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

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Contents

NeuroRegulation

Editorial – Volume 3, Number 3

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Welcome to *NeuroRegulation*, Volume 3, Number 3. We have experienced a growing interest by both clinicians and researchers submitting quality works to our journal and hope to see this trend continue. Since our last issue a search on the term "neurofeedback" in Pubmed returned 870 articles, a more recent search showed 973 publications. Neurofeedback as a learning procedure for improving human performance and reducing symptoms associated with clinical syndromes is gaining a high degree of interest, as well as functional applications.

During my time in graduate school the function of learning to change the brain was not a topic of extreme interest, except in our laboratory. Today, it has become clear that methods used in the past must be enhanced as our knowledge of the brain and learning continue to advance. Additionally, technology is advancing at a high degree, improving the likelihood that successful brain computer interfaces will enhance learning and human performance at an exponential rate. We can all benefit from learning to change and regulate our brain!

NeuroRegulation will continue to be at the forefront of publishing data concerning neurofeedback and self-regulation. The world is desperate for an alternative solution to the current model of psychiatric/psychological treatment and a model that maintains an evidence based solution space, which to date is problematic and uncertain, even more so when the topic is focused on long-term outcomes (Palermo, 2014; Roberts, Blossom, Evans, Amaro, & Kanine, 2016; Rousseau & Gunia, 2015; Stringaris, 2014). In the current issue authors utilize a variety of novel techniques and report interesting findings. Estate M. Sokhadze, Manuel F. Casanova, Ayman S. El-Baz, Heba Elsayed Farag, Xiaoli Li, and Yao Wang present data demonstrating the effects of transcranial magnetic stimulation (TMS)-based neuromodulation of evoked and induced gamma oscillations and event-related potentials in children with autism. It appears, as least by information presented, that gamma power may prove important to understanding and better treating the specific symptoms involved in autism spectrum disorders (ASD). Then, San-Yu Wang, I-Mei Lin, Erik Peper, Yu-Ting Chen, Tze-Chun Tang, Yi-Chun Yeh, Yu-Che Tsai, and Che-Cheng Chu present pilot data on the effects of neurofeedback training targeting alpha asymmetry in major depressive disorder. Finally, Keren Avirame, Limor Nuss, and Doron Todder present data utilizing neurofeedback training during sleep in a patient with severe autism. This novel approach may prove very useful in delivering neurofeedback techniques in ASD with severe symptoms.

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

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TMS-based Neuromodulation of Evoked and Induced Gamma Oscillations and Event-related Potentials in Children with Autism

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Abstract

Gamma oscillations are important for the integration of information and are involved in a variety of perceptual, cognitive, and motor process that are affected in autism spectrum disorder (ASD). We used gamma oscillations along with event-related potentials (ERP) as functional markers of response to repetitive transcranial magnetic stimulation (rTMS). The subjects were age- and gender-matched ASD and typically developing children (TDC). Behavioral evaluations along with evoked and induced gamma and ERPs during oddball task were collected at pre- and post-TMS in ASD group (N = 23) and at baseline in TDC (N = 21). ASD subjects were assigned to 18 sessions of rTMS over the dorsolateral prefrontal cortex. Baseline test showed significant differences between ASD and TDC groups in terms of responses to non-targets where ASD showed excessive gamma oscillations and larger ERPs as compared to the TDC group. Behavioral response differences were manifested in a lower accuracy of motor responses. The rTMS resulted in improved accuracy of response, attenuated evoked gamma responses to non-targets, and increased induced gamma to targets. Behavioral outcomes showed decreased irritability and hyperactivity scores and decreased repetitive and stereotype behaviors. There is discussed utility of gamma oscillations as biomarkers for functional diagnostics and predictions of TMS outcomes in ASD.

Keywords: autism; evoked and induced gamma oscillations; event-related potential; rTMS; behavior

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Background

The cerebral cortex inherent hyperexcitability demands the presence of dampening mechanisms that maintain a proper set point when acquiring and processing stimuli from other parts of the nervous system. Contrary to a tank circuit where parasitic properties decrease oscillations, the brain needs inhibition to stop runaway excitation. Inappropriate regulation of our excitatory-inhibitory (E/I) bias creates abnormal responsiveness. It is known, for example, that contusions and hemorrhages involving the cerebral cortex interfere with the action of its dampening mechanisms, thus facilitating an epileptogenic environment. Indeed, the large variety of neurological disorders manifesting seizures suggests the presence of a seesaw type of homeostatic mechanism in charge of managing neural activity that is precariously tilted in favor of excitation. The carefully crafted E/I bias of the cerebral cortex depends on the coordinated action of both pyramidal cells and interneurons. Cell fate specification studies have shown that a variety of different interneurons develop at specific laminar

locations and at different times during neurodevelopment. These cells migrate to the cortex during the entire period of corticogenesis using multiple tangential routes in order to reach their final destination (Lavdas, Grigoriou, Pachnis, & Parnavelas, 1999). The large variety of interneurons, locations, and timing of origination helps explain the clinical heterogeneity observed when studying dysfunction of excitatory-inhibitory cell dyads.

An abnormal excitation-to-inhibition (E/I) bias provides a pathophysiological mechanism capable of explaining the complex phenotype of autism spectrum disorders (ASD). Abnormalities of E/I ratio in ASD were discussed in several reviews (Rubenstein & Merzenich, 2003; Uzunova, Pallanti, & Hollander, 2015). Reviewed studies provide support to theories linking autism with an altered cortical E/I balance. The oscillations in high gamma band are sensitive to the E/I balance and may appear useful in ASD studies (Stroganova et al., 2015). The power of gamma oscillations depends on a level of excitation of the inhibitory basket cells recruited by increasing strength of excitatory input. It is very logical to agree with the authors' conclusion that the experimental manipulations capable to affect gamma activity could be very useful for the investigation of proposed inhibitory neurons dysfunction in ASD (Stroganova et al., 2015). Postmortem studies in ASD indicative of heterotopias, increased cell density in the grey-white matter junction and molecular layer, minicolumnopathy, and focal cortical dysplasias indicate the presence of a neuronal migration disorder (Casanova et al., 2013; Casanova, Sokhadze, Opris, Wang, & Li, 2015). Pathology of brain development wherein neurons are prevented from migrating to their proper location within the cerebral cortex (e.g., focal cortical dysplasias) alter the integrative action of pyramidal cell-interneuron dyads. Oscillations of pyramidal cells in minicolumns and across assemblies of minicolumns are maintained by networks of different species of inhibitory, GABA-expressing interneurons. In this regard interneurons make a critical contribution to the generation of network oscillations and help synchronize the activity of pyramidal cells during transient brain states (Mann & Paulsen, 2007). Local excitatory-inhibitory interactions help shape neuronal representations of sensory, motor, and cognitive variables, and produce local gamma-band oscillations in the 30-80 Hz range (Donner & Siegel, 2011).

A possible relation between fast EEG activity and autism comes from data on genetically mediated abnormalities in GABAergic and glutamatergic mediator systems (Shuang et al., 2004). The morphological integrity of GABAergic interneuron connections within cortical minicolumns is important for generation of normal gamma oscillations (Whittington, Traub, Kopell, Ermentrout, & Buhl, 2000). Casanova, Buxhoeveden, and Gomez (2003) suggested that such abnormal minicolumnar organization may result in a deficit of inhibitory GABAergic fiber projections, which in turn may facilitate the occurrence of epilepsy, sensory disorders, and gamma oscillation related abnormalities in autism. The presence of fast rhythms in EEG is usually considered as an electrophysiological index of cortical activation. Therefore, excess of beta and gamma rhythms in EEG of children with autism support the hypothesis of abnormally high excitation/inhibition ratio in cortical structures in this disorder (Casanova et al., 2003; Rubenstein & Merzenich, 2003; reviewed in Uzunova et al., 2015).

Abnormalities of high-frequency EEG oscillations have been associated with binding problems (the coactivation of neural assemblies) present in autism and other psychiatric conditions (Brock, Brown, Boucher, & Rippon, 2002; Grice et al., 2001). Oscillatory activity in the gamma band of the EEG has been related to cognitive functions such as attention, learning, and memory (Kaiser & Lutzenberger, 2003). Binding of widely distributed cell assemblies by synchronization of their gamma frequency activity is thought to underlie cohesive stimulus representation in the human brain (Kahana, 2006). According to this assumption, changes in gamma EEG activity have been considered indicators of processing of Gestalt-like patterns (Herrmann & Mecklinger, 2000, 2001; Herrmann, Munk, & Engel, 2004; von Stein, Rappelsberger, Sarnthein, & Petsche, 1999). Given that many of the above related functions are abnormal in ASD, gamma oscillations could therefore provide biological validation to many clinical phenomena observed in this condition.

According to some authors the "weak central coherence" (Frith & Happé, 1994; Happé & Frith, 2006) in autism results from a reduction in the integration of specialized local networks in the brain caused by a deficit in temporal binding (Brock et al., 2002). Visual and auditory perception anomalies may be attributed to a reduced coherence and synchrony of gamma activity between networks processing local features. The inability to reduce

gamma activity according to Brown (2005) leads to the inability to decide which event requires attention when there are multiple choices. Excessive gamma can therefore be linked to a reduction in the ability to focus attention. The "temporal binding deficit" hypothesis of autism (Brock et al., 2002; Rippon, Brock, Brown, & Boucher, 2007) suggests that many features of autism, such as superiority in processing detail (local processing) and disadvantages in global processing, can be explained by a failure of binding between cortical areas. Abnormalities of gamma frequency responses were reported in several studies comparing individuals with ASD with controls (Brown, 2005; Grice et al., 2001; Isler, Martien, Grieve, Stark, & Herbert, 2010; Sokhadze, El-Baz, et al., 2009; Stroganova et al., 2012; Sun et al., 2012).

The "temporal binding" hypothesis predicts that synchronized oscillatory neural activity in gamma band range is the main mechanism (Müller, Gruber, & Keil, 2000) by which various brain regions form one percept and feature binding (Gray, König, Engel, & Singer, 1989). In human EEG studies with recordings from the scalp, according to Ford, Gray, Faustman, Heinks, and Mathalon (2005) there is an accumulating evidence that gamma-range oscillations and synchrony of the oscillations between neurons and neuronal networks represent a basic mechanism of information coding and integration (Fernández, Fell, & Fries, 2002; Fries, 2009; Keil, Müller, Ray, Gruber, & Elbert, 1999; Lenz, Schadow, Thaerig, Busch, & Herrmann, 2007; Müller et al., 1996; Müller & Gruber, 2001; Singer, 1999; Werkle-Bergner, Shing, Müller, Li, & Lindenberger, 2009).

Electroencephalography (EEG) has been used to decompose oscillatory patterns into several frequency bands: delta (0.5–4.0 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–80 Hz), each of which operates over various spatiotemporal scales to control cortical activity. High-frequency EEG oscillations in the gamma range, especially those centered around 40 Hz, are intimately related to mental processes such as consciousness (Joliot, Ribary & Llinás, 1994; Llinás & Ribary, 1993), binding of sensory features into coherent percept (Engel & Singer, 2001; Tallon-Baudry, Bertrand, Delpuech, & Pernier, 1996; Tallon-Baudry, Bertrand, Hénaff, Isnard, & Fischer, 2005), object representation (Bertrand & Tallon-Baudry, 2000), attention (Fell et al., 2001; Sheer, 1976), and memory (Herrmann et al., 2004). Gamma oscillations are subdivided into spontaneous and stimulus related (steady-state, induced and evoked oscillations), but these different classes of gamma oscillations may be generated in the same neural circuits (Herrmann & Knight, 2001). High-frequency rhythms such as gamma are generated in neuronal networks involving excitatory pyramidal cells and inhibitory gamma-aminobutyric acid GABAergic interneurons (Whittington et al., 2000).

Gamma-band activity in response to stimulation can be divided into either evoked or induced: evoked gamma-band activity has been identified at a latency of around 100 milliseconds after stimulus onset (Bertrand & Tallon-Baudry, 2000; Herrmann & Mecklinger, 2001) and is highly phase locked to the onset of the stimulus; induced gamma-band activity occurs later with a variable onset although it has been reported to start at around 250 milliseconds (Brown, Gruber, Boucher, Rippon, & Brock, 2005). It has been proposed that evoked gamma-band activity reflects the early sensory processing and the binding of perceptual information within the same cortical area (i.e., intra-areal), whereas induced gamma-band activity reflects the binding of feed-forward and feed-back processing in a whole network of cortical areas (Brown et al., 2005; Müller et al., 2000; Shibata et al., 1999). Variations of such activity have been termed event-related synchronization and desynchronization (ERS/ERD) (Pfurtscheller & Aranibar, 1977) or event-related spectral perturbations (ERSP; Makeig et al., 2002) and have been associated with the activation of task-relevant neuronal assemblies (Pfurtscheller & Lopes da Silva, 1999; Rippon et al., 2007).

Karakaş, Başar-Eroğlu, Özesmi, Kafadar, and Erzengin (2001) argued that early (evoked) gamma response represents sensory processing; and basically represents a phenomenon of the sensory register. In their study it was shown that the evoked gamma responses at frontocentral recording sites at the early time window of 0–150 ms occurred irrespective of experimental paradigm and did not vary as a function of task complexity or attention allocation. According to the authors, the gamma responses obtained as a non-phase-locked response in the later time window (approximately 150–400 milliseconds), primarily under task conditions that require pattern recognition or higher order recognition processes of the short-term memory, represent perceptual–cognitive processes. In a later refinement of the interpretation of oscillatory gamma frequency responses during experimental manipulations, Herrmann et al. (2004) suggested that early (evoked) gamma responses reflect sensory–memory matching processes, whereas late (induced) gamma response might be

indexing response selection or context updating. The same information processing stages are reflected as well in exogenous (e.g., N100) and endogenous (e.g., N200, P300) event-related potentials (ERP). Therefore, there should be an association between key features of evoked and induced EEG responses in gamma range, ERPs, and perception and cognitive processes that are known to be deficient in autism.

There are only a few EEG studies employing resting-state examinations in individuals with ASD, and practically all of them report oscillatory anomalies. Specifically, eyes-open resting-state exams have shown greater relative delta and less relative alpha power in 4- to 12-year-old low-functioning children with ASD (Cantor, Thatcher, Hrybyk, & Kaye, 1986), and greater 24–44 Hz power in 3- to 8-year-old boys with ASD (Orekhova et al., 2007). Eyes-closed exams have shown greater relative 3–6 Hz and 13–17 Hz power and less 9–10 Hz power in adults with ASD (Murias, Webb, Greenson, & Dawson, 2007), and decreased delta and beta power, as well as increased theta power, in children with ASD (Coben, Chabot, & Hirschberg, 2013; Coben, Clarke, Hudspeth & Barry, 2008). Although the aforementioned results implicate an atypical oscillatory activity in ASD, findings are discrepant and probably due to between-study differences in age, level of functioning, and medication status of the ASD participants. Cornew, Roberts, Blaskey, and Edgar (2012) showed that children with ASD exhibited regionally specific elevations in delta, theta, alpha, and high-frequency beta and gamma power, supporting an imbalance of neural excitation/inhibition as a neurobiological feature of ASD. Of particular interest was the authors' report that increased temporal and parietal alpha power was associated with greater symptom severity. In the auditory domain, reduced entrainment to auditory stimulation at 40 Hz in participants with ASD (Wilson, Rojas, Reite, Teale, & Rogers, 2007) has been demonstrated. In contrast, during visual perception there is evidence for both hyperactivity and hypoactivity of gamma-band oscillations (Brown et al., 2005; Grice et al., 2001; Isler et al., 2010; Milne, Scope, Pascalis, Buckley, & Makeig, 2009; Rojas & Wilson, 2014; Stroganova et al., 2007, 2012, 2015; Uhlhaas & Singer, 2007), raising the question of the link between high-frequency oscillations and perceptual dysfunctions in the disorder. Orekhova et al. (2007) reported higher levels of EEG gamma-band activity in children with ASD. Elevations in gamma were observed in anterior temporal, posterior temporal, and occipital sites using EEG (Cornew et al., 2012). Therefore, gamma-band abnormalities have been reported in many studies of autism spectrum disorders. Gamma-band activity is associated with perceptual and cognitive functions that are compromised in autism. Despite all of the evidence, the utility of gamma-band related variables as diagnostic biomarkers is currently unexplored, suggesting an urgent need for using gamma oscillation measures as functional markers of response to interventions such as transcranial magnetic stimulation (TMS)-based neuromodulation or neurofeedback.

Repetitive transcranial magnetic stimulation (rTMS) is one of the most promising neuromodulation techniques for the treatment of ASD symptoms, as it offers a noninvasive method for altering excitability of the cortex. TMS induces a short-term functional reorganization in the human brain. The magnitude and the direction of neuroplasticity evoked by rTMS depend on the parameters of magnetic stimulation (intensity, frequency, number of stimuli per session, number of sessions, etc.) and the functional state of the cortical topography targeted by rTMS. Since effects of rTMS are not limited to the stimulated target cortex but give rise to functional changes in anatomically and functionally interconnected cortical areas, rTMS is a suitable tool to investigate mechanisms of neural plasticity within a distributed functional network (Rossi & Rossini, 2004; Ziemann, 2004). The lasting effects of rTMS offer new possibilities to study dynamic aspects of the pathophysiology of a variety of diseases and may have therapeutic potential in some psychiatric disorders. By convention, rTMS in 0.3–1.0 Hz frequency range is referred to as "slow," whereas "fast" rTMS refers to stimulation greater than 1 Hz (Pasquale-Leone, Walsh, & Rothwell, 2000). This point of view is reconsidered as a certain simplification, as some studies consider the frequency of TMS as a less important factor compared to other factors related to ability to change functional connectivity in the brain (Fitzgerald et al., 2011; Khedr, Rothwell, Ahmed, & El-Atar, 2008). Hoffman and Cavus (2002) in their review of slow rTMS studies proposed long-term depression and long-term depotentiation as models for understanding the mechanism of slow rTMS. Neocortical long-term depression and changes in the cortical excitability induced by slow rTMS appear to accumulate in an additive fashion as the number of stimulations is increased over many days. Studies of both slow rTMS and long-term depression suggest additive efficacy when higher numbers of stimulations are administered. The reversal, or depotentiation, of previously enhanced synaptic transmission due to long-term potentiation may be

the most relevant model for slow rTMS when used as a therapeutic tool. More detailed account of biophysical effects of TMS can be found in the review by Wagner, Rushmore, Eden, and Valero-Cabre (2009).

TMS is generally regarded as safe without lasting side effects. Reported side effects include a mild, transient tension-type headache on the day of stimulation and mild discomfort due to the sound of the pulses. There is a certain risk of inducing a seizure (Wasserman et al., 1996); participants with epilepsy or a family history of epilepsy are generally excluded from rTMS studies and, as a safety precaution, some rTMS studies adjust the stimulation intensity below the participant's motor threshold (e.g., 80% or 90%). Though rTMS is generally considered safe for use in pediatric populations, as no significant adverse effects or seizures have been reported (Garvey & Gilbert, 2004; Quintana, 2005), the question still remains open whether rTMS is sufficiently safe for application in children. Quintana (2005) evaluated studies that used TMS in persons younger than 18. The 48 studies reviewed involved a total of 1,034 children; 35 of the studies used single-pulse TMS (980 children), 3 studies used paired TMS (20 children), and 7 studies used rTMS (34 children). The TMS studies in persons younger than 18 has been used to examine the maturation and activity of the neurons of various central nervous system tracts, plasticity of neurons in epilepsy, multiple sclerosis, myoclonus, transcallosal inhibition, and motor cortex functioning with no reported seizure risk (Garvey & Gilbert, 2004; Lin & Pascual-Leone, 2002). Repetitive TMS has been applied in children with psychiatric disorders such as ADHD, ADHD with Tourette's, and depression. Although there are limited number of studies using rTMS in children, these studies did not report significant adverse effects or seizures. Review of state-of-art rTMS application in ASD treatment and research can be found in several current reviews (Casanova & Sokhadze, 2014; Casanova et al., 2015; Oberman, Rotenberg, Pascual-Leone, 2013; Sokhadze, Casanova, & Baruth, 2013), and they all call for the need for more research clinical trials aimed to prove efficacy of the method. rTMS has been applied to a wide variety of psychiatric (e.g., ADHD, depression) and neurological disorders (e.g., Parkinson's disease) in adult populations, and more recently rTMS has been applied in child and adolescent populations (see Croarkin, Wall, & Lee, 2011). A number of studies report an improvement in mood after repeated frontal lobe stimulation in both depressed adults (George et al., 2010) and adolescents (Wall et al., 2011). Furthermore, it has been found that rTMS may improve certain symptoms associated with anxiety disorders, like Posttraumatic Stress Disorder (PTSD) and Obsessive-compulsive Disorder (OCD; George & Belmaker, 2007). In Parkinson's disease (PD) most studies have shown beneficial effects of rTMS on clinical symptoms (Wu, Fregni, Simon, Deblieck, & Pascual-Leone, 2008). Currently only rTMS-based therapy of treatment-resistant major depression has FDA approval; however, it is very likely that in the future rTMS will be approved for the treatment of other mental and neurological disorders as well.

Recent reviews (Casanova et al., 2015; Oberman et al., 2013; Sokhadze, Casanova, et al., 2013) provide detailed account of current status of rTMS application in autism research and treatment. Within the context of autism spectrum disorder, rTMS has unique applications as a treatment modality. A wide range of deficits in autism might be understood by an increase in the ratio of cortical excitation to cortical inhibition (Rubenstein & Merzenich, 2003) and increases in local cortical connectivity accompanied by deficiencies in long-range connectivity (Just, Cherkassky, Keller, & Minshew, 2004; Minshew & Williams, 2007; Rippon et al., 2007). An increased ratio of cortical excitation to inhibition and higher than normal cortical 'noise' may explain the strong aversive reactions to auditory, tactile, and visual modality stimuli frequently reported in autism (Gillberg & Billstedt, 2000). Ogawa et al. (2004) examined the changes in high-frequency oscillations (HFOs) of somatosensory evoked potentials (SEPs) before and after slow rTMS over the right primary somatosensory cortex (0.5 Hz, 50 pulses, 80% motor threshold intensity). The HFOs, which represent a localized activity of intracortical inhibitory interneurons, were significantly increased after slow rTMS, while the SEPs were not changed. Their results suggest that slow rTMS affects cortical excitability by modulating the activity of the intracortical inhibitory interneurons beyond the time of the stimulation and that rTMS may have therapeutic effects on such disorders. This is in line of our hypothesis in which slow rTMS will increase activity of inhibitory cells in minicolumn which will then enhance spatial contrast needed to enhance functional discrimination.

Our group's prior studies were aimed to examine effects of low-frequency (0.5–1.0 Hz) rTMS on behavioral, quantitative EEG, and event-related potential (ERP) outcomes in children and adolescents with autism. In a series of studies, we used rTMS over the dorsolateral prefrontal cortex

(DLPFC) on a weekly basis for 6, 12, and 18 weeks in individuals with autism randomly assigned to active treatment group and wait-list groups. We predicted that post-TMS changes in the active treatment group, as compared to the wait-list group, can be detected during repeated tests using the same functional outcome measures (EEG, ERP, etc.) in cognitive task. Our prediction was that slow rTMS of DLPFC will result in an alteration of cortical inhibition through the activation of inhibitory GABAergic interneurons leading to an improvement in the cortical excitatory/inhibitory balance. In our methodological approach, we hypothesized that contrary to other inhibitory cells (i.e., basket and chandelier), 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) makes them the appropriate candidate for induction by a magnetic field applied parallel to cortex. Over a course of treatment 'slow' rTMS may restore the balance between cortical excitation and cortical inhibition and may lead to improved long-range cortical connectivity. Thus far we have focused on clinical, behavioral, and electrocortical outcome measures (i.e., ERPs, evoked and induced gamma oscillations), in order to access the effectiveness of rTMS treatment in ASD.

In the first of our previous investigations (Sokhadze, El-Baz, et al., 2009) we measured the EEG gamma band in eight children with ASD and five wait-list participants with ASD during a visual attention task, and then measured the EEG gamma band in the active treatment group after six sessions of 'slow' rTMS to the prefrontal cortex. Study used also 13 age-matched, typically developing children as a control group. We hypothesized that the ASD group would have excess gamma-band activity due a lack of cortical inhibition and treatment with 'slow' rTMS would help restore inhibitory tone (i.e., reduce excess gamma-band activity). We also analyzed clinical and behavioral questionnaires assessing changes in symptoms associated with ASD after rTMS treatment. The visual attention task employed Kanizsa illusory figures (Kanizsa, 1976) which have been shown to readily produce gamma oscillations during visual tasks. Subjects were instructed to press a button when they saw the target Kanizsa square and ignore all other stimuli: Kanizsa stimuli consist of inducer disks of a shape feature and either constitute an illusory figure (square, triangle) or not (colinearity feature); in nonimpaired individuals gamma activity has been found to increase during the presentation of target visual stimuli compared to non-target stimuli. We found that the power of gamma oscillations was higher in the ASD group and had an earlier onset compared to controls, especially in response to non-target illusory figures over the prefrontal cortex. Additionally, there was less of a difference in gamma power between target and non-target stimuli in the ASD group particularly over lateral frontal and parietal recording sites. After six sessions of 'slow' rTMS applied to the left prefrontal cortex, the power of gamma oscillations to non-target Kanizsa figures dramatically decreased at the frontal and parietal sites on the same side of stimulation, and there was more of a difference between gamma responses to target and non-target stimuli. According to clinical and behavioral evaluations, the ASD group showed a significant improvement on the repetitive behavior scale (RBS), which assesses repetitive and restricted behavior patterns associated with ASD (e.g., stereotyped, self-injurious, compulsive, and restricted range behaviors; Bodfish, Symons, & Lewis, 1999; Bodfish, Symons, Parker, & Lewis, 2000).

In a second study with another pool of participants (Baruth, Casanova, El-Baz, et al., 2010; Casanova et al., 2012; Sokhadze et al., 2012) we investigated gamma-band activity in 16 subjects with ASD in rTMS group and nine age-matched controls using Kanizsa illusory figures and assessed the effects of 12 sessions of bilateral 'slow' rTMS applied to the prefrontal cortices in TMS group of the ASD participants. In individuals with ASD, gamma activity was not discriminative of stimulus type; whereas in controls, early gamma power differences between target and non-target stimuli were highly significant. Following rTMS individuals with ASD showed significant improvement in discriminatory gamma activity between relevant and irrelevant visual stimuli, and there was also a significant reduction in irritability and repetitive behavior as a result of rTMS.

In one more pilot study on 16 children with ASD in 18-sessions-long 1-Hz rTMS course we also reported (Hensley, El-Baz, Sokhadze, Sears, & Casanova, 2014) that post-TMS gamma coherence to the target condition between the frontal (F3) and temporal (T7) sites improved in both the evoked (100–200 ms) and in the induced (300–600 ms) gamma range responses. In addition to improvement in coherence between pre- and post-TMS, differences were also observed in the subjects' responses to target and non-target stimuli following TMS neurotherapy. Analysis of evoked gamma coherence between F4 and T8 to both target and non-target stimuli indicate that before treatment,

non-target coherence was 0.43 and target coherence was 0.45, fairly similar values. However, after completion of TMS therapy target coherence increased to 0.56, and non-target coherence decreased to 0.42. The *p*-value of the comparison of coherence for F4-T8 between target and non-target for both pre- and posttreatment was reaching significance level ($p = 0.044$). Another significant effect of TMS treatment was observed in evoked gamma coherence between F4 and P4. As in the case above, coherence in response to the target condition increased significantly following TMS. Coherence in response to the non-target stimuli increased only slightly after the TMS course, and it was not statistically significant. The comparison of mean coherence values for F4-P4 between target and non-target stimuli pre- and post-TMS treatment reached significance. Children with ASD in the wait-list group ($N = 16$) also completed two Kanizsa tasks but did not receive TMS treatment between the first and second Kanizsa task. Analysis of evoked gamma coherence between F4 and T8 for those in the wait-list group does not show significant differences in responses to target and non-target stimuli. Similarly, no significant differences were observed in responses to target and non-target stimuli for evoked gamma coherence between F4 and P4. The changes in evoked and induced gamma power to targets, accompanied by increased phase coherence between frontal and parietal sites, along with increased centroparietal and parieto-occipital P100 and P300 (P3b) to targets, are indicative of more efficient processing of information post-TMS treatment. The findings point at the rationale for using ERP analysis in gamma oscillation studies. According to the classical view, ERPs reflect phasic bursts of activity in one or more discrete brain regions that occur time-locked to particular events of interest, whereas the background EEG comprises activity that is uncorrelated with these events and a mixture of ongoing rhythmic activity that reflects the overall state of the processing network (e.g., Gevins, Smith, McEvoy, & Yu, 1997; Pfurtscheller & Lopes da Silva, 1999) and ERPs evoked by nonexperimental events. At various times over the last 40 years, however, the classical view has been challenged by the proposal that ERPs should not be regarded as uncorrelated with the background EEG, but are instead generated by event-related reorganization of this ongoing rhythmic activity (Başar, 1980; Başar, Schürmann, Başar-Eroglu, & Demiralp, 2001; Karakaş & Başar, 1998; Karakaş, Erzengin, & Başar, 2000; Karakaş et al., 2006; Luu et al., 2001; Makeig et al., 2002). Experimental evidence suggests that sensory perceptual processes are accomplished by a dynamic matching of anticipatory self-generated activity with activity generated by incoming stimulation, therefore combining top-down and bottom-up influences (Engel & Singer, 2001). In all cases, it is important to analyze ERP along with evoked and induced gamma activity, as ERP components provide very accurate timing of information processing and inform about stages of gamma oscillation bursts even though they may have different origin and frequency range.

Information about stages of information processing can be obtained from ERP, even though the main object of our study was analysis of evoked and induced gamma responses rather than ERP responses. In general, ERPs can be categorized as short-latency (exogenous, e.g., N100) or long-latency (endogenous, e.g., P300) ERPs, which reflect early-stage, modality-specific and late-stage polymodal associative processing, respectively. It has been assumed that early components (e.g., P100, N100) reflect exogenous processes modulated by the physical attributes of the stimulus (i.e., brightness for visual stimuli), but not by cognitive processes (Coles & Rugg, 1995). However, many studies have shown that attention processes may operate at the early stage (e.g., before 200 milliseconds) and can influence stimulus processing at the later stage (Herrmann & Knight, 2001). P100 may reflect a facilitation of early sensory processing of attended stimuli, while N100 may reflect the orienting of attention towards task-relevant target stimuli (Hillyard & Anllo-Vento, 1998; Luck, Heinze, Mangun, & Hillyard, 1990; Näätänen & Michie, 1979). Posterior visual P100 are generated within the fusiform gyrus (Heinze et al., 1994), whereas N100 is probably generated by distributed dipoles in the lateral extrastriate cortex (Gomez-Gonzales, Clark, Fan, Luck, & Hillyard, 1994) with contribution from parieto-occipital and occipitotemporal areas (Yamazaki et al., 2000). Anterior P100 and N100 components occurring within a comparable time window result from frontal generators (Clark, Fan, & Hillyard, 1995).

The most studied endogenous ERP is the P300 (300–500 ms poststimulus). The P300 obtained in an oddball paradigm with three stimuli in a random order, one of them frequent (standard), another one rare (target), and one more infrequent (non-target, novel distractor). It was reported that these novels elicit a frontocentral P300, so-called P3a, whereas the rare targets elicit a parietally distributed P300, so-called P3b (Katayama & Polich, 1998; Polich, 2003; Pritchard, 1981). The P3a is recorded at the anterior locations and reflects frontal lobe activity

(Friedman, Simpson, & Hamberger, 1993; Knight, 1984). In a three-stimuli oddball task the P3a is interpreted as "orienting" and the P3b as an index of ability to sustain attention to target. Source localization techniques have claimed that multiple brain areas are involved in the generation of the visual P3b: the hippocampus and parahippocampal areas, the insula, the temporal lobe, occipital cortex, and the thalamus (Goto, Brigell, & Parmeggiani, 1996; Herrmann & Knight, 2001; Mecklinger et al., 1998; Rogers, Basile, Papanicolaou, & Eisenberg, 1993). Most studies agree that the P3b has multiple dipole sources (Halgren, Marinkovic, & Chauvel, 1998; Knight, 1997; Townsend et al., 2001).

Traditionally there was less attention devoted to such negative endogenous ERP component as N200 (N2b), detectable over centroparietal scalp locations and occurring about 180 and 320 milliseconds poststimulus (Näätänen, Gaillard, & Mäntysalo, 1978; Näätänen, Schröger, Karakaş, Tervaniemi, & Paavilainen, 1993). This component is associated with categorization, perceptual closure and attention focusing ultimately signaling that a perceptual representation has been formed (Potts, Patel, & Azzam, 2004). The posterior visual N2b is enhanced if the presented stimulus contains a perceptual feature or attribute defining the target in the task. A frontal positive component (P2a) in a latency range comparable with the posterior N2b (i.e., 180–320 ms poststimulus) has been reported in working memory and attention tasks. The P2a recorded over inferior prefrontal recording sites appears to be selectively responsive to the evaluation of the task relevance of presented visual stimuli, and source localization places dipoles of this component in the orbitofrontal cortex (Potts, Dien, Hartry-Speiser, McDougal, & Tucker, 1998; Potts, Liotti, Tucker, & Posner, 1996). Kenemans, Kok, and Smulders (1993) described this frontal positivity as a component that indexes the hierarchical selection of task-relevant features for further processing.

The goal of the current study was (1) to compare behavioral (reaction time, accuracy) and electrocortical biomarkers (frontal and parietal ERP, evoked and induced gamma amplitude) of executive functions during performance on a visual three-stimuli oddball task with illusory figures between children with autism spectrum disorder and typically developing children, (2) to analyze group differences, and (3) to explore if 18 weekly sessions of low-frequency rTMS administered bilaterally over DLPFC in children with ASD will improve behavioral, ERP and evoked and induced gamma measures during posttreatment test in the same oddball tasks. In addition, we analyzed clinical behavioral questionnaires post-TMS outcomes (ABC [Aman & Singh, 1994] and RBS [Bodfish et al., 1999]).

Methods

Participants with ASD (age range 8 to 19 years) were recruited through the University of Louisville Weisskopf Child Evaluation Center (WCEC). Diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; APA, 2000) and further ascertained with the Autism Diagnostic Interview–Revised (ADI-R; Le Couter, Lord, & Rutter, 2003). They also had a medical evaluation by a developmental pediatrician. All subjects had normal hearing based on past hearing screens. Participants with a history of seizure disorder, significant hearing or visual impairment, a brain abnormality conclusive from imaging studies, or an identified genetic disorder were excluded. Twenty participants were high-functioning children with autism (HFA) diagnosis and five had Asperger Syndrome. All had full-scale IQ > 80 assessed using the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; Wechsler, 2003) or (for adolescents) the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). Two subjects (one HFA and one Asperger boy) were excluded from the analysis as they did not comply with EEG/ERP test instructions, thus leaving only 23 children with ASD in the study (mean age 13.6 ± 3.22 [standard deviation, *SD*] years, 17 boys, 6 girls). The group of typically developing (TD) children comprised of 21 subjects (14 boys, 7 girls) with mean age 14.9 ± 4.3 years. Enrolled autistic patients (N = 23) were assigned to 1.0 Hz TMS treatment (TMS group) with pre- and post-TMS course oddball tests and clinical behavioral evaluations, while 21 TD children were assigned only to one-time oddball test and served as a contrast group. There was not a significant difference in either age, gender, or socioeconomic status of parents between the TMS and TD groups.

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 (or legal guardians) were provided with full information about the study including the purpose, requirements, responsibilities, reimbursement, risks, benefits, alternatives, and role of the local IRB. The subjects were reimbursed only for participation in oddball EEG tests ($25 per test). The consent and assent forms approved by the IRB were reviewed and

explained to all subjects who expressed interest to participate. All questions were answered before consent signature was requested. If the individual agreed to participate, both she/he and parent/guardian signed and dated the consent or assent form and received a copy countersigned by the investigator who obtained consent.

Three-stimuli oddball task with Kanizsa figures

The stimuli employed in the test were Kanizsa square (target), Kanizsa triangle (non-target), non-Kanizsa square, and non-Kanizsa triangle (standards; Kanizsa, 1976). The task represents a classic three-stimuli oddball with infrequent illusory Kanizsa target (square, 25%) and infrequent Kanizsa distractor (triangle, 25%) figures presented for 250 ms among frequent non-Kanizsa stimuli (so-called standards, 50%) with intertrial interval (ITI) varying in 1,100–1,300 ms range. In total 240 trials were presented following a brief practice block. The practice block had 20 trials only with the experimenter present in the room to make sure that subject correctly understood test conditions and recognized target stimuli. The total time of the test including sensors application and practice trial was under 30 minutes. For better habituation and adaptation to experimental setting, the participants with ASD diagnosis were encouraged to have at least one session for conditioning to EEG sensor net (without performing task) and getting familiar with laboratory environment.

Event-related potential (ERP) acquisition and processing

Electroencephalographic (EEG) signals from 128 sites were recorded with a dense-array EGI system (Electrical Geodesics, Inc., Eugene, OR). Subjects were placed in an electrically and acoustically isolated camera from the Industrial Acoustics Co. (Bronx, NY). Stimulus presentation and motor response collection was controlled using E-Prime v1.0 (Psychology Software Tools, Inc., Sharpsburg, PA). Visual stimuli were presented on a flat monitor located 45–50 cm from the subject, and motor responses were registered with a keypad (Serial Response Box; Pychology Software Tools, Inc., Sharpsburg, PA). Sampling rate of EEG was 500 Hz, and analog Notch (60 Hz, IIR) and analog elliptical bandpass filters were set at 0.1–200.0 Hz. Impedances were kept under 40 KΩ as recommended by the EGI manuals.

ERP. Stimulus-locked EEG data was segmented offline into 200 ms prestimulus baseline to 800 ms epoch poststimulus. EEG recordings were screened for artifacts and trials with eye blinks; gross movements were removed using EGI software artifact rejection tools (Fletcher, Kussmaul, & Mangun, 1996; Luu et al., 2001; Srinivasan, Tucker, & Murias, 1998). The remaining artifact-free EEG recordings for trials with correct responses were digitally filtered using Notch filter (IIR, fifth-order) and 0.3–20.0 Hz IIR elliptical bandpass filter. Averaged ERP data was baseline corrected (200 ms), and ERPs after averaging and baseline correction were re-referenced into an average reference frame. Response-locked EEGs were segmented into 500 ms preresponse to 500 ms postresponse (i.e., commission error). More detailed account for experimental procedure and EEG data acquisition and processing can be found in our prior publications that used similar methodology (Baruth et al., 2011; Baruth, Casanova, El-Baz, et al., 2010; Baruth, Casanova, Sears, & Sokhadze, 2010; Casanova et al., 2012; Casanova & Sokhadze, 2014; Sokhadze et al., 2012; Sokhadze, El-Baz, et al., 2009; Sokhadze, El-Baz, Sears, Opris, & Casanova, 2014; Sokhadze, El-Baz, Tasman, et al., 2014).

Stimulus-locked dependent ERP variables. Dependent variables for the frontal and frontocentral region of interest (ROI) were amplitude of N100 (80–180 ms), N200 (220–350 ms), and P3a (300–600 ms), and for the parietal and parieto-occipital ROI were P100 (120–180 ms), N200 (180–320 ms), and P3b (320–600 ms) ERP waves.

Response-locked dependent variables (ERN/Pe). Response-locked dependent variables in this study were amplitude and latency of the error-related negativity (ERN, peaking within 40–150 ms post-error) and error-related positivity (Pe, peaking within 100–300 ms post-error). The ROI for both ERN and Pe components included FCz, sites between FCz and FC3-C1, and between FCz and FC2-C2.

Evoked and induced gamma oscillations. Analysis of gamma oscillations was performed on a trial-by-trial basis. Data set was not re-referenced for average reference frame but rather was left with initial Cz reference to avoid gamma wave distortions. The filtering technique of individual trials of recorded EEG had several steps. EEG data collected from the task was first processed via wavelet analysis. This technique allows for visualization of the collected signals in both the time and frequency domains, providing information about the amplitude of gamma waveforms at varying frequencies within the selected time interval. A one-dimensional continuous wavelet transform was performed using the MATLAB Wavelet Toolbox. The Morlet window

was selected as the mother wavelet in this analysis. For each signal 128 wavelet coefficients were found. Following wavelet analysis, a custom Harris bandpass filter was applied to the signals to isolate frequencies of interest. This filter allowed for the passage of the gamma frequencies between 35 and 45 Hz with a 2-Hz attenuation band. A similar Wavelet Harris filtering technique was used in previous gamma analysis study on neurofeedback effects on cue reactivity in patients with substance abuse (Horrell et al., 2010) and in a study of induced gamma responses to facial expressions in autism and ADHD (Gross et al., 2012).

We selected the following EEG channels for the analysis: F1, F2, F7, F8 from the frontal area, and P3, P4, P7, P8 from the parietal area; this channel configuration allowed us to analyze gamma-band activity over both hemispheres. Reference site was midline Cz, and analysis was conducted on trial-by-trial basis. All recorded signals entered in gamma analysis were first automatically and then manually inspected for artifacts and rejected if eye movement artifacts, gross movements, or EEG sensor drifts were detected. For automatic detection, we computed the standard in a moving time window and the normalized cross correlation coefficient between the current recoded signal and previous succeeded trials; the current recorded signal was rejected if thresholds exceeded two standard deviations or exceeded normalized cross correlation. The standard deviation threshold was in the 35–50μV range, and normalized cross correlation was approximately 0.5. At least 30 trials of the non-target or target Kanizsa trials were considered a sufficient number for reliable evoked and induced gamma amplitude calculations in each condition.

Transcranial magnetic stimulation

Repetitive TMS was administered using a Magstim Rapid device (Magstim Company Ltd., Whitland, UK) with a 70-mm figure-eight coil. Threshold of motor response (MT) was identified for each hemisphere in all participants with autism by increasing the output of the stimulator by 5% until a 50 μV deflection or a visible twitch in the First Dorsal Interosseous (FDI) muscle was detected in at least three trials of stimulation over the motor cortex controlling the contralateral FDI. Electromyographic (EMG) responses were recorded with a C2 multichannel physiological monitoring device with USE3 Physiolab software (J&J Engineering, Inc., Poulsbo, WA).

The TMS was administered weekly for 18 weeks; the first six treatments were over the left DLPFC, the next six were over the right DLPFC, and the remaining six treatments were done bilaterally over the DLFC (evenly at the left and right DLPFC). The DLPFC site for magnetic stimulation was found by placing the TMS coil 5 cm anterior, and in a parasagittal plane, to the site of maximal FDI response. A swimming cap was used to make the TMS coil positioning easier. TMS was administered at 1.0 Hz frequency and 90% MT. There were a total of 180 pulses per day session with nine trains of 20 pulses each. There were 20–30 s between the trains intervals used. The decision to select 90% of the MT was based on prior publications where rTMS was used for the stimulation of DLPFC in various neuro and psychiatric disorders (reviewed in Daskalakis, Christensen, Fitzgerald, & Chen, 2002; Gershon, Dannon, & Grunhaus, 2003; Loo & Mitchell, 2005; Oberman et al., 2013; Pascual-Leone et al., 2000; Wassermann et al., 1996; Wassermann & Lisanby, 2001; Wassermann & Zimmermann, 2012).

Clinical social and behavioral evaluation outcomes

For the evaluation of social and behavioral functioning we utilized caregiver reports and clinician ratings of improvement. Every participant was evaluated before TMS course and within 2 weeks following TMS treatment. Aberrant Behavior Checklist (ABC; Aman, 2004; Aman & Singh, 1994) is a clinician-administered rating scale to assess Irritability, Lethargy/Social Withdrawal, Stereotypy, Hyperactivity, and Inappropriate Speech based on parent or caregiver report. Repetitive Behavior Scale—Revised (RBS-R; Bodfish et al., 1999) is a caregiver-completed rating scale assessing stereotyped, self-injurious, compulsive, ritualistic, sameness, and restricted range (Bodfish et al., 2000).

Statistical analysis

The primary model for statistical analyses of subject-averaged ERP, evoked and induced gamma oscillations, and behavioral response data was the repeated measure ANOVA. Dependent ERP variables were amplitude of ERPs of interest at predetermined regions of interest (ROI). The within-participant factors were as follows: *Stimulus* (non-target Kanizsat, target Kanizsa), *Hemisphere* (left, right), and *Time* (baseline, post-TMS) for the ASD group in rTMS treatment. Effects of TMS were analyzed using paired sample *t*-test. For baseline comparisons of the autistic and typical children the between-subject factor was *Group* (ASD, TD). Comparison of these two groups used independent sample *t*-test along with Levene's test for equality of

variance. Post hoc analyses were conducted where appropriate. Reaction time (RT) and error rate (commission, omission, and total error rate) were analyzed using paired sample *t*-test. The same method was used for clinical behavioral rating scores. Histograms with normal distribution curves along with skewness and kurtosis data were obtained for each dependent variable to determine normality of distribution and appropriateness of data for ANOVA and *t*-tests. For more reliable determination of normality of distribution residual plots (i.e., normal probability plot and histogram versus fits and order) were created to indicate that treatment with ANOVA and *t*-test is justified. All dependent variables in the study had normal distribution. Greenhouse-Geisser correction on *p*-values were employed where appropriate in all ANOVAs. A priori hypotheses related to TMS effects were tested with the Student's *t*-tests for two groups with equal variance. Confidence intervals (95% of mean, [95% CI]) were calculated for each RT, ERP, and gamma oscillation data sets entered for *t*-tests. For the estimation of the effect size and power in gamma oscillation analysis with ANOVA we used partial eta squared (η^2) and observed power measures computed using α = 0.05 (Murphy & Myors, 2004). SPSS 23.0 and Sigma Stat 3.1 statistical packages were used for analysis of data.

Results

Behavioral responses (reaction time and accuracy, post-error RT)

Baseline differences: ASD vs. TD. There were no differences in reaction time (RT) between ASD and TD groups. In total, the ASD group committed more errors as compared to controls (10.0 ± 12.51 in ASD vs. 2.30 ± 3.84 % in TD group, t = 3.04, df = 43, p = 0.004). The differences in accuracy were mostly driven by differences in commission errors (mean difference 5.89 ± 2.21 %, t = 2.63, df = 43, p = 0.011, 95% CI from 1.38 to 10.27%). The most pronounced difference between groups was found in post-error RT change (52.45 ± 12.51 ms, t = 4.19, df = 43, p < 0.001, 95% CI from 27.2 to 77.9 ms). Control subjects showed normative post-error slowing (mean 28.9 ± 47.6 ms) while children with ASD did not show expected slowing but rather demonstrated speeding post-error (–21.3 ± 42.1 ms).

Effects of TMS. Effects of TMS on RT to targets were not significant. Accuracy post-TMS improved, as total error rate decreased by 5.52 ± 14.04 %, t = 2.08, df = 22, p = 0.047, though predominantly mediated by an improvement in commission error rate (mean decrease by –5.22 ± 12.36 %, t = 2.23, df = 22, p = 0.034, 95% CI –0.43 to –10.01 %). Most significant effects of neuromodulation were found in the post-error RT change, in particular, pretreatment speeding changed into a normative post-error slowing (mean 24.5± 37.9 ms) and difference was highly statistically significant (45.89 ± 51.43 ms, t = 4.72, df = 22, p < 0.001; 95% CI from 25.9 to 65.8 ms).

Response-locked frontal and frontocentral ERN and Pe

Three subjects from the TD group and two subjects from the ASD group at the baseline oddball test did not show sufficient number of commission errors and were excluded from the analysis. Therefore, comparison of ERN and Pe measures was conducted for 18 TD subjects and 20 ASD subjects. ASD and TD groups at the baseline test showed significant differences in ERN amplitude at ROI (five frontal and frontocentral sites) using *t*-test for independent samples (mean difference 3.99 ± 1.42 μV, t = 2.82, df = 36, p = 0.008, 95% CI from 1.09 to 6.92 μV). Latency of ERN did not yield any statistically significant group differences. There were not found any between-group differences in amplitude and latency of Pe component.

Effects of rTMS. Paired sample *t*-test revealed statistically significant increase in negativity of the ERN amplitude at the frontal and frontocentral ROI post-TMS treatment in the ASD group (mean 4.89 ± 5.50 μV, t = 3.62, df = 19, p = 0.002, 95% CI from 2.51 to 7.62 μV). Latency of the ERN decreased post-TMS (mean decrease –27.5 ± 44.6 ms, t = 2.61, df = 19, p = 0.018, 95% CI from –5.28 to –49.7 ms). Amplitude and latency of the Pe component did not show any post-TMS changes.

Stimulus-locked ERP components

Frontal and frontocentral ERP components.

Frontal N100 at baseline. Amplitude of N100 was more negative to non-target stimuli in the ASD group than in the TD group, especially at the left hemisphere (mean difference –1.27 ± 0.55 μV, t = 2.29, df = 41, p = 0.025, 95% CI from –2.37 to –0.16 μV, group sample variance was equal, p = 0.006). N100 to targets was also more negative in the ASD group (at midline frontal sites, –1.24 ± 0.55 μV, t = 2.25, df = 41, p = 0.028, 95% CI from –2.34 to –0.14 μV; variance was equal, p = 0.003).

Effects of rTMS on N100. TMS course had main effect on N100 amplitude (F = 4.69, p = 0.049), but there were not found any interactions using

Hemisphere (left, right) or *Stimulus* (non-target, target Kanizsa) and *Time* (pre-, post-TMS) factors. At the post-TMS test, N100 amplitude became less negative only to non-target Kanizsa stimuli (at the left frontocentral ROI by 1.34 ± 1.95 μV; t = 2.57, df = 22, p = 0.023, 95% CI from 2.47 to 0.21 μV; while at the midline ROI only by 1.01 ± 1.72 μV; t = 2.21, df = 22, p = 0.045).

Frontal N200 at baseline and post-TMS. Amplitude of N200 component did not show any statistically significant differences between ASD and TD groups. We could not find any main effects of stimulus type or TMS factors, but post-TMS test did show statistically significant reduction of N200 to non-target Kanizsa items (mean 1.38 ± 2.52 μV, t = 2.33, df = 20, p = 0.032, 95% CI from 2.64 to 0.13 μV).

Frontal and frontocentral P300 (P3a) at baseline. Amplitude of P3a component was higher in the ASD group both to non-target and target Kanizsa stimuli (accordingly at midline in non-target condition by 2.66 ± 1.19 μV, t = 2.23, df = 41, p = 0.030, 95% CI from 0.27 to 5.07 μV, equal variance at p = 0.05; in target Kanizsa by 4.34 ± 1.37 μV, t = 3.18, df = 41, p = 0.004, 95% CI from 1.62 to 7.12 μV, equal variance test at p = 0.02, see Figure 1).

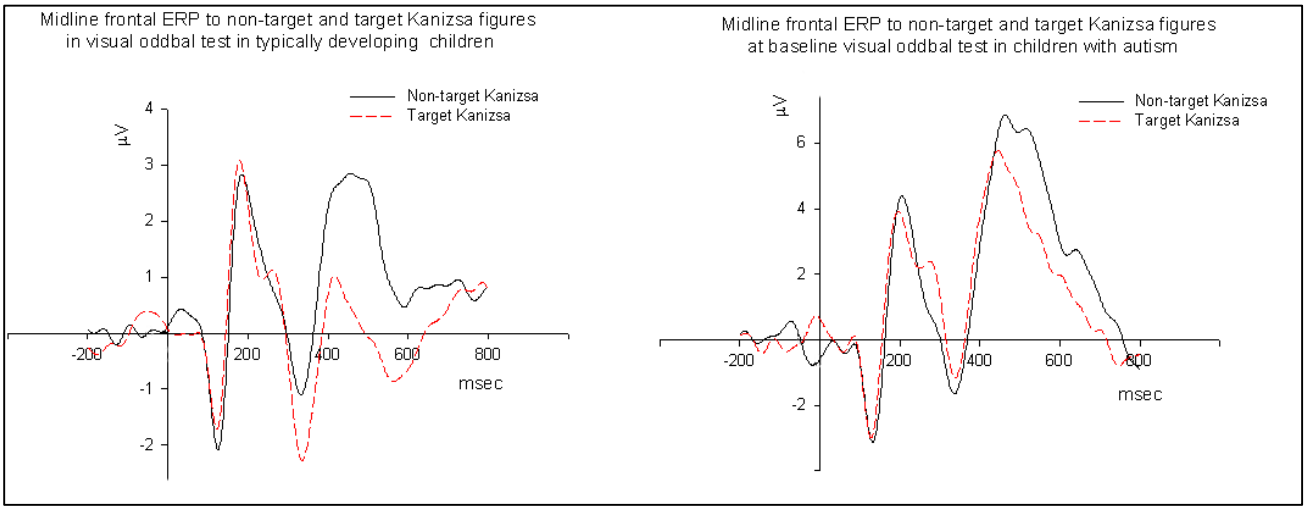

Figure 1. Midline frontal (Fz) ERPs to non-target and target Kanizsa illusory figures in the baseline visual oddball task in typically developing children (N = 21, left) and in children with ASD (N = 23, right). The ASD group shows higher amplitude of the P3a components both to non-target and target Kanizsa figures.

Effects of rTMS on P3a. Post-TMS changes can be described as a decrease of P3a amplitude to both non-target and target Kanizsa figures at all recording sites without any hemisphere or stimulus type interactions. TMS course had strong main effect on P3a amplitude (F = 10.14, p = 0.004). Decrease of P3a amplitude at the midline frontal and frontocentral ROIs was significant (non-targets, –2.03 ± 3.28 μV, t = 2.96, df = 22, p = 0.007, 95% CI from –0.61 to 13.44 μV; targets, –2.81 ± 5.56 μV, t = 2.42, df = 22, p = 0.024, 95% CI from –0.41 to –5.21 μV, see Figure 2).

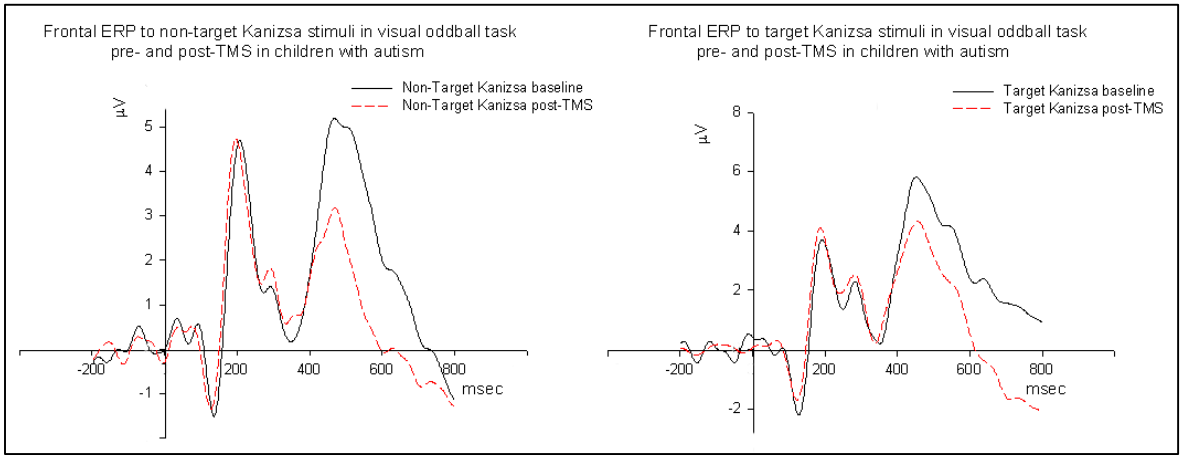

Figure 2. Left frontal ROI (F1, F3, F7) ERPs to non-target (left) and target (right) Kanizsa illusory figures at the baseline and post-TMS oddball tests in typically developing children (*N* = 21, left) and in children with ASD (*N* = 23, right). The ASD group post-TMS shows lower amplitude of the P3a component to non-target and at a lesser extent to target Kanizsa figures.

Parietal and parieto-occipital ERP components. *P100 and P200.* The only group difference in parietal and parieto-occipital P100 between ASD and TD groups was found in response to non-target Kanizsa stimuli, as it was of higher amplitude in the ASD group (mean 1.25 ± 0.61 μV, t = 2.07, df = 41, p = 0.042, 95% CI from 0.04 to 2.45 μV; adjusted for unequal variance at p = 0.17). TMS course had no main effects on P100 component's amplitude. There were not found any statistically significant post-TMS differences in P100 amplitude. Parieto-occipital N200 component was more negative to targets in the ASD group (across both hemispheres by −1.74 ± 0.76 μV, t = 2.27, df = 41, p = 0.026, 95% CI from −0.21 to −3.28 μV; variance was equal at p = 0.04).

Effects of rTMS. TMS procedure had main effect on posterior N200 amplitude (F = 7.31, p = 0.014). Effect was primarily due to significant decrease of N200 post-TMS (across both hemispheres by −1.83 ± 2.72 μV, t = 3.08, df = 22, p = 0.006, 95% CI from −0.59 to −3.07 μV) with effect being significant both at the left (p = 0.006) and the right (p = 0.017) ROIs, see Figure 3.

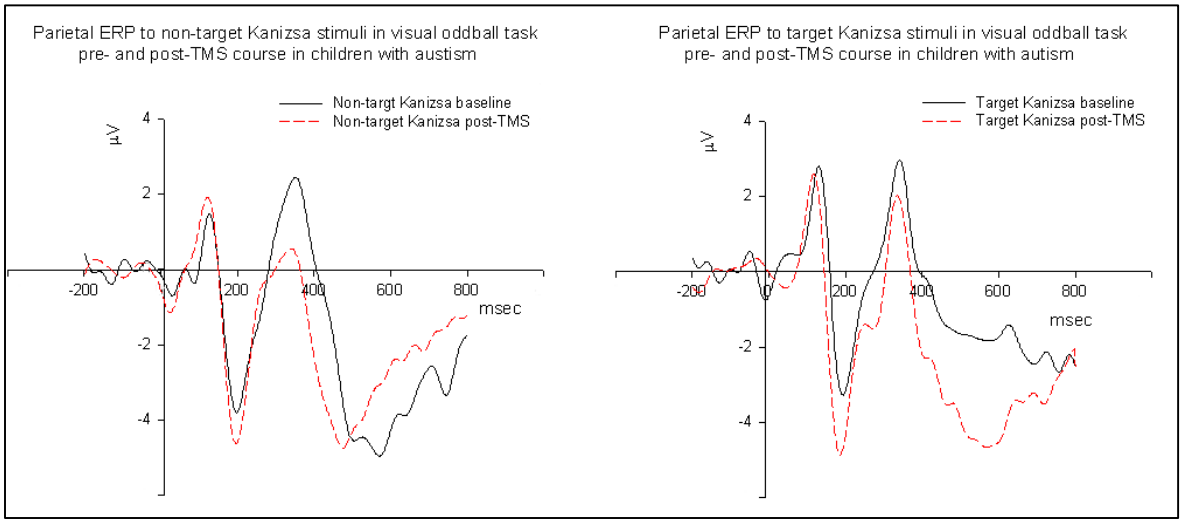

Figure 3. Bilateral parietal ROI (P3, P7, P4, P8) ERPs to non-target (left) and target (right) Kanizsa illusory figures at the baseline and post-TMS oddball tests in typically developing children (*N* = 21, left) and in children with ASD (*N* = 23, right). The ASD group post-TMS shows lower amplitude of the N200 component to both non-target and target Kanizsa figures.

Parietal P3b. There were no baseline differences in the parietal P300 (P3b) amplitude between ASD and TD, and the treatment with rTMS had only insignificant main effect on P3b response to target vs. non-target Kanizsa figures (p = 0.08). There were no other statistically significant outcomes to report regarding P3b amplitude.

Evoked and induced gamma oscillations

Evoked gamma at baseline. Mean amplitude of the early (evoked) gamma at the baseline test was higher in the ASD group to non-target Kanizsa figures at F8 site (by 0.91 ± 0.39 [standard error] μV, t = 2.26, df = 41, p = 0.029, 95% CI from 0.09 to 1.70 μV; equal variance assumed at p < 0.001), and also to target Kanizsa stimuli at F1 site (by 0.68 ± 0.24 μV, t = 2.79, df = 41, p = 0.008, 95% CI from 0.19 to 1.17 μV, adjusted for non-equal variance at p = 0.34). Parietal evoked gamma responses showed similar tendency, slightly higher in the baseline test in the ASD group at P8 to non-targets (0.82 ± 0.41 μV, t = 2.01, df = 41, p = 0.049, 95% CI from 0.01 to 1.64 μV, equal variance at p = 0.002), and barely reached significance at P7 site to target Kanizsa figures (0.64 ± 0.32 μV, t = 2.01, df = 41, p = 0.05, 95% CI from 0.01 to 1.28 μV, equal variance at p = 0.027, see Figure 4).

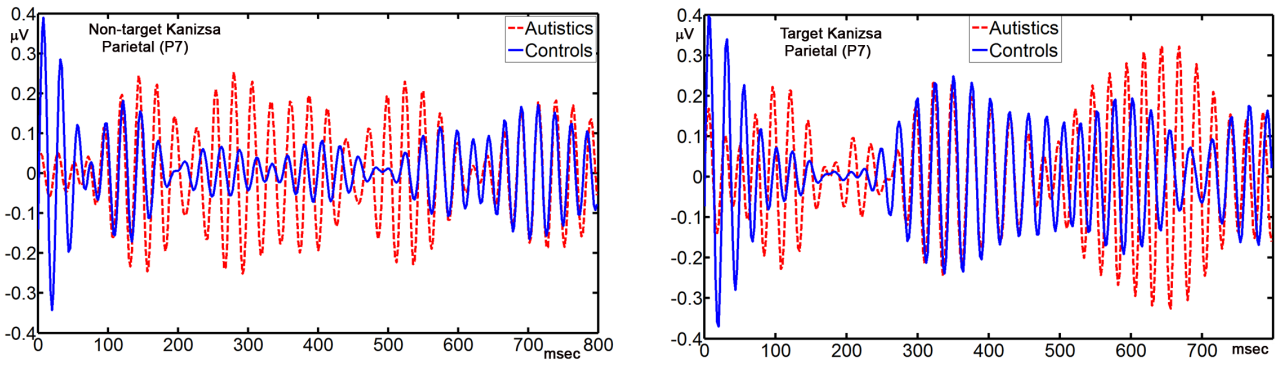

Figure 4. Evoked and induced gamma oscillations to non-target (left) and target (right) Kanizsa figures in a visual oddball task with illusory figures in ASD and TD groups of children. Grand averages of gamma responses in 23 children with ASD and 21 age- and gender-matched typical children at the left lateral parietal site (P7). The ASD group shows higher amplitude of the early evoked gamma (within 100–150 ms window poststimulus). Induced gamma to non-targets also was of higher amplitude in the ASD, while late gamma response to targets was not different those in control subjects within 250–450 ms window poststimulus, but shows tendency to increase 150–200 ms later.

Effects of TMS course on early gamma. Main effect of TMS on stimulus type factor (non-target vs. target Kanizsa) was significant both at the frontal (e.g., F7, F8; F = 9.18, p = 0.005) and parietal sites (e.g., P3, P4; F = 4.88, p = 0.032). Using repeated measure ANOVA most significant interactions were found for the inferior parietal P7 and P8 sites. *Stimulus* (non-target, target) x *Time* (pre-, post-TMS) interaction was reaching significance level (F = 4.28, df = 1,41, p = 0.045, partial η^2 = 0.097, observed power = 0.52 at α = 0.05) and can be described as a decrease of evoked gamma to only non-target Kanizsa stimuli post-TMS. Even more significant was *Stimulus* X *Hemisphere* X *Time* interaction (F = 5.56, df = 1,41, p = 0.023, partial η^2 = 0.12, observed power = 0.63 at α = 0.05). Lateralization effect was characterized by more significant decrease of evoked gamma amplitude to non-targets at the left hemisphere post-TMS. Paired sample t-test showed decrease of evoked gamma to non-target Kanizsa figures at the frontal F1 site (by –0.78 ± 0.34 μV, t = 2.25, df = 22, p = 0.029, 95% CI from –0.08 to –1.48 μV, equal variance test at p = 0.014) and at the parietal P7 site (–0.96 ± 0.44 μV, t = 2.18, df = 22, p = 0.034, 95% CI –0.07 to –1.85 μV, equal variance at p = 0.005, see Figure 5). Amplitude of the evoked gamma at the parietal P4 site only tended to increase (p = 0.058).

Induced gamma at the baseline. Independent sample t-test with Levene's test for equality of variance did not reveal any group differences in late (induced) gamma other than higher induced gamma amplitude to non-target stimuli at P7 site in children

with ASD (mean difference 0.85 ± 0.41 μV, *t* = 2.09, *df* = 41, *p* = 0.040, 95% CI from 0.02 to 1.68 μV; adjusted assuming that sample had unequal variance at *p* = 0.45). Induced gamma response at the same parietal site had tendency to be higher to target stimuli, but it reached significance only if window for analysis was expanded by additional 150 ms (up to 600 ms). In such case amplitude of late gamma to target was significantly higher in the ASD group (mean difference 0.90 ± 0.30 μV, *t* = 3.01, *df* = 22, *p* = 0.005, 95% CI from 0.29 to 1.51 μV; variance of samples equal at *p* = 0.023).

Effect of TMS course on late gamma. Main effect of rTMS on induced gamma amplitude was significant (*F* = 9.69, *p* = 0.003). We found significant *Stimulus* (non-target, target) X *Hemisphere* (left, right) X *Time* (pre-, post-TMS) interaction for the parietal P3-P4 sites (*F* = 6.21, *df* = 1,40, *p* = 0.016, partial η^2 = 0.103, observed power = 0.68 at α = 0.05). The effect can be described as a more significant increase of late gamma oscillations to target Kanizsa figures at the left hemisphere. Eventually, only left parietal sites (P3, P7) showed significant increase post-TMS to targets using paired sample *t*-test (accordingly for P3- increase by 0.41 ± 0.17 μV, *t* = 2.34, *df* = 22, *p* = 0.023, 95% CI from 0.06 to 0.77 μV; for P7, 0.59 ± 0.26 μV, *t* =2.23, *df* =22, *p* = 0.03, 95% CI from 0.06 to 1.13 μV). Left frontal F1 site also showed increase of induced gamma response to targets post-TMS (0.33 ± 0.16 μV, *t* = 2.05, *df* = 22, *p* = 0.045, 95% CI from 0.07 to 0.65 μV, see Figure 5).

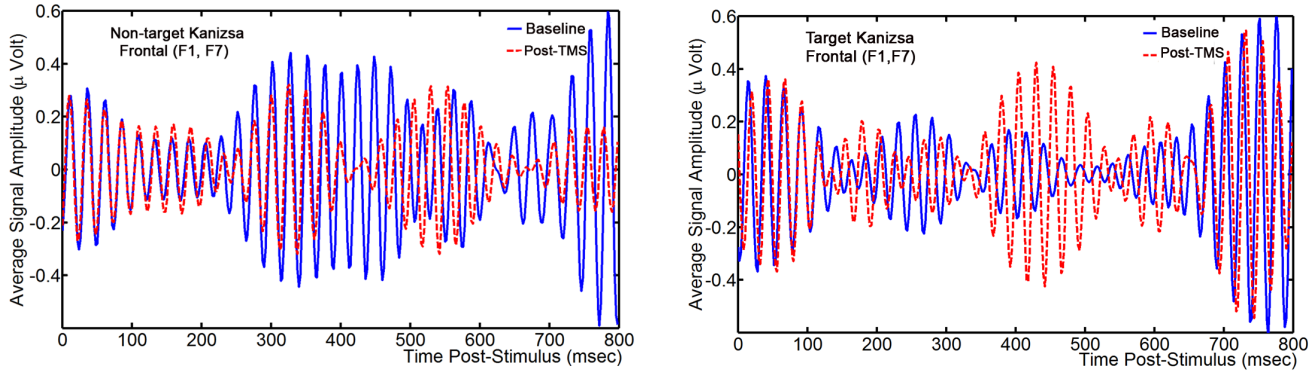

Figure 5. Evoked and induced gamma oscillations to non-target (left) and target (right) Kanizsa figures in a visual oddball task with illusory figures before and after 18 sessions of 1 Hz rTMS course in 23 children with ASD. Gamma oscillation response averaged across two frontal sites (F1 and F7) shows lower amplitudes of evoked gamma post-TMS to non-targets, along with an increase of induced gamma oscillations amplitude to target stimuli. Main effect of TMS on induced gamma was significant.

Clinical behavior evaluations post-TMS

The Student's paired sample *t*-test showed a significant post-TMS reduction in *Irritability* subscale ratings as measured by the ABC (Aman, 2004; Aman & Singh, 1994) from 10.39 ± 7.82 down to 7.87 ± 6.27 (i.e., decrease being –2.52 ± 5.22, *t* = 2.31, *df* = 22, *p* = 0.03; 95% CI from –0.26 to –4.78). *Lethargy/Social Withdrawal* and *Hyperactivity* subscales also showed statistically significant score reductions (*Lethargy/Social Withdrawal*, –1.65 ± 3.73, *t* = 2.21, *df* = 22, 95% CI from –0.36 to –3.26; *Hyperactivity*, –4.21 ± 8.29, *t* = 2.44, *df* = 22, *p* = 0.023, 95% CI from –0.83 to –7.80).

We found a significant decrease in stereotype, repetitive and restricted behavior patterns following rTMS course as measured by the RBS-R (Bodfish et al., 1999) and analyzed them using a paired sample Student's *t*-test. Total RBS-R score decreased from 21.65 to 17.61, mean decrease being –4.04 ± 6.07, *t* = 3.19, *df* = 20, *p* = 0.004, 95% CI from –1.41 to –6.67. Both *Stereotypic Behavior* subscale and *Ritualistic/Sameness* behavior subscale scores showed significant decrease (accordingly –0.78 ± 1.75, *t* = 2.13, *df* = 22, *p* = 0.044, 95% CI from -0.23 to –1.54; and –1.30 ± 2.24, *t* = 2.78, *df* =20, *p* = 0.011, 95% CI from –0.33 to –2.27). *Compulsive* behavior rating also decreased post-TMS (–1.17 ± 2.46, *t* = 2.28, *df* = 22, *p* = 0.032, 95% CI from –0.10 to –2.23).

Discussion

Differences between ASD and TD children in RT, ERP and gamma band responses

In our study children with ASD did not differ from typical children in terms of reaction time, though they committed more errors, mostly commission errors, and did not show normative post-error RT slowing as TD children did. This is in concordance with our own prior results using this particular and other three-stimuli type oddballs (Baruth, Casanova, Sears, et al., 2010; Sokhadze, Baruth, et al., 2009; Sokhadze, Baruth, El-Baz, et al., 2010) and with the majority of reaction time tests in children with ASD that note differences mostly in error rate and post-error correction function rather than reaction time (Baruth, Casanova, Sears, et al., 2010; Sokhadze et al., 2012). We proposed that deficits in error correction and impulsive key press may have connection with abnormality of error monitoring function, specifically reflected in lower magnitude of ERN (Sokhadze et al., 2012; Sokhadze, Baruth, Tasman, et al., 2010; Sokhadze, El-Baz, Sears, et al., 2014; Sokhadze, El-Baz, Tasman, et al., 2014). This difference in ERN amplitude was reported in several studies (Bogte, Flamma, van der Meere, & van Engeland, 2007; Henderson et al., 2006; Thakkar et al., 2008; Vlamings, Jonkman, Hoeksma, van Engeland, & Kemner, 2008) with indication that children and adult patients with ASD show reduced error processing capacity and deficient behavioral correction after an error is committed. This finding could be explained as a reflection of ASD patients' lower sensitivity to behavioral errors and/or reduced behavior correction ability. Most studies still agree with our finding that there are no differences in the Pe component between ASD and controls. After an error, ASD patients did not show accuracy improvement through post-error RT slowing as typical controls did. Normally, performance on the trials immediately after a committed error is improved as a result of a change in speed–accuracy strategy, which reflects executive control functioning (Burle, Possamaï, Vidal, Bonnet, & Hasbroucq, 2002). The worsened post-error performance of ASD children suggests the presence of an executive control deficiency that may have important consequences in daily life as optimal error correction is necessary for adequate behavioral responses (Sokhadze, Baruth, Tasman, et al., 2010).

Frontal and frontocentral ERPs showed larger amplitude of exogenous N100 component to non-targets followed by prolonged latency and amplitude of the endogenous P3a component in a similar way that we reported earlier using this oddball paradigm (Sokhadze, Baruth, et al., 2009) and other types of novelty tasks (Baruth, Casanova, Sears, et al., 2010). At the posterior site we found increased P100 to non-targets almost at the same timing as anterior N100 increase to non-targets only. On the other hand, we could not find any P3b group differences. Children with autism diagnosis have been found to differ from typical children mainly with respect to the P3b in standard oddball tasks. Kemner and colleagues have reported an abnormally small occipital P3b in response to target visual stimuli (Kemner, van der Gaag, Verbaten, & van Engeland, 1999; Kemner, Verbaten, Cuperus, Camfferman, & van Engeland, 1994; Kemner, Verbaten, Cuperus, Camfferman, & van Engeland, 1995). In autism the most consistent and frequently reported abnormality is P3b amplitude attenuation with auditory stimulus presentation (Bomba & Pang, 2004; Bruneau, Roux, Adrien, & Barthélémy, 1999; Oades, Walker, Geffen, & Stern, 1988; Seri, Cerquiglini, Pisani, & Curatolo, 1999; Townsend et al., 2001). However, in a simple visual target detection task there were no P3b amplitude differences found between autism and typical control subjects (Ciesielski, Courchesne, & Elmasian, 1990; Courchesne, Lincoln, Yeung-Courchesne, Elmasian, & Grillon, 1989). Our studies (Baruth et al., 2011; Baruth, Casanova, El-Baz, et al., 2010; Baruth, Casanova, Sears, et al., 2010; Casanova et al., 2012; Sokhadze et al., 2012; Sokhadze, Baruth, et al., 2009; Sokhadze, Baruth, Tasman, et al., 2010; Sokhadze, El-Baz, et al., 2009; Sokhadze, El-Baz, Sears, et al., 2014; Sokhadze, El-Baz, Tasman, et al., 2014) suggest that non-target responses (either ERP or evoked and induced gamma) in oddball paradigms should be routinely studied along with target responses in order to improve the diagnostic capabilities of cognitive ERPs. Notably, non-target responses may help to decide whether abnormal responses to target (e.g., induced gamma or P300) are related or not to a deficit in the mobilization of attentional resources (García-Larrea, Lukaszewicz, & Mauguière, 1992).

We found higher amplitude of both evoked and induced gamma oscillations in children with ASD to non-target illusory figures both at the left frontal and parietal sites, and tendency to higher induced gamma only if analysis included more delayed burst of late gamma. Deviations from typical gamma-band activity have been reported in several studies on neurological disorders, including epilepsy, Alzheimer's disease, ADHD, and autism (Herrmann & Demiralp, 2005). Individuals with ASD experience atypical visual perception, yet the etiology of this

phenomenon still remains not sufficiently well studied (Milne et al., 2009).

Our prior studies (Baruth et al., 2011; Sokhadze, El-Baz, et al., 2009) indicated that individuals with autism had a minimal difference in evoked gamma power between target and non-target Kanizsa stimuli at all EEG channels of interest. In fact, evoked gamma power responses were slightly larger in response to non-target Kanizsa stimuli relative to targets. In contrast, the control group had a significantly higher evoked gamma power to target Kanizsa stimuli compared to non-target Kanizsa stimuli showing clear differences in visual stimulus discrimination. Additionally, the control group showed a greater difference in evoked gamma power between frontal and parietal regions to all stimuli over the left hemisphere: controls had more frontal as compared to parietal gamma activity, while the ASD group showed negligible topographic differences.

These findings are similar to the findings of Grice et al. (2001) where individuals with autism did not show significant differences in frontal gamma activity during the processing of upright and inverted faces, whereas control subjects showed clear discriminative increases in frontal gamma activity when the faces were presented upright vs. inverted. These findings also correspond to our previous investigation (Sokhadze, El-Baz, et al., 2009) where we found positive differences in gamma oscillation power (i.e., 30–80 Hz, 0–800 ms poststimulus) between target and non-target Kanizsa stimuli were decreased, especially over the lateral frontal (F7, F8) and parietal (P7, P8) EEG sites, in adolescents and young adults with autism; this was mainly due to significant increases in gamma power at all recording sites, especially evoked gamma (i.e., approximately 100 milliseconds) over frontal channels, to non-target Kanizsa stimuli. Our results indicated that in ASD evoked gamma activity is not discriminative of stimulus type, whereas in controls early gamma power differences between target and non-target stimuli are highly significant.

There are a few plausible explanations as to why the gamma response does not allow for discrimination between stimuli in ASD. It is well known that ASD is associated with amplified responses to incoming sensory information. Studies suggest that the neural systems of individuals with ASD are overactivated (Belmonte & Yurgelun-Todd, 2003a, 2003b), and there is a lack of cortical inhibitory tone (Casanova et al., 2006; Casanova, Buxhoeveden, Switala, et al., 2002a, 2002b; Rubenstein & Merzenich, 2003). In a network that is overactivated and 'noisy', local cortical connectivity may be enhanced at the expense of long-range cortical connections, and individuals with ASD may have difficulty directing attention. It may not be possible for them to selectively activate specific perceptual systems based on the relevance of a stimulus (i.e., target vs. non-target).

The topic of neural and functional connectivity abnormalities was always considered as an extremely important one in current autism neuropathology theories (Belmonte et al., 2004; Courchesne & Pierce, 2005; Just et al., 2004; Minshew & Williams, 2007; Welchew et al., 2005). Some authors consider autism a disorder of neural connectivity (Coben et al., 2013). The modern theoretical view suggests that autism reflects a global processing neurodevelopmental defect produced by an excessive local connectivity and deficient distal connectivity resulting in functional disconnectivity of networks important in behavior and social cognition. The combination of local sensory hyperarousal and low-level overprocessing of incoming sensory stimuli, and at the same time abnormalities in attention selectivity and focus, according to Baron-Cohen and Belmonte (2005) may tap at the overconnected low-level processing neural networks in autism spectrum disorders. In such overwired networks, signal is insufficiently differentiated from noise or task-irrelevant information and as a result information processing capacity is drastically reduced (Belmonte & Yurgelun-Todd, 2003a, 2003b; Rubenstein & Merzenich, 2003). The brain's limited long-range wiring cannot directly sustain coordinated activity across arbitrary cortical locations, but it can convey patterns of synchronous activity as oscillatory neuronal fluxes, represented by local field potentials measured by EEG. Coordination of EEG oscillations at varying interacting frequencies allows for relatively efficient and unconstrained segregation in varying forms and across hierarchical cortical levels. Long-range abnormal neural connectivity model is suggested to explain dysfunctions deficits in high-level complex information processing functions where rapid and integrated operation of many separate neural systems is required (Brock et al., 2002; Minshew, Goldstein, & Siegel, 1997; Welchew et al., 2005).

Gamma response as such represents attention-related processes: it reflects stimulus evaluation and response selection activity related to different stages of information processing. Furthermore, since the evoked gamma oscillations to the target illusory

figure, the deviant illusory figure, and the standard nonillusory stimuli were similar in response amplitude and relative power, the early gamma oscillation could be even considered as an attention–trigger process that gives information about the arrival of a stimulus and about the need for more detailed processing that is occurring later in time and is reflected in cognitive ERP (N200, P300) and late (induced) gamma response.

The gamma frequencies, particularly those centered about 40 Hz, have been tied to visual, attentional, cognitive, and memory processes (Başar et al., 2001). Functional mechanisms of oscillatory activity in the gamma frequency range detected in various studies in animal models (Gray et al., 1989) and human electroencephalogram (EEG; Başar et al., 2001; Herrmann et al., 2004; Herrmann & Demiralp, 2005; Herrmann & Mecklinger , 2001; Tallon-Baudry et al., 1996) and magnetoencephalogram (Herrmann & Knight, 2001; Port et al., 2015; Tallon-Baudry, 2003; Tallon-Baudry et al., 2005; Tallon-Baudry, Bertrand, Peronnet, & Pernier, 1998) include perceptual feature binding, memory, object representation, and attentional processes (Böttger, Herrmann, & von Cramon, 2002; Padmanabhapillai et al., 2006). The studies of oscillatory responses in gamma-band activity proved to be very useful in understanding of the mechanisms how brain processes information (Başar et al., 2001).

Effects of rTMS on behavior, ERP, and gamma responses in children with ASD

Effects of rTMS on behavioral measures of performance in oddball tasks were manifested in reduced error rate, mostly due to lower commission errors and in significant improvement of the normative post-error reaction time slowing. Response-locked ERN increase pointed to more efficient motor error detection. We already reported similar results on improvement of accuracy of behavioral responses and improvement in error-monitoring function in children with autism in our prior studies using rTMS (Sokhadze et al., 2012; Sokhadze, El-Baz, Sears, et al., 2014). It should be noted that in our prior studies we also could not find any changes in the Pe component post-TMS. Posttreatment changes in anterior ERPs were featured mostly in decrease of the frontal negativities (N100, N200) only to non-target Kanisza figures, along with decrease of the P3a amplitude both to target and non-target stimuli. Posterior EEG sites showed decrease of the parietal N200 amplitude to targets bilaterally, but no changes were found in the P3b amplitude. Since there were no other studies using ERP as outcomes of rTMS treatment reported to date, we could only compare these ERP outcomes with our prior studies using similar rTMS with posttreatment assessment ERP outcomes (Baruth et al., 2011; Casanova et al., 2012; Casanova & Sokhadze, 2014; Sokhadze et al., 2012; Sokhadze, Baruth, Tasman, et al., 2010; Sokhadze, El-Baz, et al., 2009; Sokhadze, El-Baz, Sears, et al., 2014; Sokhadze, El-Baz, Tasman, et al., 2014). The outcomes of behavioral evaluations using RBS-R (Bodfish et al., 1999) and ABC (Aman & Singh, 1994) questionnaires showed improvements in autism symptoms (e.g., irritability and hyperactivity on ABC; stereotype and repetitive behaviors on RBS) similar to those that we reported in our other study when 18-sessions-long 1-Hz rTMS course was used in 27 children with ASD (Sokhadze, El-Baz, Sears, et al., 2014) and in a study where rTMS was combined with 18 sessions of neurofeedback training (Sokhadze, El-Baz, Tasman et al., 2014).

One of the most important goals of this study was the analysis of evoked and induced gamma oscillation changes post-TMS course in children with autism. We detected significant TMS effects on early gamma oscillations on non-target stimuli, in particular, a decrease of amplitude of evoked gamma post-TMS. In addition, we found a lateralization effect which can be described as a more significant decrease at the left hemisphere, both at the frontal and parietal sites. Effects of rTMS course on induced gamma were manifested in an increase of late gamma oscillations in response to target Kanizsa figures. This effect was more pronounced at the left parietal sites. There is a certain concordance with our ERP findings (mostly frontal N100 and N200, and parietal N200 changes) though we did not make any attempt to analyze correlations between gamma oscillation responses and specific ERP components. For the purpose of this study it was sufficient to see that the main changes of both type responses were occurring in the same time window and probably were reflecting different aspects of the same attentional, perceptual, and cognitive processes.

We can consider several mechanisms contributing to the normalization of initially excessive sensory reactivity (e.g., higher magnitude of exogenous ERPs and higher evoked gamma) following inhibitory rTMS treatment course in children with autism. As it was already noted by Belmonte and Yurgelun-Todd (2003a, 2003b), perceptual filtering of incoming stimulation in autism is thought to occur in an ‘‘all-or-none’’ mode without relevance to task specificity for the stimulus. The attention in

individuals with autism seems to be dependent more on the coarse control of general arousal than on selective activation of specific sensory systems. Abnormalities of arousal control and their role in atypical attention style in ASD was noted also by other authors (Orekhova & Stroganova, 2014). It is reasonable to suggest that active inhibition of irrelevant distractors, or in other words normative habituation, is not properly functioning and allows both task-relevant and task-irrelevant stimuli to pass through earlier filtering processes creating an overload on later stages of stimulus processing. It was outlined by several studies that an increased ratio of excitation/inhibition in cortical systems and high ‘‘cortical noise’’ have been considered one of the core abnormalities in autism (Casanova et al., 2003; Rubenstein & Merzenich, 2003; Uzunova et al., 2015). In this current study we used slow rTMS over the DLPFC of children with ASD in our continuing efforts to increase the inhibitory surround of minicolumns in this prefrontal area. Due to the phenomenon of diaschisis and the connectivity of this brain region we expected the intervention not to be limited only to the site of magnetic stimulation (e.g., DLPFC) but rather to generalize to other cortical areas.

A focal electrical current induced by rTMS orthogonal to the pial surface results in a short-term functional reorganization of cortical activity. Since the effects of rTMS are not limited to the stimulated target cortex but give rise to functional changes in anatomically and functionally interconnected cortical areas, rTMS can strengthen functional connectivity between cortical areas. Low-frequency rTMS has been reported to operate via long-term depression of cortical activity (Hoffman & Cavus, 2002), which we hypothesize preferentially activates radially-oriented double-bouquet axons. Current findings of post-TMS improvement in executive functions such as error monitoring, more effective detection of target, less distraction to non-target items processing, etc. may add new insight to understanding of neuropathological mechanisms underlying ASD symptoms. We showed that treatment with rTMS decreased excess gamma activity to non-target distractors and amplified ERP and gamma responses to target items in ASD patients during visual task, thus improving the signal differentiation between processing relevant and irrelevant Illusory stimuli. Additionally, it seems that rTMS improved the activity at different regions of the brain (e.g., frontal and parietal cortices) and significantly improved repetitive and restricted behavior patterns associated with ASD assessed using clinical behavior evaluation instruments. Our results suggest that low-frequency rTMS may improve the inhibitory tone and decrease the ratio of cortical excitation to inhibition in ASD. This may lead to improved long-range connectivity within prefrontal and midfrontal mesial cortical structures and also along fronto-parietal attention networks. In describing the presence of a minicolumnopathy in autism, our group gave as predictive validity possible alterations in the blueprint of white matter connectivity, gamma frequency abnormalities, and the use of low-frequency (inhibitory) rTMS as a possible therapeutic intervention (Casanova, Buxhoeveden, & Brown, 2002; Casanova et al., 2012, 2015; Casanova & Sokhadze, 2014; Sokhadze, Casanova, & Baruth, 2013; Sokhadze, El-Baz, et al., 2009). These predictions were based, in part, on the compartmentalization of minicolumnar abnormalities in the peripheral neuropil space across all different laminae of the cerebral cortex. The resultant defect in lateral inhibition has now been proven using EEG and responses to tactile vibratory stimuli (Kéïta, Mottron, Dawson, & Bertone, 2011; Puts, Wodka, Tommerdahl, Mostofsky, & Edden, 2014; Tavassoli et al., 2016).

There are several limitations that should be mentioned: the design of the project does not incorporate a control group with rTMS treatment as the Institutional Review Board prohibited active treatment in typically developing children. In this regard we could be criticized that the study represents a case series study rather than a controlled study. The only type of control we used was a comparison of behavioral, ERP, and gamma responses at the baseline stage between children with ASD and typically developing children that served as a contrast group. The outcomes of the rTMS part of the study were not controlled. In the past we did a wait-list controlled trial using similar rTMS regimen (Baruth et al., 2011; Casanova et al., 2012; Sokhadze et al., 2012; Sokhadze, El-Baz, Sears, et al., 2014; Sokhadze, El-Baz, Tasman, et al., 2014) and now prepare to conduct sham-TMS-controlled, randomized clinical trial. The current study should therefore be considered as exploratory in nature and aimed at selecting target EEG gamma and ERP outcomes to refine them in future studies. This explains also our decision to use and report outcomes of only a limited number of behavioral and clinical questionnaires, as our focus was first of all on electrophysiological markers and outcomes.

Our study did not compare evoked and induced responses of frequencies other than gamma, and we did not analyze cross-frequency coupling of gamma band with other EEG frequencies; this can be

considered as yet another limitation. Gamma oscillations are known to be involved in various cognitive processes and are considered by many researchers as carrying fundamental functions for information processing within the brain. While gamma oscillations, specifically those evoked in response to stimulation like in our study, have been shown to correlate with other EEG rhythms and evoked oscillation in different frequency ranges, to date there have been few empirically supported evidence presented to support a casual influence of gamma oscillations on other EEG rhythms. For instance, Grosse-Wentrup, Schölkopf, and Hill (2011) presented results supporting relations of gamma oscillations and sensorimotor rhythm (SMR) in healthy subjects during motor imagery, in particular positive correlation of SMR with gamma power at the frontal-occipital and negative correlation at the centroparietal sites.

There is an important methodological issue that refers to the interpretation of topographical distributions in studies in which 128-channel montages were used. The problem is the selection of the EEG reference for analysis (Müller et al., 2000). In our studies we used Cz as reference and did not try to transform the Cz recording reference to the average reference prior to wavelet analysis. As with every choice of a nonactive reference, the question arises as to whether our findings with respect to a given electrode reflect activity of the cortex under that electrode topography or result from potentials variations of the reference. For example, it has been argued that the average reference may produce so-called 'ghost fields' and can produce distortions of focal features (Desmedt & Tomberg, 1990; Desmedt, Tomberg, Noël, & Ozaki, 1990) when applied to time-locked signals. It seems likely that this is also possible with induced responses. While some alternate approaches (e.g., the use of spline Laplacians) may overcome reference electrode and some other problems, they may act as a form of spatial filtering and underestimate actual gamma response values.

Analysis of evoked and induced EEG gamma oscillations could provide for important outcome measures, a potential cortical "fingerprint," of activation patterns associated with core behavioral and cognitive abnormalities that characterize ASD. Furthermore, when analyzed along with behavioral (reaction time, accuracy, etc.) and event-related potential data, the gamma-oscillations-based biomarkers will offer insights into the psychophysiology of ASD. The relative low cost of EEG methods means that the proposed biomarker will be accessible to many individuals and to those studies requiring large samples. EEG modalities are noninvasive and can be tolerated by many individuals who would otherwise not be able to participate in alternative studies, for example, runctional magnetic resonance imaging (fMRI).

Author Notes

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NeuroRegulation

The Efficacy of Neurofeedback Among Patients with Major Depressive Disorder: Preliminary Study

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Abstract

Introduction: Alpha asymmetry of the left and right frontal hemisphere is a potential biomarker for major depressive disorder (MDD). Neurofeedback (NFB) is a clinical intervention program for regulating brain activity and decreasing alpha asymmetry. The purpose of this study was to explore the efficacy of NFB among patients with MDD. **Methods:** Fourteen patients with MDD were randomly assigned to a NFB group that received neurofeedback training 1 hr weekly for 6 weeks and to a control group that was treated without training. A 5-min resting baseline of electroencephalogram (EEG) was recorded at F3 (left) and F4 (right) before and after NFB, and the alpha power was analyzed as an asymmetry index (A1). **Results:** The A1 of the control group decreased from pre- to post-interventions while the A1 of the NFB group increased from pre- to post-interventions. Anxiety and depression scores of the responder group decreased from pre- to post-interventions, while the scores of the non-responder group increased from pre- to post-interventions. **Conclusion**: Patients who respond to the NFB training showed a decrease in anxiety and depression scores compared to those who do not. This study indicated that NFB could improve left frontal hypoarousal or right frontal hyperarousal among patients with MDD.

Keywords: major depressive disorder; neurofeedback; electroencephalogram; alpha asymmetry

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Introduction

Major depressive disorder (MDD) is one of the common mental disorders that cause individual physical discomfort and emotional suffering, as well as interpersonal problems, and impaired social and career functioning. Depression is usually treated with antidepressant medications; however, recent research suggests that for children and teenagers with major depression, 13 out of the 14 antidepressant drugs do not work and can increase teenage suicide rates (Le Noury et al., 2015). Even in adults, selective serotonin reuptake inhibitors, such as Prozac, may not work any better than placebo; in addition, almost all studies that have demonstrated positive pharmaceutical effects have been directly or indirectly sponsored by pharmaceutical companies (Ebrahim, Bance, Athale, Malachowski, & Ioannidis, 2016). To avoid antidepressant side effects and offer patients MDD treatment, neurofeedback (NFB) is a promising new approach.

Electroencephalographic (EEG) studies have found greater alpha power over the left than the right frontal regions among patients with MDD (Debener et al., 2000; Gotlib, Ranganath, & Rosenfeld, 1998). Davidson (1984) indicated that the frontal alpha asymmetry with an active left frontal lobe is related to the behavioral approach system (BAS), leading to more positive emotions, motivation, and behavioral approaches. On the other hand, an active right prefrontal lobe is related to behavioral inhibition system (BIS), leading to more negative emotions,

escape-related motivation, and behavioral withdrawal.

Davidson (1998) calculated the alpha asymmetry score (A score) from the alpha power at the left frontal (L or F3) and right frontal (R or F4) lobes. Baehr, Rosenfeld, and Baehr proposed two equations for the A score: $A1 = log (R) - log (L)$ and $A2 = (R - L) / (R + L)$ (Baehr, Rosenfeld, & Baehr, 1997; Rosenfeld, Baehr, Baehr, Gotlib, & Ranganath, 1996). When the alpha power at the right frontal lobe is higher than that in the left frontal lobe, the A1 score is positive and is associated with more positive emotions (such as happiness and joy), motivation, and approach behavior from the BAS system. When the alpha power at the right frontal lobe is lower than that in the left frontal lobe, the A1 score is negative and is associated with more negative emotions (such as fear, disgust, and sadness), escape-related motivation, and behavior withdrawal from the BIS system (Davidson, 1984). The prefrontal alpha asymmetry suggests brain lateralization (hemispheric laterality; Davidson, 1984, 1993, 1998).

Patients with MDD show lower alpha asymmetry scores as compared to healthy adults (Cantisani et al., 2015; Coan and Allen, 2004; Debener et al., 2000; Kemp et al., 2010). Similar alpha asymmetry was also observed in patients with remission from MDD (Stewart, Coan, Towers, & Allen, 2011).

Based on the concept that alpha asymmetry is a potential biomarker for depression, Baehr et al. (1997) developed a neurofeedback protocol, the Alpha Asymmetry (ALAY) protocol, to train patients to change the frontal alpha asymmetry as neurofeedback training for depression. The goals were to decrease the left frontal alpha power at F3 to improve positive emotion and increase the right frontal alpha power at F4 to decrease depression. Case reports found that the ALAY protocol could improve the frontal alpha asymmetry and decrease depressive symptoms (Baehr et al., 1997; Dias & van Deusen, 2011; Rosenfeld et al., 1996). The treatment effectiveness was maintained through 1- to 5-year follow-ups (Baehr, Rosenfeld, & Baehr, 2001).

Several studies have shown that neurofeedback has long-term benefits and show significant improvement in the frontal alpha asymmetry and depressive symptoms. Choi et al. (2011) conducted a randomized sham control group study comparing a 1-hr twice a week for 10 weeks NFB group (ALAY protocol) with a psychotherapy group. The NFB group as compared to the psychotherapy group showed higher A1 scores, increased positive autonomic thoughts, decreased negative autonomic thoughts, and improved performance of the executive function tests, such as semantic and phonological fluencies. Peeters, Oehlen, Ronner, van Os, and Lousberg (2014) confirmed that the neurofeedback with the ALAY protocol did decrease the depression score, but did not decrease the A1 score after 10 sessions for decreasing left frontal alpha power.

Previous studies have found that the average number of sessions of the NFB protocol were between 10 and 36 sessions (Baehr et al., 1997, 2001; Choi et al., 2011; Peeters et al., 2014; Rosenfeld et al., 1996). The average treatment sessions to complete the NFB protocol are 20–22 sessions (Hammond, 2005). After 3–6 sessions of 30-min each of NFB, patients may feel the difference between pre- and post-interventions. After 10–12 sessions, patients feel a significant improvement. For sustained, long-term changes and clinical benefits of neurofeedback, 30 to 60 sessions may be required, which depends on compliance and motivation (Linden, Habib, & Radojevic, 1996). Hammond (2005) indicated that patients might feel the differences after 3–6 sessions of neurofeedback; however, this has not been systematically explored. The purpose of this study was to examine: (1) a short-term six-session ALAY protocol of NFB among patients with MDD, and (2) the efficacy of the ALAY protocol in increasing the alpha asymmetry score and decreasing depressive symptoms among patients with MDD in Taiwan.

Methods

Participants

Fourteen patients with MDD were referred by psychiatrists based on the criteria of Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) at an outpatient clinic of Kaohsiung Medical University Hospital (American Psychiatric Association, 2013). Patients with MDD with serious physical and mental disorders (e.g., cancer, heart disease, kidney disease, Alzheimer's disease, Parkinson's disease, schizophrenia, bipolar disorder, substance abuse, etc.) were excluded from this study. The institutional review board approval was obtained from the ethics committee of the Kaohsiung Medical University Hospital (KMUH-IRB-20110063), and written informed consent was obtained from each participant before the experiment.

All participants were assigned randomly to the NFB group and the control group. There was no

significant difference between the two groups in age, sex, Beck Anxiety Inventory (BAI), Beck Depression Inventory-II (BDI–II), and duration of disorder. Participants in both groups received medications by psychiatrists; however, there was no group difference in the categories of medications (Table 1). All participants in both groups received neither psychotherapy nor other nonpharmacological treatment at the same time. The equal group design was confirmed in this study. Participants in the NFB group received 1 hr per week for 6 weeks of neurofeedback that was based on the ALAY protocol (Baehr et al., 1997). The ALAY protocol included down-training of the alpha power (8–12 Hz) at F3 and up-training of the alpha power (8–12 Hz) at F4, and the treatment goal was to increase the A1 score (Baehr et al., 1997; Baehr, Rosenfeld, Baehr, & Earnest, 1998). Participants in the control group received the pharmacological treatment only.

Table 1
The Demographic Characteristics of All Participants

Variable	NFB group (n = 7)	Control group (n = 7)	t / χ^2
Age (years)	49.86 (3.98)	47.43 (13.84)	–0.45
Sex			
Women	5	6	
Men	2	1	0.42
Beck Anxiety Inventory	17.86 (10.51)	16.00 (9.92)	–0.34
Beck Depression Inventory-II	30.14 (10.25)	22.86 (13.03)	–1.16
Duration of disorder (years)	8.83 (2.71)	6.68 (5.37)	–0.88
Medications			
Benzodiazepine	6	5	0.42
Selective serotonin reuptake inhibitors	1	2	0.42
Atypical antidepressants	5	4	0.31
Sedative-hypnotic	4	2	1.17

Psychological questionnaires

All participants completed self-report questionnaires that covered demographic characteristics (such as age, sex, and years of disorder), BAI, and BDI–II at pre- and post- interventions of neurofeedback. The BAI and BDI–II are self-report questionnaires that measure the symptoms of anxiety and depression disorder over the course of a period, respectively.

EEG equipment and measurement

The BrainAvatar Version 4.0 (BrainMaster Technologies, Inc., Bedford, OH) EEG system was used for EEG data collection, with a 19-channel EEG cap which was placed on the participants' scalps, and linked-ear was the reference to collect EEG raw signals. All participants were measured for a 5-min baseline with eyes closed at pre- and post-NFB intervention. The BioGraph Infiniti Version 6.1.1 (Thought Technology Ltd., Montreal, QC, Canada) was used with a bipolar-channel at F3 and F4 based on the International 10-20 system, Cz was the reference, and the left earlobe served as ground (Baehr et al., 1997). The impedances of the electrode were set below 5 kΩ; band-pass was 1–30 Hz, notch filter was at 60 Hz, and the sampling rate was 256 Hz.

Data reduction and statistical analysis

The EEG raw signal was analyzed using MATLAB R2008a (The Math Works, Natick, MA), and the EEG power spectrum was transformed to the alpha power (8–12Hz) by EEG insight software (Delorme & Makeig, 2004). The frontal alpha asymmetry score (A1 index) was computed with the natural logarithms (ln) by subtracting the left alpha power from the right alpha power, $A1 = log\ (R) - log\ (L)$ (Baehr et al., 1997).

The *t*-tests and χ^2 test were used to examine the equal group design on the demographic characteristics. The paired *t*-tests were used to examine the differences in the A1 score, BAI, and BDI–II at pre- and post-intervention for the NFB group and control group. In addition, the change-score of *A1 = (A1 at post-intervention – A1 at pre-intervention)* was used to separate participants in the NFB group and control group into a responder group and non-responder group. Participants in the responder group showed an increased A1 score; the non-responders had no change in the A1 score. In addition, this study also examined the differences in the A1 score, BAI, and BDI–II at pre- and post-interventions between the responder group and the non-responder group.

Results

The treatment effectiveness of neurofeedback on the A1 score

The A1 score was increased slightly in the NFB group from pre-intervention (*M* = 0.11, *SD* = 0.13) to post-intervention (*M* = 0.12, *SD* = 0.13); the A1 score was decreased slightly in the control group from pre-intervention (*M* = 0.04, *SD* = 0.07) to post-intervention (*M* = 0.02, *SD* = 0.07; Table 2). Although an overall increase in the alpha power at F3 and F4 was observed from pre- to post-intervention in both NFB and control groups. However, there was no significant difference between the two groups in the A1 score.

Table 2
The Changes in the Alpha Power from Pre- to Post-interventions in the NFB Group and the Control Group

Alpha Power	Pre-intervention	Post-intervention	*t*
NFB group (*n* = 7)			
F3	10.10 (4.58)	12.77 (5.23)	–1.07
F4	10.91 (4.27)	14.42 (5.75)	–1.26
A1	0.11 (0.13)	0.12 (0.13)	–0.24
Control group (*n* = 7)			
F3	5.51 (3.95)	7.27 (5.42)	–1.18
F4	5.80 (4.14)	7.57 (5.76)	–1.24
A1	0.04 (0.07)	0.02 (0.07)	0.63

The responders showed an increased A1 score as compared to the non-responders in the NFB group.

This study used the change-score of A1 to separate participants in the NFB group into a responder group and a non-responder group. Although the A1 score was not different between the two groups, four participants (57.14%) showed increased A1 score from pre- to post-interventions; however, three of them (42.86%) showed decreased A1 score after neurofeedback training (Figure 1).

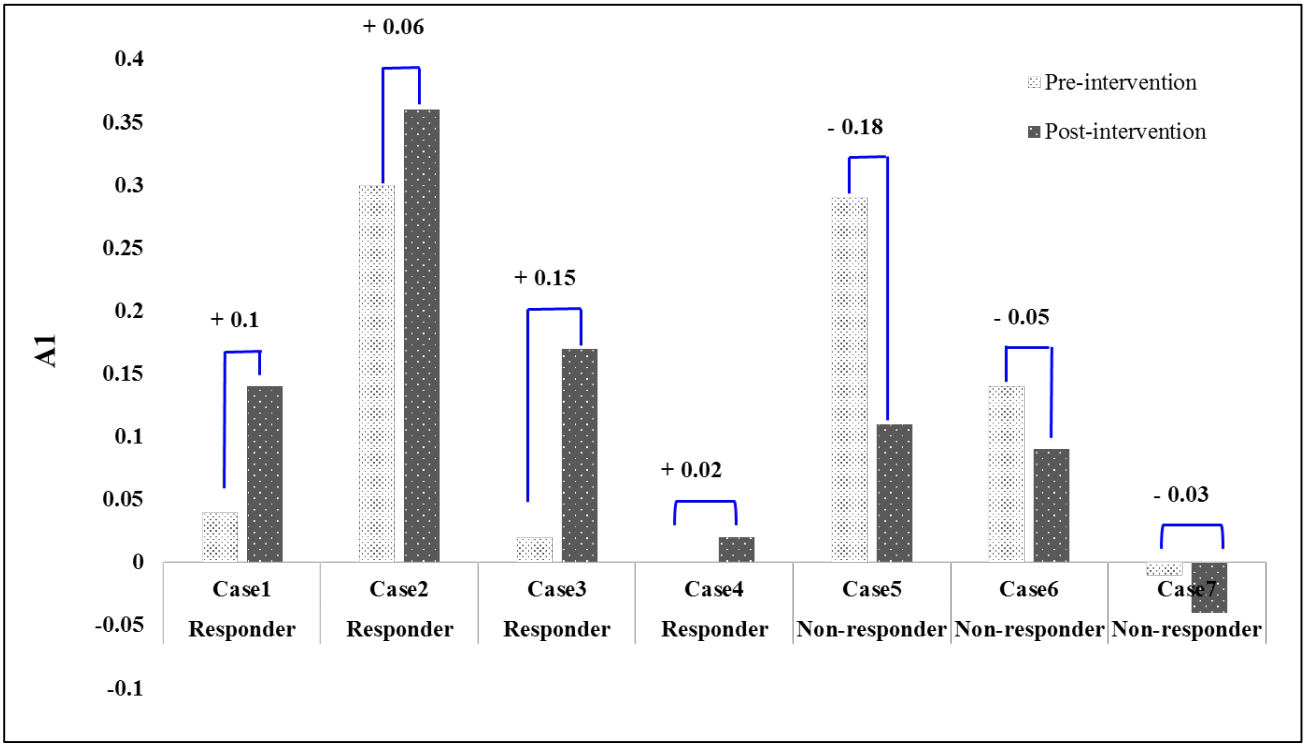

Figure 1. The A1 score at pre- and post-interventions between the responders and non-responders in the NFB group.
Note: Change-score of *A1 = (A1 at post-intervention) – (A1 at pre-intervention)*.

The responders showed a decrease in anxiety and depression scores as compared to the non-responders in the NFB group.

In the NFB group, anxiety and depression scores were decreased slightly from pre- to post-interventions (BAI: 23.00 to 18.00; and BDI–II: 35.75 to 29.25, respectively) in the responder group (t = 0.99, $p > 0.05$; and t = 1.32, $p > 0.05$); otherwise, anxiety and depression scores were increased slightly from pre- to post-interventions (BAI: 11.00 to 24.67; and BDI–II: 22.67 to 28.33, respectively) in the non-responder group (t = –1.39, $p > 0.05$; and t = –0.87, $p > 0.05$; Figure 2).

In addition, we used similar analysis of the responder group and non-responder group for the control group. The results showed that in the control group, the scores of anxiety and depression decreased slightly from pre- to post-interventions in the responder group (BAI: 15.00 to 10.75; and BDI–II: 19.00 to 13.75, respectively); otherwise, anxiety and depression scores were increased or did not change from pre- to post-interventions (BAI: 17.33 to 19.33; and BDI–II: 28.00 to 28.00, respectively) in the non-responder group (Figure 2).

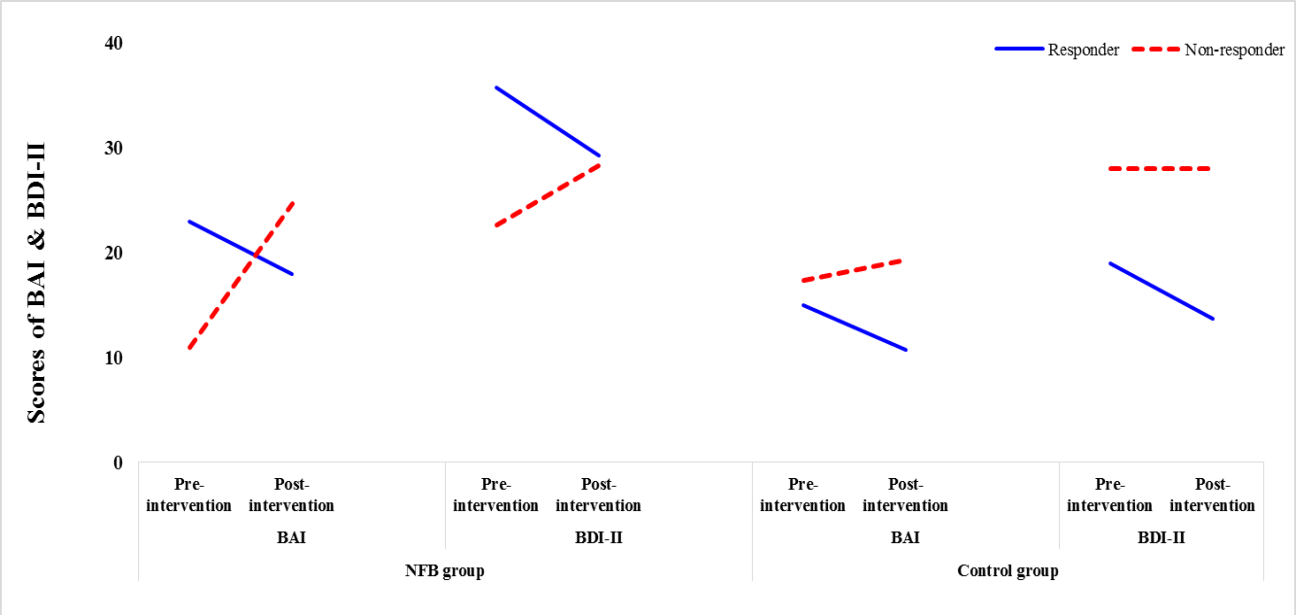

Figure 2. The scores of BAI and BDI-II at pre- and post-interventions between the responders and non-responders for the NFB and control groups.

Discussion

Preliminary results show that patients with MDD showed increased A1 score after neurofeedback training in the NFB group. The responder group responded to the neurofeedback with more improvement in anxiety and depression than the non-responder group. By separating the responders and non-responders, the study points out that it is not the number of training sessions that is important, but whether the skill mastery has been achieved. Clinical conclusions should only be drawn from those participants who mastered the skill. These results suggest that six training sessions were either insufficient for the non-responders and they needed more sessions to develop mastery or that the training protocol was inappropriate and they needed a different type of intervention (Shellenberger & Green, 1986).

This study indicated that neurofeedback training increases the A1 score by improving frontal alpha asymmetry because of two reasons: (1) increased right frontal alpha power means decreased right frontal activity, and (2) decreased left frontal alpha power means increased left frontal activity. This result was consistent with previous studies that showed decreased depressive symptoms after neurofeedback training (Baehr et al., 1997; Baehr et al., 2001; Choi et al., 2011; Dias et al., 2011; Peeters et al., 2014; Rosenfeld, 2000). We found that patients with MDD with increased A1 score after neurofeedback training (responder) also showed decreased anxiety and depression; on the other hand, patients with MDD with decreased A1 score after neurofeedback training (non-responder) showed increased anxiety and depression.

However, this study found that not all patients with MDD increased A1 score after neurofeedback training. Even though the ALAY protocol of neurofeedback was followed to address frontal alpha asymmetry, not all patients with MDD had A1 score lower than zero. Some patients with MDD had A1 score higher than zero. Overall, this study found that increased A1 score was related to decreased symptoms of anxiety and depression (r = –0.27). However, this result may due to the placebo effect and needs to be reassessed in the same experimental conditions.

Depressive disorder is a heteroscedastic disorder, the pathophysiological mechanisms of which are still controversial. Some depressive disorders are comorbid with anxiety disorder or anxiety symptoms (Bruder et al., 1997), with melancholia or non-melancholia (Quinn, Rennie, Harris, & Kemp, 2014), and psychomotor retardation (Cantisani et al., 2015). These heteroscedastic characteristics may reflect different EEG patterns in different brain regions. For example, patients with MDD with comorbid anxiety had higher activity in the right parietal-temporal lobe than those with MDD without anxiety (Bruder et al., 1997).

Several limitations should be noted in this study. First, only 14 patients with MDD were included in this present study. The insufficient sample size may decrease the statistical power and cause no significant finding. Second, the neurofeedback protocol for patients with MDD needed at least 10–36 sessions in the previous studies (Baehr et al., 1997; Choi et al., 2011; Peeters et al., 2014; Rosenfeld et al., 1996); however, our participants in the NFB group only received 1 hr per week for 6 weeks of neurofeedback training which may limit the efficacy of neurofeedback. More practice may improve neuroplasticity (Malkowicz & Martinez, 2009). Third, the pathophysiological mechanism of alpha asymmetry was not confirmed for all patients with MDD, even though there was higher alpha asymmetry score among patients with MDD than in the healthy controls (Debener et al., 2000; Kemp et al., 2010). Fourth, because of the heterogeneity of depressive disorders, some patients with MDD with comorbid mild anxiety symptoms in our study showed a BAI score of 17.86 in the NFB group and 16.00 in the control group. Previous studies found hyperactivity in the right posterior regions in patients with comorbid MDD and anxiety symptoms (Bruder et al., 1997; Heller, Etienne, & Miller, 1995), and the pathophysiological mechanism of EEG patterns may differ between MDD with anxiety and MDD without anxiety (Bruder et al., 1997). Therefore, the individualized neurofeedback protocol should be set up for these patients. Fifth, depressive symptoms in some patients were caused by stressful life events or adjustment problems and some patients with MDD improved significantly after few sessions of neurofeedback; however, some of them showed increased severity of depression during neurofeedback training. Hammond (2005) indicated that not all individuals with frontal alpha asymmetry will be depressed, and some persons can experience negative life events and still become depressed in the absence of frontal alpha asymmetry. Some patients did not improve significantly because of other stressful life events during neurofeedback training, such as a loss in their family (Hammond, 2005). Therefore, stressful life events may be a confounding factor in the outcome evaluation. Sixth, some studies examined the learning curve across and within neurofeedback sessions (Baehr et al., 1997; Zuberer, Brandeis, & Drechsler, 2015) to confirm a linear trend of EEG changes. However, this study did not measure the scores of frontal alpha asymmetry under each session, and hence, the trend of treatment effectiveness is still unknown.

In conclusion, there was partial support for the efficacy of neurofeedback among patients with MDD, especially for those who were responders. Patients in the responder group showed decreased symptoms of anxiety and depression, as well as improved frontal alpha asymmetry. However, some of them did not improve significantly and probably needed more training sessions. Finally, the sample size should be increased in future studies.

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NeuroRegulation

Safety and Feasibility of Neurofeedback Training (NFB) During Sleep in Uncooperative Child with Autism: Case Report

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Abstract

Purpose: Neurofeedback (NFB) training has demonstrated significant potential in achieving symptoms reduction in children with Autism Spectrum Disorder (ASD). However, children with low-functioning ASD are often uncooperative with the treatment. To evaluate whether NFB can eventually be administrated during sleep, a safety and feasibility pilot study was performed. **Methods:** A 9-year-old male patient diagnosed with ASD underwent NFB training for 30 min twice a week. This was operated at home during sleep by the parents. The NFB protocol aimed at increasing sensorimotor rhythm (SMR) while simultaneously decreasing theta activity over the sensorimotor strip. **Results:** NFB during sleep was feasible and did not yield adverse side effects. Parents reported improved behavioral and emotional symptoms and enhanced language development following NFB training. Subsequently, the patient could participate in regular sessions of NFB in wakefulness. **Conclusion:** Overall, parental reports suggest that applying NFB during sleep in low-functioning ASD is feasible and might offer promising therapeutic avenues.

Keywords: sleep; neurofeedback; Autism; sensorimotor rhythm

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Introduction

Neurofeedback is a specific form of biofeedback aiming at changing EEG oscillations through operant conditioning (Sterman, 2000). Normally, NFB protocols are determined on the basis of spectral parameters of spontaneous EEG in resting-state conditions. This EEG signal is processed and compared to database of normal subjects in order to reveal a profile of abnormalities (Coben & Padolsky, 2007). Changes in EEG patterns as a result of NFB have been associated with regulation of cerebral blood flow, metabolism, and neurotransmitter function (Lubar, 1997). On the behavioral level, changes in cognitive and emotional functions have been documented in healthy individuals (Gruzelier, 2014), as well as in neuropsychiatric patients (e.g., Hammond, 2005; Sterman & Egner, 2006).

The relationship between NFB training and sleep can be viewed as two-way counter paths. From the beginning, NFB has been frequently used to treat sleep disturbances since facilitating specific oscillations during wakefulness selectively enhances similar brain patterns during subsequent sleep period (Hoedlmoser et al., 2008). Particularly, it was proposed that improvement of physiological regulation of sensorimotor rhythm (i.e., low-beta frequency band 12–15Hz) stabilizes sleep state through optimization of thalamic-cortical circuits (Sterman, 2000). Sensorimotor rhythm (SMR) is also thought to be related to the intrinsic function of the reticular activating system (RAS), which, among

other things, is connected to the regulation of wakefulness and sleep-wake transitions (Sterman & Bowersox, 1981).

The parallel, yet opposite, approach is to modulate brain activity during sleep in order to alter long-term behavior at wakefulness. According to Tononi and Cirelli (2006), sleep promotes homeostasis by reducing the strength of synaptic connections to a level that is energetically sustainable and thus primes new learning. Arzi and colleagues (2014) recently reported that olfactory aversive conditioning during sleep significantly reduced cigarette-smoking behavior for several days. Moreover, methods of neuromodulation such as transcranial direct current stimulation (tDCS) were found to enhance retention of learned material when applied during sleep, pointing to the possibility of "night-treatment" for memory enhancement (Marshall, Mölle, Hallschmid, & Born, 2004). Together, these studies confirm that sleep might be particularly beneficial for learning (Dudai, 2012).

ASD is a pervasive developmental disorder including a variety of cognitive, sensory, and social deficits such as impaired communication skills and sociability, as well as restricted and repeated behaviors (Hill & Frith, 2003). NFB training in ASD with theta suppression and SMR enhancement were reported to induce positive short- and long-term effects on executive functions, social interaction, and communication skills (Kouijzer, de Moor, Gerrits, Buitelaar, & van Schie, 2009; Kouijzer, de Moor, Gerrits, Congedo, & van Schie, 2009). Enhancement of SMR is reported to improve response inhibition and promote synchronization by regulating the sensorimotor system (Gruzelier & Egner, 2005), while suppression of theta is reported to promote more flexible functioning of the brain by activating the default mode network (Kouijzer, de Moor, Gerrits, Buitelaar, & van Schie, 2009).

Although a considerable number of children with ASD cooperate with NFB training, some with more pronounced symptoms of restlessness, hypersensitivity, and aggression cannot receive treatments due the severity of their symptoms. This is unfortunate in the face of a growing number of studies revealing the benefits of NFB in children and adults diagnosed with ASD (Holtmann et al., 2011). Given it is important to accommodate NFB to a wide range of patients, treatment during sleep could act as a possible solution for lack of cooperativeness. Similar to many medical interventions, NFB can induce adverse effects when it is commonly implemented in wakefulness (Rogel et al., 2015); here, we were specifically concerned about inducing sleep disturbance as a result of the night-treatment.

Thus, the purpose of this pilot was to evaluate whether NFB training during sleep is safe and feasible and whether it could be behaviorally beneficial for children with ASD. Here we applied NFB training using a reward sound during sleep. The training was set to up-regulate SMR (11–14 Hz) and down-regulate theta (4–7 Hz) located across the sensorimotor strip. This protocol was chosen since it has been shown to regulate altered neuronal excitability (Sterman, 2000). Of note, uncooperativeness observed in this kind of patient often dictates prototypic use of research-based protocols, as EEG could not be properly recorded and analyzed. Along the treatment, the parents needed to evaluate (a) adverse side effects, specifically, in regard to sleep, (b) feasibility, that is, how easy it is to operate the treatment during sleep, and (c) efficacy, whether they observed reduction in ASD symptoms.

Neurofeedback

NFB was administered at central electrode sites (C4, Cz, and C3) with BrainMaster 2EB system with the 3.7i software (BrainMaster Technologies, Inc., Bedford, OH). Patients received feedback in a form of auditory sound on their real-time EEG signal, while sleeping. The volume of the auditory sound was adjusted by the parents to ensure that sleep is not interrupted. EEG data were obtained from the active electrode placed on the scalp at the location(s) of interest. The active electrode was stabilized on the desired location with Ten20 conductive electrode paste. Both the reference and the ground electrodes were linked to the ipsilateral earlobe. Sampling rate was 256 Hz. Reward threshold levels were automatically adjusted based on the digitally filtered real-time EEG signal every 180 s. The percent of reward was 70% of the time for the up-regulation of SMR and 70% of the down-regulation of theta (inhibition level of 30% ends with 70% rewards). The time period for getting a reward was fixed to 250 ms. Therefore, the patient received rewards for maximum 49% of the time. The treatment was operated by the parents following the installation of the BrainMaster software on their private laptop. Finally, the parents were trained to attach the electrodes and to use the system through the home training configuration option.

Procedure

This is a retrospective summary of treatment performed on one patient. NFB sessions were administered twice per week for 30 min approximately 30 minutes after the child fell asleep. The treatment was performed using a laptop at the child bedroom. The parent had to ensure that the treatment was carried on during sleep. In case the child woke up during the session or the child repeatedly moved, the treatment was interrupted. The volume of the reward sound was modulated by the parent to maintain sleep. All subjective reports were sent by the parents to the therapist in charge via emails. These reports were filled out at the end of each session, indicating behavioral changes which took place in between the two last sessions. Due to technical problems related to the computer used for home training, EEG data during the training was not properly saved and therefore could not be presented in this case report. The range of SMR and theta bands was minimally modified when needed, as explained below.

SV

SV is a right-handed, 9-year-old male diagnosed with ASD. He attends a special needs school and follows speech therapy due to severe communication disability. His main symptoms included: speech limited to single syllables, lack of eye contact, restlessness, and aggression. After we failed to perform 19-channel EEG recording and to do regular NFB in wakefulness, the parents were offered to try NFB during sleep. The parents were given detailed explanation about the lack of evidence to support the effectiveness of such procedure. Following their decision, they signed an informed consent form for this treatment.

The treatment started with 30 min of NFB training for SMR (12–15 Hz) uptraining and theta (4–7 Hz) downtraining over C4. This protocol was delivered for eight sessions. Already after the second session, SV was more calm and cooperative and made more efforts to name objects. This improvement was also noticeable during his speech therapy. The first protocol was followed by 30 min of NFB training for SMR (11–14 Hz) uptraining and theta (4–7 Hz) downtraining over C4 for another 24 sessions. The change in SMR frequency range resulted from increasing boisterousness which disappeared shortly after the change took place.

From the 15th session, the patient showed increased attention, environmental awareness, and responsiveness to others. He also started to say words of three-syllable length, pronounce words more clearly, mumble non-words, produce sounds, and simulate music tunes. For the rest of the sessions, the electrode was located on C3 in order to increase left-hemisphere functions such as language development. Consequently, the patient showed improved understanding and was more successful in accomplishing complex tasks and following instructions. Overall, SV received 60 sessions during sleep. No side effects were reported during treatment period. After 60 sessions his behavior improved to the point that he could participate in regular sessions of NFB in wakefulness.

Discussion

Here we applied for the first time NFB treatment during sleep in a patient with low-functioning ASD who was uncooperative during wakefulness due to his symptoms. We applied a conventional protocol focusing on SMR and theta activity without prior examination of spontaneous EEG oscillations because the patient was uncooperative with the examination. Of note, the use of EEG norms during sleep is not applicable since all EEG norms were analyzed and measured during wakefulness and not during sleep. We found that home training during sleep is similar to supervised training during wakefulness in the clinic. In other words, the change in settings doesn't necessarily undermine the efficacy of the treatment. However, it is important to optimize the use of home application of NFB system to the point that training sessions could be stored and then analyzed, not only for ensuring the quality of the treatment, but also for plotting a learning curve to examine the changes in the trained brain waves.

In regard to safety concerns, the treatment did not cause sleep disturbances in this patient. In fact, the parents did not observe changes in sleep patterns (e.g., increased movement, waking up, speaking, dreaming) and wakefulness (e.g., tiredness, daydreaming, alertness, etc.) as a result of the treatment. Other adverse side effects were not reported. Along the treatment, the parents observed a variety of benefits ranging from improved speech and comprehension to increased attention, as well as decrease in uncooperativeness, restlessness, and aggression. In other words, regulating SMR and theta during sleep led to positive long-term effects in wakefulness. Importantly, the patient improved to the point of being able to cooperate with the regular treatment procedure, which involved

watching a film for 30 min with electrodes on the ears and scalp, while keeping focus on the screen and minimal movement.

The possible mechanisms of the treatment-induced benefits are open for discussion. One explanation might posit that the observed effects result from improving sleep patterns or regulating epileptic activity. Indeed, the association between ASD and epilepsy was found to be higher in low-functioning ASD (Tuchman, 2000); higher predisposition to chronic disturbances in sleep-wake cycle was found in low-functioning ASD in dependence of the degree and severity of their cognitive impairment (Sajith & Clarke, 2007). Obviously, there is the possibility that the observed improvements stem from treating ADHD like symptoms, which are in high co-morbidity in ASD (Holtmann, Bölte, & Poustka, 2007). In other words, improved daytime behavior in this patient might be mediated by optimizing sleep patterns, improving seizure activity, and reducing hyperactivity.

Although many questions regarding the underlying mechanisms of these reported improvements remain unclear, it is first necessary to validate the current pilot through controlled trial on a group of children with ASD. Taking into account that researchers have identified a number of Autism subtype EEG patterns (Coben, Linden, & Myers, 2010), other protocols should also be considered. At this point, we only attempted to test the feasibility and safety in applying NFB training during sleep. Given these treatment effects were reported by the parents of the patients, future research should target specific symptoms that can be evaluated by standardized measurements.

To conclude, NFB training is a promising technique for normalizing and optimizing brain activity. Due to the automaticity of operant-conditioning NFB is also applicable in states of reduced consciousness such as state of unresponsive wakefulness (Keller & Garbacenkaite, 2015) as well as in coma (Ayers, 1999). Here we applied it successfully for the first time during sleep in line with multiple reports on its beneficial effects on children with ASD. Despite the various limitations that this preliminary work entails, the sleep training was found to be safe and feasible, and enabled to later continue with regular training in wakefulness.

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Informed consent was obtained from the patient included in the study.

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