (α3 as per Moretti) are disappointing as there is no cognitive, behavioral, nor attentional improvement in the MMSE 18/20 group. Williams's photic study, centered in 10 Hz, however, produced improvement in memory. It seems, therefore, that stimulation techniques in NAG, MCI, and AD must be narrowly centered in 10 Hz and 40 Hz. Protocols of AVS in median frequencies may help refresh cognitive function.

Discussion: Microglia

As the reader might have noted, there is not any explanation of a causal, direct relationship or link between any stimulation therapy and changes in microglia.

In AD, there seems to exist a basic problem which is that microglia do not function correctly. Cherry, Olschowka, and O'Banion (2014) propose that microglia is chronically activated in M1 and that this status is not the right one for βA cleaning, having to

change to M2 status (M2a, M2c) for alternative activation. The change is activated by TREM2, which increases phagocytosis of plaques and M2 number. TREM2 level increases in presymptomatic aMCI due to the growing accumulation of amyloid and tau, some years before (Suárez-Calvet et al., 2016).

Gamma photic entrainment, used in Iaccarino´s manuscript (2016), could possibly have an action mechanism of: 1) microglia activation to a phagocytosis state, or mobilization to amyloid, 2) reduction in the amount of amyloid and/or tau (Aron & Yankner, 2016), and/or 3) stimulation of interneurons and effect via neurotransmitters or in the milieu (intersynapsis).

In optogenetic mice studies, we have also seen that there would be a wave longitude effect (white, red, blue, and NIR Light) and possibly a frequency one. It would not work for the resonance effect on brain circuitry but for mere photic stimulation in different levels under the cellular one, be it genetic or metabolic.

Conclusion: Neurotherapies in Aging and Alzheimer's

EEG diagnosis to check the MCI status seems a valid method to obtain data on the subjects, in order to check the advance of AD, since the spread seem to be a silent one, producing probably compensatory hiding mechanisms, while keeping normal MMSE rates. The use of combined markers seems to be the most sensible, having in mind the correlation of some of them with atrophy or hypoperfusion in some brain areas and the appearance of AD phenotypes.

Neurotherapies seem reliable and safe in the population range having in mind the impairment status. We hope from future investigations the clarification of protocols applicable to MCI status which can limit conversion to Alzheimer´s disease and improve psychological well-being, daily functioning, and cognitive status. Studies should include AD well-being aspects other than memory such as psychomotor functioning, verbal improvement, anxiety, and other aspects which are not currently considered and constitute part of quality of life.

AD AVE studies should be accompanied with biomarkers which could reflect the outcome impact in a follow-up period. Known effects of the γ stimulation—such as psychological and behavior activation and concentration capacity—must be taken into account and evaluated. There also opens a panorama of investigation with the different effects of audio and photic stimulation in the frequencies of 36 to 40 Hz which we have mentioned.

The new fields of investigation of neurotherapies must be the face of the future, and we must take into account not only the Cajal cells but also the Hortega ones.

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NeuroRegulation

Biofeedback Intervention for Anger Management: A Case Study

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Abstract

Stress is usually tied into anger, both of which have been shown to have negative health effects. Biofeedback has been shown to reduce stress (which can be anger-inducing) and has been suggested as an intervention. This study will determine the effects of biofeedback on anger management by monitoring heart rate variability (HRV) through focused breathing and positive thoughts (such as that of a loved one). The settings were at home and in public. The baseline was 12 days; interventions occurred twice daily, with times of each increasing every 7 days and tracked for 4 consecutive weeks. Consistently applied, the intervention indicated a significant reduction in the number of anger events as well as a marked decrease in the intensity of each event.

Keywords: anger; biofeedback; intensity; intervention; stress

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Introduction

Many studies discuss biofeedback and its effect on stress relief as well as other health conditions (Greenspoon & Olson, 1986; Shellenberger, Turner, Green, & Cooney, 1986; Wyner, 2015), yet few appear to solely address the effects of biofeedback on anger as its own construct. One of those studies, conducted in the United Kingdom, determined that self-intervention, along with self-monitoring, was effective in treating anger management versus self-monitoring alone (Fernandez & Beck, 2001). Another study suggests that heart rate variability (HRV) can be manipulated to address the response to stimuli that produce anger. Although not conclusive, the results did provide support for the use of biofeedback as a method of tracking and regulating emotions (Francis, Penglis, & McDonald, 2016).

Anger is prevalent in our society, and crimes involving anger add to an already overburdened justice system. Anger is costly in terms of lost wages/jobs, medical care for victims, friendships lost, and families broken. This is especially true when anger manifests as domestic violence. For example, the Spokane (WA) County Regional Health District, citing data provided by the Washington Association of Sheriff and Police Chiefs, reports the rate of Spokane County domestic violence offenses reported to law enforcement in 2013 as 8.7 per 1,000 population—an almost 50% increase above the statewide rate of 5.9 per 1,000 population in the same time frame. Spokane Cares, citing a report from the Washington State Coalition Against Domestic Violence, states that Spokane County had two domestic-violence-related homicides and two suicides in 2013; in 2014, the numbers increased to four and two, respectively. In 2015, Spokane County had eight domestic-violence-related homicides and one suicide.

This particular case study, an assignment for a university Behavior Modification course, is intended to determine what effects, if any, biofeedback has on anger management. It is not designed to address stress relief for two reasons: (1) subject reports

becoming angry even when there is no noticeable stress, and (2) it is assumed that any stress levels that exist will lessen should the anger decrease.

Medically defined, *anger* is:

> An emotional reaction characterized by extreme displeasure, rage, indignation, or hostility. It is considered to be of pathological origin when such a response does not realistically reflect a person's actual circumstances. However, expressions of anger vary widely in different individuals and cultures and may be considered functional under certain controlled circumstances (Mosby's, 2009).

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*:

> A process that enables 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 "feed back" 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 (AAPB, 2008).

Method

Participant

The subject, a 54-year-old male, indicates lifelong, high-intensity anger issues and extreme difficulty controlling his temper. He reports daily physical, emotional, and verbal abuse throughout childhood by the male parent. Attempts in childhood and early adulthood to address the condition yielded no results. Anger arousal and expression have cost him jobs and relationships and caused issues with campus personnel. Previous to the biofeedback intervention, he has not been effective in the implementation of anger management tools he has learned, as his anger escalates immediately upon a stressor being presented; the hypothesis is that biofeedback will allow him to have time to use the techniques he has learned by beginning at a lower intensity level, resulting in not getting as angry as quickly.

Of his own volition, subject has been regularly attending anger management counseling for over one year and has recently been introduced to biofeedback as a possible intervention.

Apparatus

In addition to ongoing counseling, the emWave2 portable biofeedback unit from HeartMath, Inc. (Boulder Creek, CA) was utilized. According to one of HeartMath's instructional flyers, the object is to create "coherence," which they define as "a state of synchronization between your heart, brain, and autonomic nervous system…achieved and sustained by activating a positive feeling. It is not the same as relaxation, rather reflects a state of relaxation and revitalization at the same time (being in an optimal state of efficiency)." Readouts are lighted electronic display (LED), obtained by attaching the earclip electrode to the ear and plugging the other end into the unit. Upon activation, the electrode reads the subject's heart rate and displays the appropriate level of coherence as either a red, blue, or green LED.

Design and Procedure

Subject defines anger events as behavior resulting from stimuli that produce a negative verbal and/or physical reaction and that negatively affect mood for more than two to three minutes. The design is across settings (at home and in public). Frequency and intensity are measured, with intensity being reported on a scale created by the subject of 0 (*not angry*) to 10 (*homicidal*). Thirty-two anger events occurred during the 12-day baseline (M = 2.6667, where N = 12, p = 29, h = 3; N = total number of days, p = in public, and h = home).

The base intensity at home was usually a 1; in public, usually a 2 (subject states that just being out in public increases his base intensity level). Reinforcement behavior included replacing angry thoughts with thoughts of his fiancée.

In addition to ongoing counseling, and with few exceptions where noted, subject followed the HeartMath protocol for Quick Coherence. Beginning by focusing on his heart, subject then imagined himself breathing through it, slower and deeper than normal. Interventions were twice daily, beginning at 2–3 min each, with additional interventions as required. Subject chose 7-day intervals between

increasing intervention times, with an 8-day period coinciding with month's end in February. After 7 days, times increased, first to 5–6 min, then to 7–8 min, and finally to 10–11 min. During that 4-week period, there were 7 nonconsecutive days with only one intervention. There are four challenge levels on the unit; subject performed the intervention using the lowest level.

The graph below shows both mean frequency (in blue) and mean intensity (in red) for anger events occurring during the baseline and for each week of intervention over the course of the study. For convenience, these numbers have been rounded up or down accordingly prior to creation of the graph.

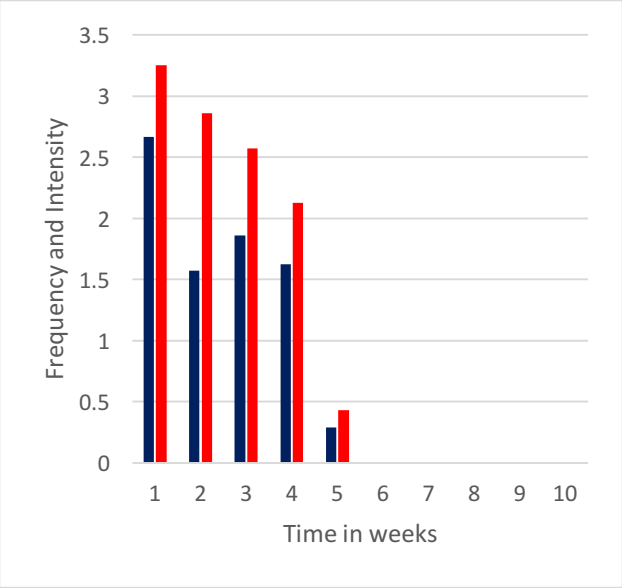

Figure 1. Mean frequency and mean intensity for anger events occurring during the baseline and for each week of intervention.

Results

During the first week of intervention, 10 anger events occurred (M = 1.4286; N = 7, p = 8, h = 2); intensity M = 3. The second week saw a slight increase with 13 anger events occurring (M = 1.8751; N = 7, p = 12, h = 1); intensity M = 3. The third week (8 days) the anger events leveled off at 13 (M = 1.625; N = 8, p = 13, h = 0); the intensity dropped (M = 2.5333). During the last 7 days of intervention, there were only two anger events (M = 0.2857; N = 7, p = 2, h = 0); and the intensity was reduced even further (M = 0.6667).

No anger events occurred on 2 days during the 12-day baseline, equating to 16.667% of the time (N = total number of days, n = number of 0 anger event days). During the first and second 7-day periods of intervention, there were 2 days each with no anger events, or 28.57% of the time (N = 7, n = 2 for each). The third week of intervention (8 days) had 3 days with no anger events, or 37.5% of the time (N = 8, n = 3). The last 7 days of intervention had the most days with no anger events, 6 days, or 85.7% of the time (N = 7, n = 6). During the 29 days of intervention, there were 13 days with no anger events, or 44.83% of the time (N = 29, n = 13).

Discussion

The results of this case study coincide with the results of Fernandez and Beck's study (2001) and appear to support the conclusions reached by Francis, Penglis, and McDonald (2016), both mentioned at the beginning of this case study. The results support the hypothesis presented earlier—that the consistent use of biofeedback as an intervention can be a beneficial tool for the management of anger. The results imply that biofeedback intervention can also be useful in reducing the number and severity of domestic violence cases as well as other anger-related criminal offenses.

The dramatic drop in the number of anger events and the decrease in the intensity of each event is unexpected, given the short amount of time to date; much of this improvement is attributed to the consistent application of the intervention. It is highly doubtful that these results would be seen without duly applying the intervention. Of his own accord the subject has agreed to the continuation of this study until the equipment must be returned mid-June. Given the results experienced to date, he is eager to see how successful the intervention will be at 60 and 90 days. Bearing in mind that the results will vary from individual to individual, further research on biofeedback's effectiveness as an intervention for anger management is highly encouraged. The limitations of this case study are twofold: a single participant and self-administered.

Author Note

A few days prior to the submission of this revision, the author's mother passed away. This paper and the results experienced are dedicated to her memory.

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

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The original published version of this manuscript included a typographical error on page 43, in the "Statistical Analysis" subsection of the Methods.

The original text read:
"All *p*-values were assessed using an experiment-wise error rate of $\alpha = 0.05$ adjusted for multiple testing and comparisons with Bonferroni correction. With 19 comparisons, the Bonferroni corrected significance level was $\alpha_B = 0$."

The "**0**" was a typographical error. The Bonferroni corrected significance level for the study is 0.05/19, $\alpha_B = 0.0026$, and the Methods section text has now been corrected to reflect this.

The text now reads:
"All *p*-values were assessed using an experiment-wise error rate of $\alpha = 0.05$ adjusted for multiple testing and comparisons with Bonferroni correction. With 19 comparisons, the Bonferroni corrected significance level was $\alpha_B = 0.0026$."

The authors regret any confusion that this error may have caused.