Self-regulation of brain oscillations as a treatment for aberrant brain connections in children with autism

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A R T I C L E   I N F O

A B S T R A C T

Autism is a highly varied developmental disorder typically characterized by deficits in reciprocal social interaction, difficulties with verbal and nonverbal communication, and restricted interests and repetitive behaviors. Although a wide range of behavioral, pharmacological, and alternative medicine strategies have been reported to ameliorate specific symptoms for some individuals, there is at present no cure for the condition. Nonetheless, among the many incompatible observations about aspects of the development, anatomy, and functionality of the autistic brain, it is widely agreed that it is characterized by widespread aberrant connectivity. Such disordered connectivity, be it increased, decreased, or otherwise compromised, may complicate healthy synchronization and communication among and within different neural circuits, thereby producing abnormal processing of sensory inputs necessary for normal social life. It is widely accepted that the innate properties of brain electrical activity produce pacemaker elements and linked networks that oscillate synchronously or asynchronously, likely reflecting a type of functional connectivity. Using phase coherence in multiple frequency EEG bands as a measure of functional connectivity, studies have shown evidence for both global hypoconnectivity and local hyperconnectivity in individuals with ASD. However, the nature of the brain's experience-dependent structural plasticity suggests that these abnormal patterns may be reversed with the proper type of treatment. Indeed, neurofeedback (NF) training, an intervention based on operant conditioning that results in self-regulation of brain electrical oscillations, has shown promise in addressing marked abnormalities in functional and structural connectivity. It is hypothesized that neurofeedback produces positive behavioral changes in ASD children by normalizing the aberrant connections within and between neural circuits. NF exploits the brain's plasticity to normalize aberrant connectivity patterns apparent in the autistic brain. By grounding this training in known anatomical (e.g., mirror neuron system) and functional markers (e.g., mu rhythms) of autism, NF training holds promise to support current treatments for this complex disorder. The proposed hypothesis specifically states that neurofeedback-induced alpha mu (8–12 Hz) rhythm suppression or desynchronization, a marker of cortical activation, should induce neuroplastic changes and lead to normalization in relevant mirroring networks that have been associated with higher-order social cognition.

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Introduction

Autism is a highly varied developmental disorder typically characterized by deficits in reciprocal social interaction, difficulties with verbal and nonverbal communication, and restricted interests and repetitive behaviors. In the current Diagnostic and Statistical Manual of Mental Disorders. 4th ed. (DSM-IV) [1], autism is considered the prototype for the category called pervasive developmental disorders (PDD). Of the pervasive developmental disorders, autistic disorder (AD), Asperger's disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS) are informally referred to as the autism spectrum disorders (ASD). ASD was once considered to be of psychogenic origin but is now widely recognized to be a developmental disorder involving genetic and environmental factors and multiple functional brain networks. Among the many incompatible observations about aspects of the development, anatomy, and functionality of the autistic brain, it is widely agreed that autism is a disorder of connectivity [2,3].

Epidemiological studies show that ASD prevalence rates have been increasing in recent years, with current CDC reports indicating an average rate of about 1% (1/110), with increases of 8–17% per year [4]. While only 68% of the increase can be attributed to increased awareness and updated diagnostic criteria, the remaining 32% of cases represent a real increase in prevalence [5]. Although a wide range of behavioral, pharmacological, and alternative

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medicine strategies have been reported to ameliorate specific symptoms for some individuals (for recent reviews see [6–8]), there is at present no cure for the condition. With no clear biological marker or risk factor associated with the onset of ASD, the inherent heterogeneity of endophenotypical presentation makes clinical management challenging.

In clinical studies, the most effective type of therapy for ASD is behavioral intervention, with an efficacy rate of approximately 48% [9–11]. Unfortunately, like most clinically validated therapeutic approaches for ASD, behavioral therapy is time consuming and costly for such a low potential benefit. Thus, alternative interventions would be beneficial and warrant serious consideration. While the precise mechanisms of neurofeedback (NF) are not yet well understood, the evidence suggests it can capitalize on the implicit plasticity of the brain to induce neural, functional, and ultimately behavioral changes. Furthermore, with the use of quantitative electroencephalography (qEEG) and specific NF protocols (e.g., amplitude and coherence training) for individual subjects, NF can be targeted to fit the heterogeneity of autistic symptoms. Therefore, the present review uses promising observations from a variety of sources to support the hypothesis that NF training is a viable treatment option for autism.

Aberrant connectivity in the autistic brain

The numerous and diverse observations of structural abnormalities in grey and white matter in the autistic brain (see Table 1) have led many researchers to question the specific nature of this apparent aberrant connectivity. The development of functional connectivity magnetic resonance imaging (fcMRI) has largely supported initial observations about neural connectivity derived from anatomical work. Initially studied by Biswal et al. [12], fcMRI measures synchronized fluctuations in BOLD signal activity that, by inference, correlate with the connectivity of networks in the brain [13,14]. Functional connectivity is based on the idea that cognitive and social capabilities emerge from the collaborative activity of large-scale cortical networks, operationally defined by the synchronicity of their hemodynamic activity.

First described by Just et al. [15], the underconnectivity hypothesis of ASD posits that "autism is a cognitive and neurobiological disorder marked and caused by under functioning integrative circuitry that results in a deficit of integration of information at the neural and cognitive levels." Decreases in connectivity in ASD are consistent across studies using various cognitive, emotional, and social tasks [16–18]. While many fcMRI studies have used tasks to demonstrate differences in cortical networks, other studies have used an analysis of the "resting state." This method examines spontaneous fluctuations in hemodynamic activity that appear even in the absence of task performance [19]. Networks that co-activate during task performance often show high within-network correlations of these spontaneous fluctuations even during rest. Many studies show that these correlations are also reflected in structural connectivity measures [20]. These findings support the use of "resting state" connectivity as a proxy for task-related functional connectivity, and in some cases structural connectivity. One consistent finding of these resting state fcMRI studies is a correlated network of regions thought to be involved in introspection, daydreaming, or self-referential thought, commonly known as the "default mode network" [21]. Activation in this network tends to be negatively correlated with goal-directed networks [22]. Across studies, individuals with ASD demonstrate decreased resting state connectivity in the default mode network compared to typically developing controls [23], as well as a reduced "switching" from this network to task-related networks during task performance [24]. Still, a number of studies have amended the original hypothesis, suggesting that while there may be reduced local connectivity, there may actually be increased long-range connectivity [25]. The discrepancies in many fcMRI findings and methodologies have warranted several skeptical meta-analyses [3].

Nonetheless, the recent surge of papers on the topic of connectivity in ASD make it clear that there is *atypical* or *aberrant* connectivity, though it is too early to specify its exact nature. In a recent host of both resting state and task-related fcMRI studies, a general theory of a disordered connectivity has emerged [16,17,23,26–32]. As Müller et al. [3] point out, "Among the few neuroscientific findings that appear solid are those of abnormal white matter growth

Table 1
The neuroetiology of autism spectrum disorder: anatomical markers.

Main finding	Method	Representative publications
Increased head circumference; higher rates of macrocephaly	Anatomical measurements	[143]
Increases in cerebral volume	Magnetic resonance imaging (MRI)	[144–146]
Increases in frontal and temporal gray matter volume	MRI	[147]
Increased neuron counts and brain weight in prefrontal cortex	Post-mortem anatomical analysis	[148]
Gray matter increases in regions related to social cognition, communication, and repetitive behaviors, as well as auditory and visual perception	MRI	[149]
Decreases in parietal lobe volume	MRI	[150]
Lack of asymmetry in planum temporale volume	MRI	[151]
Increased cortical thickness in temporal and parietal lobes		[152]
Decreases in gray matter density in ventromedial aspects of the temporal cortex	MRI	[147]
Cortical thinning in regions related to the mirror neuron system, emotional recognition, and social cognition	MRI	[82]
Increases in local density and computation in cortical minicolumns	Post-mortem anatomical analysis	[153]
Increased white matter growth, especially in the prefrontal cortex and cerebellum	MRI	[144,145]
Increases in the cerebral white matter specifically in the parietal, occipital, and frontal lobes	Transverse relaxation time imaging	[154]
Decreases in corpus callosum volume	MRI, Diffusion tensor imaging (DTI)	[155,156]
Reduced fractional anisotropy in a variety of white matter regions, especially corpus callosum, frontal, and temporal regions	DTI	[34–36,157–159]
Mean diffusion increases in various regions including corpus callosum, arcuate fasciculus, and temporal areas	DTI	[33,34,36]
Increased connectivity volume between the superior temporal sulcus and amygdala	fMRI, DTI	[160]

trajectories and impaired connectivity." To bring some level of reconciliation among these various studies, several investigators have proposed a *local overconnectivity-long range underconnectivity hypothesis* [32] that is supported by noisy local processing in minicolumns [32] and reduced integrity in extensive white matter tracts [33–36].

The neurofeedback hypothesis

Aberrant connectivity in the ASD brain, be it increased, decreased, or otherwise compromised, may complicate healthy synchronization and communication among and within different neural circuits, thereby producing abnormal processing of sensory inputs necessary for normal social life. These anomalies in neural connections could be responsible for the abnormal social behaviors in children with autism. It is hypothesized that neurofeedback, an intervention based on operant conditioning that results in self-regulation of the electroencephalogram produces positive behavioral changes in ASD children and does this by normalizing the aberrant connections within and between neural circuits. Thus, in order to fully address the behavioral symptoms of ASD, it is crucial to understand the gap between connectivity and cognition. Informed by knowledge of the neural underpinnings associated with the social dysfunctions present in ASD, methods such as EEG have made it possible to concurrently measure connectivity between brain regions and corresponding behaviors and to remediate the problem.

The use of EEG biomarkers

It is widely accepted that the innate properties of brain electrical activity produce pacemaker elements and linked networks that oscillate synchronously or asynchronously, likely reflecting a type of functional connectivity [37]. Although the periodicity of such oscillations varies in distinct frequency bands as a function of neural architecture [38], consensus exists that at least three types of oscillating relationships recorded as scalp EEG arise from cortex [39–41]. First, in the columnar architecture of cortex, synchronous activities are created locally between neighboring columns and these "local" oscillations produce high frequency components above 30 Hz, often labeled as gamma rhythms. Synchronization in the gamma band has been proposed as a type of neural binding mechanism that subserves perceptual and cognitive functions [42,43]. Oscillations can also occur between cortical columns separated by a short distance (e.g., several centimeters). These intermediate or "regional" oscillations appear to produce intermediate frequency components such as high alpha/mu (10–12 Hz) and beta components. Finally, oscillations develop between cortical regions that are much further apart, such as frontal and parietal or occipital and frontal cortices. These "global" oscillations are more closely related to slower frequency band components, such as delta (1–4 Hz), theta (4–8 Hz), and low alpha/mu (8–10 Hz). Various types of oscillations can occur spontaneously as a function of non-contingent firing in cellular networks, as part of thalamocortical re-entrant interactions and pacemaker cells that make up thalamic nuclei, or as activity time-locked to extrinsic stimuli during the processing of a task.

Resting state fcMRI findings have been replicated by a limited number of qEEG studies that have also observed decreased resting state connectivity. Similar to fcMRI, qEEG measures the synchronicity of brain networks, but with less spatial precision and higher temporal resolution. Using phase coherence in multiple frequency bands as a measure of functional connectivity, studies have shown evidence for both global hypoconnectivity and local hyperconnectivity in individuals with ASD [44–47]. Several of these studies have noted increased coherence in gamma frequency bands over the parietal [44] and temporal lobes [48], suggesting increased local connectivity. Likewise, Murias et al. [46] found locally elevated coherence in the theta (3–6 Hz) frequency range in ASD subjects, particularly over left frontal and temporal regions. Meanwhile, there was lower coherence in the ASD subjects in the lower alpha range (8–10 Hz) within frontal regions [46]. In a qEEG study with 20 autistic children, Coben et al. [47] found patterns of hypocoherence in ASD, including decreased intrahemispheric delta and theta coherences across short to medium and long inter-electrode distances. Children with ASD had lower interhemispheric delta and theta coherences across the frontal region, and delta, theta and alpha hypocoherence was also evident over temporal regions. In posterior regions, low delta, theta and beta coherence were observed in children with ASD [47]. Thus, while these findings are diverse and multifaceted, there is an emergent framework of local hyperconnectivity and global hypoconnectivity in the autistic brain.

Although the characterization and specific nature of neural connectivity in ASD is incomplete, awareness of the brain's experience-dependent structural plasticity [49,50] suggests that these abnormal patterns may be reversed with the proper type of treatment [51,52]. Plasticity in this case refers to not only the changing of synaptic strengths but to processes that contribute to the homeostasis of network activity. Atypical fcMRI and qEEG results may be the consequence of early aberrations of white matter development and "disturbances in experience-driven network formation through regressive and constructive processes, such as synaptic pruning and stabilization" [3], and may therefore be amenable to additional induction of plasticity.

Self-regulation of EEG oscillations

Of specific interest to neurotherapeutic interventions such as NF is whether brain oscillations are causally implicated in brain function, or whether they are simply epiphenomenological or byproducts of other, underlying mechanisms? Animal intracranial recordings and human electrophysiology have shown that neural oscillatory mechanisms are directly related to and play a critical role in a number of cognitive functions including learning, memory, attention, feature binding and sensory selection and gating [38,53,54]. However, less direct evidence exists on the effects, whether short- or long-term, of the modulation or entrainment of these oscillations and their relationship to brain plasticity [55].

As noted previously, brain oscillations are instantiated across different spatial scales [38] from single pacemaker neurons [56], to neuronal circuits [57], to re-entrant thalamo-cortical and large scale cortico-cortical networks [58]. It is assumed that one of the computational processes these oscillations enable is the dynamic routing and gating of information through the synchronization of various elements [59–61]. Indeed, multi-frequency synchronies are thought to be critical for linking spatially distributed neuronal assemblies into functionally integrated and specialized networks, and shown to play a role in sensory registration [62], perceptual integration [63], and selective attention [64]. From a computational perspective, the rhythmic stimulation of the oscillating neural population can be modeled as a periodic force acting in a certain direction on the phase vector [65,66], while from a system level perspective, EEG responses to sensory stimuli can partially be explained through transient, stimulus-induced adjustment of the phase of ongoing oscillations via phase-resetting [67–69].

The possibility of volitional modulation or entrainment of these oscillations raises an interesting set of questions. Is it possible to promote/enhance or inhibit/suppress oscillations in distinct, neuronal elements/networks *in vivo* via indirect "internal" signaling similar to directly stimulating them (e.g., through transcranial stimulation protocols)? In other words, can we modulate these oscillations volitionally through some periodic internal input or

drive? Provided that these oscillations play a causal role for a specific cognitive function, it is at least theoretically plausible that their modulation/entrainment can have a functional impact. A brain computer interface, which allows real-time information of brain activity to be fed back to a user by means of a computer in a closed 'neurofeedback' loop, enables control and natural operation of brain oscillations across cortical networks in vivo and in real time [70–72]. Although the specific aims of NF approaches differ, most use a simple visual stimulus or game to train the individual to increase/decrease a certain bandwidth of EEG signal. With training, most individuals can develop a remarkable level of control over his/her brain oscillations. During NF, subjects are exposed to the same visual/auditory feedback or reward stimuli, and hence the entrained EEG differences most likely represent the modulation of some internal or 'background' brain state(s) associated with the event rather than to external factors.

The role of the mirror neuron system

The discovery of mirror neurons in monkeys and a Mirror Neuron System (MNS) in the human brain has provided a neurobiological substrate for understanding many key concepts in human social cognition directly relevant to the behavioral and cognitive deficits observed in ASD [73], including the ability to comprehend actions, glean intentions, and learn through imitation. First described by Rizzolatti and co-workers [74] in the macaque monkey, mirror neurons are thought to be involved in both self-initiated action and the representation of action performed by others. Neurons in the pars opercularis of the inferior frontal gyrus (IFG) show increased firing while executing and observing the same action, representing a potential mechanism for mapping seeing into doing [75,76]. It is well reported that individuals with ASD have marked impairment in social skills, from joint attention to understanding the intentions of others, often termed "mind-blindness" [77,78]. As has been noted in a number of recent reviews, deficits in MNS activity may explain the poor socialization skills prevalent in the disorder.

Although some studies have raised questions about the role of mirror neurons in human social behavior [79,80], an increasing amount of work suggests that a dysfunction in the MNS does contribute to social deficits [81–86]. Specifically, deficits likely arise from an inability to "form and coordinate social representations of self and others via amodal or cross-modal representation processes" [87] – the type of function ascribed to mirror neurons. A particularly striking fMRI study by Dapretto et al. [84] demonstrated decreased activation in the inferior frontal gyrus (pars opercularis) in autistic individuals, and found that activity in this region was inversely related to symptom severity in the social domain. Similarly, EEG studies (described in later sections) have shown that putative electro-biomarkers of MNS activity show abnormalities in ASD compared to typically-developing children [83,86,88,89]. Despite the excitement generated by these observations, few if any investigations have focused on operationalizing insights into MNS function towards practical solutions to the early diagnosis and possible repair of MNS deficits in clinical disorders.

The MNS and mu rhythms

While functional hemodynamic studies have delineated areas in the human brain that might act as analogs to the monkey MNS, direct recording of neural activity by electromagnetic methods have unveiled neural activation patterns correlated with mirroring. Particularly relevant are scalp-recorded EEG patterns of activity in the alpha (8–13 Hz) and beta (15–25 Hz) range that are most evident over the central region of the scalp overlying the sensorimotor cortices and modulated by motor activity [90]. Traditionally these patterns of oscillations have been labeled "mu rhythms" (reviewed by [76]). The major characteristic of the mu rhythms is that they reach maximal power in the absence of overt movements, when the participant is at rest. In fact, mu rhythms are desynchronized and their power reduced when a hand or a foot movement is prepared, and disappears when the movement is actually performed. Initially, these rhythms were considered to be the default rest state of the brain ("idling rhythms," [76,91], present as part of the normal waking state. However, newer data showing different patterns of event-related de-synchronization (ERD) and power suppression have linked these phenomena with cognitive functions such as memory [92–94], selective attention [95,96] as well as affect [97–99]. Particularly relevant to this chapter is evidence for mu suppression not only when participants perform movements but also when they observe such movements [100–102]. During the self-initiation, observation, or even imagination of action in typically developing individuals, the MNS network is active and power in the mu rhythm is suppressed [90,101,103,104].

Indeed, the phenomenology of the mu rhythm resembles the phenomenology of mirror neuron activity. Both are sensitive to movement, as well as to motor and cognitive imagery (i.e., observed meaningful actions). Their overlapping neural sources in sensorimotor frontoparietal networks supports the argument that they are related and involved in linking perception to action, which may be a critical component in the development of social cognition. Mu rhythms appear to reflect the translation of "seeing" and "hearing" into "doing" [76]. This function requires the entrainment of multiple domain-specific generators. These domains exhibit synchronized and desynchronized activity in a locally independent manner but become entrained when they are coherently and globally engaged in translating perception into action [76]. These patterns suggest a link between MNS and mu rhythms and raise the possibility that brain mechanisms manifested by EEG mu rhythms reflect social interaction, including imitation behavior and theory of mind [105]. If so, it stands to reason that the modulation of mu rhythms might be dysfunctional in ASD individuals whose performance in these domains is impaired.

The integration of fMRI and EEG techniques during tasks that activate the MNS have demonstrated that mu rhythm suppression occurs in typical MNS regions, namely the inferior parietal lobe, dorsal premotor cortex, and primary somatosensory cortex [105]. In autistic individuals this mu rhythm suppression is not observed, supporting the role of an altered MNS in ASD [86,106]. Oberman et al. [86] compared mu suppression in a group of 10 individuals with high functioning ASD ranging in age between 6 and 47 years with age-matched typically developing (TD) controls in four different conditions: (a) performing a simple hand movement, (b) observing a video showing the same hand movement performed by the experimenter, (c) observing two balls bouncing, and (d) observing visual white noise (as baseline). As expected, there was no mu suppression for observing non-biological movement in either group; both groups exhibited significant mu suppression while performing the hand movement, but only in the TD group was mu rhythm significantly suppressed in the observe-only condition. These results provide evidence for a defective MNS associated with ASD and have recently been replicated by others [83].

Conclusions

The observations linking brain oscillations to function have important implications for therapies of brain disorders associated with abnormal cortical rhythms, particularly mu rhythms, and support the use of EEG-based NF as a noninvasive tool for establishing a causal link between rhythmic cortical activities and their functions [107]. The proposed hypothesis is that neurofeedback-induced alpha mu (8–12 Hz) rhythm suppression or

desynchronization, a marker of cortical activation [108], should induce neuroplastic changes in relevant networks. In contrast, beta mu (12–15 Hz) synchronization, which has been associated with cortical deactivation [109] and motor inhibition [110], might produce an opposite pattern. With knowledge of the brain's inherent plasticity and with mu suppression as a potential electrophysiological marker of MNS activity, we can use EEG to train the brain to develop volitional control over its waveforms, and by extension, its functional connectivity.

Evaluation of the hypothesis

The treatment of epilepsy using NF training is arguably the best-established clinical application of EEG operant conditioning [110]. Sterman initially described an EEG oscillation with a frequency of 12–20 Hz, similar to EEG sleep spindles, which has been referred to as the "sensorimotor rhythm" or SMR [111]. During the testing of a highly epileptogenic compound, Sterman and co-workers found elevated seizure thresholds in cats that had previously taken part in SMR conditioning, suggesting that the SMR training had somehow predisposed the cats against experiencing seizures. These findings have been successfully extrapolated to humans where it has been documented that seizure incidence is lowered significantly through SMR training [112]. SMR rhythms have been shown to originate in the ventrobasal nuclei (nVB) of the cat thalamus [113], an area involved in the channeling of afferent somatosensory information to cortex. During conditioning, the firing patterns of nVB cells shift from fast and non-rhythmic discharges to systematic, rhythmic bursts that are associated with suppression of somatosensory information flow [113,114]. This reduction causes the nVB cells to hyperpolarize. However, instead of sustaining a stable level of inhibition, the cells begin to gradually depolarize as a function of a slow calcium influx. This eventually causes the nVB neurons to discharge a burst of spikes that is then relayed to sensorimotor cortex and thalamic reticular nucleus (nRT) neurons. Stimulation of the nRT leads to inhibition of VB relay cells, returning them to a hyperpolarized state and initiating a new cycle of slow depolarization producing rhythmic thalamocortical volleys and consequent cortical EEG oscillations [115].

Consistent with the work by Sterman and co-workers, Ros et al. [107] have shown that self-regulation of EEG rhythms in quietly sitting, naive humans significantly affects the subsequent corticomotor response to transcranial magnetic stimulation (TMS), producing durable and correlated changes in neurotransmission. More specifically, the intrinsic suppression of alpha cortical rhythms produced robust increases in corticospinal excitability and decreases in intracortical inhibition of up to 150%, lasting more than 20 min. Likewise, Hinterberger et al., [116] showed that brain regulation of the slow cortical potential (SCP) to activate an external device led to activation of specific brain areas. That is, a successful positive SCP shift compared with a negative shift was closely related to an increase in the BOLD response in the basal ganglia. Successful negativity was related to an increased BOLD response in the thalamus compared with successful positivity. These results indicate learned regulation of a cortico-striatal-thalamic loop modulating local excitation thresholds of cortical assemblies.

Finally, Beauregard and Lévesque [117] scanned 15 unmedicated ADHD children randomly assigned to an experimental group that received NF, and five other ADHD children assigned to the control group who did not receive NF. Subjects from both groups were scanned 1 week before the beginning of training and 1 week after, while they performed a Counting Stroop task. Prior to training, the Counting Stroop task was associated with significant focus of activation in the left superior parietal lobule for both groups but no activation in the anterior cingulate cortex (ACC). Following training, the Counting Stroop task was still associated with increased activation of the left superior parietal lobule for both groups, but for the experimental group only there was a significant activation of the right ACC. The results suggest that NF training has the capacity to normalize the functioning of the ACC in ADHD children. These precedents for NF treatment suggest that it may also be effective in modulating EEG signals associated with deficits in ASD, particularly in the realm of social cognition.

Neurofeedback treatment for ASD

NF as a technique for modifying behavior has been used primarily in clinical settings, and support for its efficacy is based largely on case studies with only a few randomized, controlled, and blinded studies. Nonetheless, a substantive amount of work supports the rationale for NF use in the context of treatment. As previously discussed, there is already evidence supporting the efficacy of this approach for a variety of neuropsychological conditions, including ADHD [118–120], epilepsy [121–125], traumatic brain injury [126,127], anxiety [128], and substance abuse [129].

In terms of ASD, it is well recognized that more than 50% of individuals with ASD demonstrate significant electrophysiological abnormalities on EEG [130–132]. Upwards of 30% develop clinical seizures by adolescence, and even when clinical seizures have not been identified, more than 50% show paroxysmal sharp discharges on EEG, especially during sleep. Additional daytime EEG abnormalities include altered spectral profiles, abnormal patterns of coherence, and reduced mu rhythm activity. These observations have led many clinical practitioners to use EEG-based interventions as a therapeutic strategy.

Cowan and Markham [133] conducted one of the earliest case studies of neurofeedback and autism. QEEG analysis on an eight year-old high functioning female showed abnormally high alpha (8–10 Hz) and theta (4–8 Hz) activity in the posterior regions of the brain. Following more than 20 weeks of NF training, the child showed improvements in sustained attention as assessed by the Test of Variables of Attention (TOVA), decreased autistic behaviors, such as inappropriate giggling, and spinning, and improved socialization based on parental and teacher assessments. Sichel [134] also reported positive changes in all DSM-IV-R diagnostic criteria for autism in a single case study. A few years later, two scientifically controlled studies reported significant reductions in autistic symptoms following NF training. Jarusiewicz [135] reported an average of 26% improvement (sociability (33%), speech/language/communication (29%), health (26%), and sensory/cognitive awareness (17%)) in the ATEC in 12 children diagnosed with autism compared to 3% improvement in a control group. Coben and Hudspeth (cited in [136]) studied 14 ASD children with significantly high levels of mu rhythm activity and a lack of mu suppression during observational activity. Participants were assigned to an interhemispheric bipolar training or a coherence training group designed to increase connectivity between central and peripheral frontal regions via assessment guided NF. Both groups improved significantly on neurobehavioral and neuropsychological measures, but only in the coherence training treatment group was mu activity significantly reduced. Increased coherence was associated with diminished mu and improved levels of social functioning [137].

In a series of two experiments, Pineda et al. [138] examined whether neurofeedback could lessen abnormal mu rhythms and behavioral outcomes in 27 children with high functioning autism. In the first study, eight ASD males were randomly assigned to an experimental or placebo group. NF training included 30 sessions of 30 min each with rewards for mu-like activity (8–13 Hz) and inhibits for EMG (30–60 Hz). The ATEC showed changes (9–13%) in two of the four experimental participants. In the second study, 19 children with verified high functioning ASD were randomly

assigned to an experimental or placebo group. NF training was similar to study one except the reward band was now 10–13 Hz (or high mu band). Parent ratings showed a significant reduction in symptoms as measured by the ATEC Total score, although there was an increase in ratings of Sensory/Cognitive Awareness in excess of 40% that did not occur in the placebo control group, suggesting that participants improved in some areas and regressed in others.

Coben and Padolsky [136] used assessment guided NF on 37 patients over the course of 20 sessions to reduce hyperconnectivity in posterior-frontal to anterior-temporal regions. Following NF, parents reported symptom improvement in 89% of the experimental group, with very little change in the control group. Improvement also occurred in the areas of attention, visual perceptual functioning, language, and executive functioning, with a 40% reduction in core ASD symptoms as assessed by the ATEC total scores. There was also decreased hypercoherence in 76% of the experimental group as measured by a post-training qEEG. The results suggest that decreased hyperconnectivity could have produced the positive changes in treatment outcomes.

In more recent studies, Kouijzer et al. [139] reported positive results of NF training in children with ASD compared to a waiting list control group. Treatment consisted of 40 sessions of neurofeedback and included inhibition of theta activity (4–7 Hz) and rewarding low beta activity (12–15 Hz) over the right hemisphere. It was hypothesized that this induced change in EEG-power would enhance activation of the ACC, which has been found to be under activated in ASD individuals [23]. Consistent with this hypothesis, NF training revealed a linear decrease in theta power and an increase in low beta power over 40 sessions. In the treatment group, there was significant improvement on tasks of executive functioning in the treatment group for attention control, cognitive flexibility, and planning. Measures of social behavior revealed significant improvements in general and non-verbal communication in the treatment but not the control group. Furthermore, parents of children in the treatment group reported more improvement in levels of social interaction, communication, and typical behavior. A follow-up after 12 months revealed maintenance of the described outcomes on both executive functioning and social behavior, suggesting that NF treatment can have long-term effects.

All in all, anecdotal reports, as well as clinical and controlled scientific studies suggest that NF approaches can lead to symptom improvement [140]. Additional randomized and controlled studies are needed to establish "best practices" for NF and determine the optimal set of protocols. Recently, Coben and Meyers [141] compared the results of two published controlled NF studies examining whether a symptom based approach or an assessment/connectivity guided based approach was more effective. Both methods demonstrated significant improvement in symptoms of autism, but connectivity-guided neurofeedback showed a greater reduction on various subscales of the ATEC. Overall, children with autism who successfully reduce delta and theta power through NF therapy have shown improved cognitive flexibility, enhanced social and communicative skills, executive set-shifting functions, and a general decrease of theta power, all of which were maintained long after post-treatment.

Consequences of the hypothesis and discussion

It is hypothesized that operant conditioning methodology, such as NF, produces its behavioral and electrophysiological effects by gaining access to and control over regulatory mechanisms that increase or decrease synchronous or desynchronous activity in brain networks. This assumes that the cortex works in terms of resonant loops and that such functional resonances operate spontaneously or are driven by cellular pacemakers. Oscillations in the network project strong afferent volleys to cortical targets, which could result in a cascade of motor alterations enhanced by long-term potentiation [142]. Furthermore, these changes are stabilized and consolidated over time affecting function beyond the neurofeedback context. Thus, NF is believed to influence, among other things, thalamic pacemakers and consequently thalamocortical resonances. Long-term consequences of this change in activity could induce changes in the patterns of connectivity between different brain regions and ultimately generalized and noticeable improvements in behavior. Primarily a disorder of connectivity, autism is a very suitable target for such treatment.

In a recent review of the literature, Coben et al. [137] argued that while further research is necessary, the variety of studies using neurofeedback in autism support a Level 2 determination ("Possibly efficacious") for the application of neurofeedback for autistic disorders. Nonetheless, it must be acknowledged that a number of limitations characterize many of the NF studies in the field. Given the heterogeneity of ASD, the use of single case studies and small group sizes reduces statistical power. Group studies provide stronger support but there is a pressing need for proper use of random assignment, appropriate control groups, and more blinded protocols to control for placebo effects. Replication by multiple independent laboratories is crucial to establish efficacy, as is the correlation between behavioral changes and functional/structural changes in the brain. Equally important is the need to resolve the discrepancies in outcome measures used, as well as address EEG spatial limitations, perhaps through the use of and comparison with magnetoencephalography- and fMRI-based NF. There is also the clear necessity of delineating common ASD comorbidities, namely ADHD and OCD. Finally, it is important to extend the reach of NF treatments to address the multiple core symptoms of autism – not just social dysfunctions, but also emotional regulation, language problems, and repetitive behaviors. While discrepancies in methodology and outcome measures make comparison between studies difficult, ameliorating these differences will lead to a stronger understanding of NF's efficacy and potential. Our hope is that a continued commitment to overcoming these experimental limitations and challenges will ultimately help establish neurofeedback as a beneficial treatment for children and parents dealing with this difficult disorder.

Conflict of interest statement

The authors have nothing to declare.

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