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Review Article

The Potential of Magnetic Resonant Therapy in Children with Autism Spectrum Disorder

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Abstract

Autism Spectrum Disorder (ASD) is a neurologically based behavioral disorder resulted from changes in the central nervous system. Children on the spectrum present with impaired social interactions, reciprocity, and communication skills. Approximately1in 88 children in the United States are considered to be on the autism spectrum representing a significant increase in prevalence of 600% over the past 20 years. Children with ASD often present with comorbid conditions. Depression and anxiety are more prevalent in patients on the spectrum as compared to the general population.

Current clinical care has platitude and is directed primarily at treating symptoms and modifying behavior. Currently, novel anatomic and functional modalities including MRI, functional MRI, and EEG are reliably documenting abnormalities in children on the spectrum. Functional MRI has documented a disparity in the relationship between cerebral metabolism and cerebral blood flow in these children. Electro Encephalography (EEG) studies of children with ASD demonstrate reduced synchronization of frontal brain wave activity and cortical connectivity indicated by altered/abnormal EEG patterns as compared to that in normal children. It is likely that EEG end phenotypes may exist which is predictive of developing cognitive impairment and may identify infants at risk for ASD.

Magnetic Resonant Therapy (MRT) has been cleared by the Food and Drug Administration for neuromodulation treatment of posttraumatic stress disorder and of Major Depressive Disorder. Its use is additionally being explored for the treatment of children with ASD. Though it is difficult to make definitive conclusions based upon the current literature regarding the success of MRT in this population, the consistentabnormalitiesintheelectrophysiology of children with ASD would suggest that MRT is an appropriate therapeutic option to further pursue, especially given the minimal morbidity associated with such.

Keywords: Magnetic resonant therapy; Autism spectrum disorder

Introduction

Autism is a neuro behavioral syndrome caused by a dysfunction of the central nervous system that leads to interrupted development. According to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV, 2000), the onset of symptoms in autism occurs within the first three years of life. However, the composite of symptoms varies in form and severity in each affected child. Management of children with autism is costly and complex and burdens families emotionally, physically, and financially. It has been reported that, economically, the cost of providing care to an individual on the spectrum is greater than 3 million dollars over their life time. Currently clinical care is directed primarily at treating symptoms and modifying behavior.

Due to the diversity of clinical symptoms and severity, the illness is often referred to as Autism Spectrum Disorders which include Autism Spectrum Disorder (ASD), Asperger's Disorder, and Pervasive Developmental Disorder–Not Otherwise Specified. Symptoms are marked by severe impairment in several developmental areas, including social interaction, reciprocity and communication, and the presence of restricted, repetitive and stereotyped patterns [1].

It is expected that many more children will be diagnosed with autism in the near future than children with childhood leukemia or brain tumors, new onset juvenile diabetes, or Acquired Immune Deficiency combined. It is believed that over 3 million individuals are impacted by autism in the United States alone. Statistics from the U.S. Centers for Disease Control and Prevention note that approximately 1 in 88 to110 children in the United States are diagnosed as being in the children autism spectrum. The prevalence is an average of 4 to 5 times more often in boys. A long with the increase in autism prevalence, the diagnostic criteria for the illness and similar disorders have changed several times since "autism" was first defined over 5 decades ago.

Comorbid Conditions

In addition to these prominent symptoms, it is also found that children with ASD often have Comorbid mental health difficulties, particularly anxiety and depression, which occur at a substantially increased rate compared to the general population [2-4] with prevalence rates of anxiety ranging from 13.6 percent [2] to 84% [5]. Anxiety-related concerns though are not believed to be phenomenological characteristics of ASD, in the clinical setting.

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However are among the most common presenting problems for children and adolescents with ASD [6,7].

There cognition of anxiety in children and adolescents on the spectrum is not novel. Infact, recognition of anxiety int his population is not new. Kanner in 1943 described children and adolescents with "classic" autism, and documented a high incidence of anxiety in this population [8]. Despite this, the diagnosis and subsequent treatment of anxiety disorders in children and adolescents on the spectrum has only recently become a source of concern. A significant variable contributing to the difficulties in recognizing anxiety in this population is based upon our current diagnostic methodologies. In the current DSM-IV and ICD-10 classifications, anxiety related disorders are excluded in the presence of a comorbid diagnosis of autism spectrum disorder which serves as an exclusion criterion. Thus, the presence of anxiety disorders inpatients on the spectrum are considered to be part of the presentation rather than a variable involved in the etiology of the autism spectrum. It becomes difficult to discern between the presenting symptoms of ASD and a comorbid anxiety disorder in this population. It additionally becomes difficult to discern between repetitive behaviors such as flapping and obsessive-compulsive personality disorders.

Regardless of the debate in phenomenology, prior studies have shown that frontal lobe abnormalities in ASD patients have substantial resemblance to those with clinical anxiety disorder.

Effective treatment for anxiety has demonstrated remarkable effects on other behavioral abnormalities. While some patients have immediate improvement in attention, language, and communication, others show much greater response to behavioral treatment after an effective treatment for anxiety. Thus, neural abnormalities associated with anxiety may play a critical role in the pathophysiology of ASD. Currently there is an urgent need for the development of an effective system to assess and treat anxiety in children with ASD [7,9] in combination with other behavioral treatments.

Current Treatment Modalities

Children and adolescents with ASD who manifests problems related to anxiety are frequently referred for psychological evaluation and potential treatment. The success of such referrals in interventions in the ASD population may be promising, though there remains a paucity of information in the peer review literature [10-12]. The services offered to these individuals and their families include medical management, individual and family counseling, cognitive behavior therapy or applied behavior analysis.

What remains problematic is the ability of individuals on the spectrum to sustain a therapeutic response to cognitive behavior therapy or applied behavior analysis given their ASD specific neuropsychological deficits. We remain uncertain as to the impact of difficulties with communication, comprehension of social cues, difficulties with motivation and/or transition, compromised imagination and emotional response on the ability of children and adolescents on the spectrum to respond to therapy for anxiety.

The presentation and understanding and anxiety in this population become more complex given the underlying difficulties associated with ASD. Children and adolescents on the spectrum may manifest anxiety in a context that is different from what is usually observed. Additionally, they may have difficulties describing the emotional state of anxiety or distress in general. Difficulties with emotional responses, certain cues, and the control of such in addition to concrete thought process sees and/or beliefs can further compromise both the initiation and response to such therapies.

More recent studies, in conjunction with other neural imaging measures, have shown that EEG may predict the state energy metabolism in the brain as well as how the cognitive information is processed.

Functional Imaging

Whereas magnetic resonance imaging studies have documented increased white matter in children with ASD [13,14], functional imaging has demonstrated abnormal neural connections as manifested by a lack of relationship between cerebral metabolism and cerebral blood flow [15,16].

EEG

Electroencephalography (EEG) is a gross measure of neural electric activity at the scalp with the amplitude of such reflecting the degree of neuronal synchronization under the recording lead. EEG signals are believed to derive from pyramidal cells aligned in parallel in the cerebral cortex and the hippocampus. The broad frequency bands identified may help to identify abnormal or damped processing circuit characteristics in children with ASD.

The recorded magnitude of frequency distribution reflects the brain status at the time of recording. As we will discuss, often the dominant alpha EEG (approximately 10Hz) is reduced in both amplitude and coherence, particularly in the frontal lobe in ASD children. Additionally, EEG studies of individuals with ASD indicate that they frequently manifest reduced frontal synchronization and cortical connectivity on EEG [17].

Additionally, ASD patients usually have lower cortical coherence or synchronization. We believe that future studies need to be directed at evaluating the potential impact of normalizing the EEG and the relationship of such to clinical improvement in autistic symptoms. We will discuss the treatment potential of Magnetic Resonant Therapy (MRT) in children with ASD.

Coherence

EEG coherence is indicative of the stability of the phase difference between different EEG signals or frequencies when compared over time. These signals may have different phases but remain coherent if the phase difference remains constant. High coherence values are indicative of strong connectivity between disparate cortical regions. The underlying substrate resulting in the behavioral presentation of ASD remains poorly understood, but likely is much more complex than simple states of under or over connectivity and indicative of connections between cortical regions that varies in both extent and location. Additionally, it is likely that these electrical phenomena change as the brain matures in an individual and become more salient when compared to clinical manifestations. Based upon these findings, the potential to determine changes in neural connectivity could potentially serve as an additional diagnostic variable indicative

of atypical connectivity development in children and adolescents with ASD. The potential understanding of synchrony between neural networks can be gleaned from EEG coherence measurements (coherence) reflecting the signal relationship between regionally disparate cortices. Whereas high coherence is indicative of neuronal synchrony, which is functional, low coherence is indicative of neuronal asynchrony, which is less functional and suggestive of multifocal cortical regions of varying signal [18].

Murias, et al. reported elevated theta (3–6 Hz) coherence in the left hemispheric, frontal and temporal regions. Children with ASD also demonstrated reduced alpha range (8–10 Hz) coherence both within the frontal region and between frontal regional connections. They concluded that ASD subjects in the eyes closed resting state demonstrated Robust patterns of over- and under-connectivity [19]. Cerebral coherence has also been reported to be altered in children with ASD.

Focal elevations of left hemispheric theta coherence in conjunction with reduced frontal lobe alpha coherence have been described [19]. Diffuse cortical decreases in intrahemispheric delta and theta have also been reported [20]. Increased coherence of the left hemisphere as opposed to the right has been described following stimulation in children with ASD but not at rest [21]. Isler described diminished connectivity between the right and left visual cortex during visual stimulation [22]. Greater coherence between the left occipital region with both proximal and distal cortical regions during rapid eye movement (REM) sleep has been reported. They also reported right frontal coherence [23]. Increased bilateral temporal lobe gamma coherence has also been reported [24].

Neuronal Networks

Neuronal networks are notable for the significant downstream connectivity resultant from a progressive branching of synaptic connections [25]. This scale free network is modified with age [26-28]. The more complex Neuronal networks consist of dense clusters of local synaptic connections with decreased downstream synaptic connections [26]. There are numerous physiologic variables that are specific to each region that potentially can be quantified by assays such as functional magnetic resonance imaging. FMRI has demonstrated global scale-free synaptic networks which differ from the more hierarchical networks and interregional connectivity found in normal children [29].

Studies utilizing Magnetic Resonance Imaging (MRI) tractography of white matter tracts has demonstrated progressive changes in connectivity as a child's brain develops with evidence of both continuous synaptogenesis and network modification in both local and disparate cortical regions [29]. Thus, abnormal network connectivity may be a key to understanding developmental disabilities.

Predictive Electrophysiology

Bosl, et al. described the potential of EEG endophenotypes, namely cognitive findings which may predict subsequent cognitive impairments. They proposed that modified Multi Scale Entropy (mMSE) which can be computed on the basis of resting state EEG data could be used as a biomarker of normal brain development. In this capacity it could potentially identify infants with increased risk for ASD [30].

Changes in EEG in Patients with Neurological Dysfunction

Altered neuronal connectivity (coherence) is a potential contributor to the characteristics noted in children with ASD. Numerous studies have evaluated differences in EEG coherence findings between children with ASD and controls [5,20-24,31]. Duffy and Als utilized principal components analysis in 463 children and adolescents diagnosed with autism ranging from 1 to 18 years. Discriminant function analysis was utilized to determine the spectral coherence factors' discrimination success for both controls and those on the spectrum. They documented specific coherence differences in the ASD group. Utilizing principal components analysis they identified 40 EEG spectral coherence factors which explained 50.8% of the total population variance. Short distance coherences were reduced and long-distance coherences were both reduced and increased in the ASD groups. The authors concluded that their classification identified a stable coherence loading pattern that was specific to the ASD group. They suggested that the short distance coherences could be indicative of poor local network function. The resultant increase in long-distance coherences could then potentially represent neural compensation. Overall they suggested that this could represent an EEG coherence- based phenotype of childhood autism [32]. When assessing the factor loading patterns, the authors documented no evidence for clear inter- relationships among spectral bands, number of coherences per factor, increased coherence, decreased coherence, lateralization or regional involvement. They documented dominance of slow beta across all conditions with peak loadings in the slow beta range. Most significantly, the authors identified that the ASD population coherence patterns tended to be unusually stable across broad spectral ranges (>10 Hz wide) which may be specific for this populations abnormal neurophysiology.

Approved Uses

To date, a number of systems have been cleared by the Food and Drug Administration (FDA) for neuromodulation purposes, including treatment of Major Depressive Disorder and other off label uses of MRT technology.

Taghva, et al. prospectively reviewed 16 veterans consecutively treated for Post-Traumatic Stress Disorder (PTSD). Following Magnetic Resonance Therapy (MRT) patients were evaluated on the PTSD checklist (PCL-M) and the comparison of pre- and post-treatment EEGs. Significant Clinical improvements on the PCL-M were noted ($p < 0.0001$) and global EEG alpha-band power increased and delta-band power decreased following MRT ($p < 0.05$). This study documented trends toward normalization of EEG and concomitant clinical improvement using following MRT for PTSD [33].

Initial Studies

Preliminary Data communicated from Peking University in China is optimistic. Over 5 year duration, more than 60 patients with ASD were treated using quantitative EEG/ECG-guided Transcranial Magnetic Stimulation (MeRTSM). Forty-two percent of patients who completed treatment for 4 weeks or longer showed clinically

significant responses with a greater than 30% reduction from baseline measure in total CARS score at the end of the treatment. MRT Stimulation is an individualized TMS treatment protocol, which utilizes individual's intrinsic alpha EEG frequency and its closest frequency relationship with the higher harmonic of heartbeat to determine the magnetic stimulus rate. Stimulus location was set at the most apparent abnormal EEG site revealed by quantitative EEG mapping, and the magnetic output intensity was set at 80% of the individual's motor threshold. Each patient was treated 6 sec/min, 30 min / day for 5 days / week. Treatment was delivered with the MagVenture TMS generator (MagPro R30) coupled with a diffused and static cooled coil (MCF-B65 Butterfly). 39 patients who completed the study.

They found that the average 41% symptom reduction to be statistically significant ($p < 0.05$). No adverse effects were noted in any patients either after acute or chronic treatment. Two patients with severe comorbid epileptic seizure (180 episodes/day and 600 episodes/day, respectively) showed significant improvement (1 episode/week and 40 episodes/day, respectively) after the treatment. The minimal side effect may be explained by the individualized and low intensity stimulation protocol. Compared to 120% motor threshold stimulation intensity in the FDA approved protocol, MRT intensity is only 80% motor threshold. This sub-threshold stimulation will not trigger the neuronal firing and therefore is unlikely to cause seizure.

Conclusion

It is difficult to make definitive conclusions based upon the current peer review literature given that throughout the multiple studies there are differences in experimental design, choice of molecular spectra, analysis utilized, the potential for electrical artifact given the patient population, and the anatomic location of recording which may be institution specific. Additionally current studies are plagued by small sample sizes, variations in age, and level of impairment. These issues clutter our understanding as to whether the findings are indicative of aberrant brain function in children with ASD or rather variability in study design.

At the cellular level, EEG likely records activity from cortical and hippocampal pyramidal cells which are aligned in parallel. These pyramidal cells act as interconnected nonlinear oscillators. Given the scale free organization of neurons, EEG recordings of these complex, non-linear signals may be indicative of asynchrony and lack of coherence and not only indicative of aberrant neuronal networks but may also represent a potential avenue for therapeutic intervention.

Despite this, given our understanding of the EEG and the consistent abnormalities in the electrophysiology of children with ASD, we would suggest that MRT is an appropriate therapeutic option to further pursue. The existing literature in depression and posttraumatic stress disorder in addition to preliminary studies in children with ASD all support its potential impact as a therapeutic option.

References

1. Norris M, Lecavalier L. Screening Accuracy of Level 2 Autism Spectrum Disorder Rating Scales. A Review of Selected Instruments. Autism. 2010; 14: 263-284.
2. Kim JA, Szatmari P, Bryson SE, Streiner DL, Wilson FJ. The prevalence of anxiety and mood problems among children with autism and Asperger syndrome. Autism. 2000; 4: 117-132.
3. Simonoff E, Pickles A, Charman T, Loucas T, Chandler S, Baird G. Psychiatric disorders in children with autism spectrum disorders: Prevalence, comorbidity, and associated factors in a population-derived sample. Journal of the American Academy of Child and Adolescent Psychiatry. 2008; 47: 921-929.
4. Ozsivadjian A, Knott F. Anxiety problems in young people with autism spectrum disorder: A case series. Clin Child Psychol Psych. 2011; 16: 203-214.
5. Muris P, Steerneman P, Merckelbach H, Holdrinet I, Meesters C. Comorbid anxiety symptoms in children with pervasive developmental disorders. Journal of Anxiety Disorders. 1998; 12: 387-393.
6. Ghaziuddin, Mohammad. Asperger syndrome: Associated psychiatric and medical conditions. Focus on Autism and Other Developmental Disabilities. 2002; 17: 138-144.
7. White SW, Oswald D, Ollendick T, Scahill L. Anxiety in Children and Adolescents with Autism Spectrum Disorders. Clinical psychology review. 2009; 29: 216–229.
8. Kanner L. Autistic disturbances of affective contact. Nervous Child. 1943; 2: 217-250.
9. Lord C, Wagner A, Rogers S, Szatmari P, Aman M, Charman T, et al. Challenges in Evaluating Psychosocial Interventions for Autistic Spectrum Disorders. Journal of Autism and Developmental Disorders. 2005; 35: 695-708.
10. Chalfant A, Rapee R, Carroll L. Treating anxiety disorders in children with high functioning autism spectrum disorders: a controlled trial. Journal of Autism and Developmental Disorder. 2007; 37: 1842-1857.
11. Sofronoff K, Attwood T, Hinton S. A randomized controlled trial of CBT intervention for anxiety in children with Asperger syndrome. Journal of Child Psychology and Psychiatry. 2005; 46: 1152-1160.
12. Sofronoff K, Attwood T, Hinton S, Levin I. A randomized controlled trial of a cognitive behavioural intervention for anger management in children diagnosed with Asperger syndrome. Journal of Autism and Developmental Disorders. 2007; 37: 1203-1214.
13. Courchesne E, Karns CM, Davis HR, Ziccardi R, Carper RA, Tigue ZD, et al. Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. Neurology. 2001; 57: 245-254.
14. Herbert MR, Ziegler DA, Makris N, Filipek PA, Kemper TL, Normandin JJ, et al. Localization of white matter volume increase in autism and developmental language disorder. Ann Neurol. 2004; 55: 530-540.
15. Just MA, Cherkassky VL, Keller TA, Kana RK, Minshew NJ. Functional and anatomical cortical under connectivity in autism: Evidence from an FMRI study of an executive function task and corpus callosum morphometry. Cerebral Cortex. 2007; 17: 951-961.
16. Koshino H, Carpenter PA, Minshew NJ, Cherkassky VL, Keller TA. Just MA. Functional connectivity in an fMRI working memory task in high- functioning autism. NeuroImage. 2005; 24: 810.
17. Wang J, Barstein J, Ethridge LE, Mosconi MW, Takarae, Sweeney JA. Resting state EEG abnormalities in autism spectrum disorder. J Neurodev Disord. 2013; 5: 24.
18. Nunez PL, Srinivasan R. Electric fields of the brain: The neurophysics of EEG. 2006; 2.
19. Murias M, Webb SJ, Greenson J, Dawson G. Resting State Cortical Connectivity Reflected in EEG Coherence in Individuals with Autism. Biol Psych. 2007; 62: 270-273.
20. Coben R, Clarke AR, Hudspeth W, Barry RJ. EEG power and coherence in autistic spectrum disorder. Clin Neurophysiol. 2008; 119: 1002-1009.
21. Lazarev VV, Pontes A, Mitrofanov AA, deAzevedo LC. Interhemispheric asymmetry in EEG photic driving coherence in childhood autism. Clin

Neurophysiol. 2010; 121: 145-152.

22. Isler JR, Martien KM, Grieve PG, Stark RI, Herbert MR. Reduced functional connectivity in visual evoked potentials in children with autism spectrum disorder. Clin Neurophysiol. 2010; 121: 2035-2043.

23. Leveille C, Barbeau EB, Bolduc C, Limoges E, Berthiaume C, Chevrier E, et al. Enhanced connectivity between visual cortex and other regions of the brain in autism: A REM sleep EEG coherence study. Autism Res. 2010; 3: 280-285.

24. Sheikhani A, Behnam H, Mohammadi MR, Noroozian M, Mohammadi M. Detection of abnormalities for diagnosing of children with autism disorders using of quantitative electroencephalography analysis. J Med Syst. 2012: 36: 957-963.

25. Buzsáki G. Rhythms of the Brain. 2006.

26. Barabasi AL. Scale-free networks: a decade and beyond. Science. 2009; 325: 412-413.

27. Bassett DS, Bullmore E. Small-world brain networks. Neuroscientist. 2006; 12: 512-523.

28. Ravasz E, Barabási AL. Hierarchical organization in complex networks. Phys Rev E. 2003; 67: 1-7.

29. Supekar K, Musen M, Menon V. Development of large-scale functional brain networks in children. PLoS Biol. 2009; 7.

30. Bosl W, Tierney A, Tager-Flusberg H, Nelson C. EEG complexity as a biomarker for autism spectrum disorder risks. BMC Medicine. 2011; 9: 18.

31. Barttfeld P, Wicker B, Cukier S, Navarta S, Lew S, Sigman M. A big- world network in ASD: dynamical connectivity analysis reflects a deficit in long-range connections and an excess of short-range connections. Neuropsychologia. 2011; 49: 254-263.

32. Duffy FH, Als H. A stable pattern of EEG spectral coherence distinguishes children with autism from neuro-typical controls - a large case control study. BMC Medicine. 2012; 10: 64.

33. Taghva A, Silvetz R, Ring A, Kim KA, Murphy KT, Liu CY, et al. Magnetic Resonance Therapy Improves Clinical Phenotype and EEG Alpha Power in Posttraumatic Stress Disorder. Trauma Mon. 2015; 20: e27360.

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