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

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ABSTRACT

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.

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]