Effect of Repititive Transcranial Magnetic Stimulation in Patients with Autism Spectrum Disorder

Thesis

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Abstract

Autism spectrum disorder (ASD) is a complex neurodevelopment disorder characterized by persistent deficits in social communication and interaction, and stereotyped behaviors, interests, and activities.The clinical, social and financial burden of Autism Spectrum Disorder (ASD) is staggering. The underlying brain mechanisms causing these symptoms are unknown and there currently exists no cure.

Transcranial magnetic stimulation (TMS) is is beginning to be used by a number of centers worldwide as promising, emerging tool for the study and potential treatment of ASD. Repetitive TMS (rTMS) may represent a novel treatment strategy for reducing some of the core and associated ASD symptoms.

The current study tested the potential therapeutic effect of rTMS in patients diagnosed with ASD. A sham controlled study in 15 patients diagnosed with ASD received active rTMS intervention and matched for age, gender, symptoms severity and IQ with 15 patients diagnosed as ASD and received sham rTMS stimulation. rTMS was administered weekly for 12 weeks with the 1st six treatments over the left DLPFC, whereas the remaining six treatments over the right DLPFC at 1.0 Hz frequency and 90% MT, total of 180 pulses per day session with nine trains with 20 pulses each. There will be 20-30 seconds intervals between the trains.

Both active rTMS and sham rTMS groups were assessed twice at the baseline and after completion of 12 weekly sessions of rTMS clinically and using assessment scales for severity using Child Autism Rating Scale (CARS) and DSM5 Clinician-Rated Severity of Autism Spectrum and Social Communication Disorders, for effectiveness of the treatment using Autism Treatment Evaluation Checklist (ATEC) and for IQ and level of functioning Vineland Adaptive Behavior Scale (VABS).

Keywords: Repititive Transcranial - autism spectrum disorders - Centers for Disease Control

Introduction

The autism spectrum disorders (ASD) describes a range of conditions classified as neurodevelopmental disorders in the fifth revision of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5). These disorders are characterized by social deficits and communication difficulties, stereotyped or repetitive behaviors and interests, sensory issues, and in some cases cognitive delays ***(American Psychiatry Association APA, 2013).***

The Centers for Disease Control and Prevention (CDC) estimates that 1 in 68 children (or 14.7 per 1,000 eight-year-olds) children (1 in 54 boys and 1 in 252 girls) ***(Baio 2012).*** This is more children than are affected by diabetes, AIDS, cancer, cerebral palsy, cystic fibrosis, muscular dystrophy and Down syndrome combined ***(Child and Adolescent Health Measurement Initiative 2012).***

ASD is diagnosed clinically, based on the presence of key behavioral symptoms, but the underlying brain mechanisms causing these symptoms are unknown and there currently exists no cure. Most empirically supported treatments for the core symptoms of ASD focus on early intensive behavioral interventions ***(Reichow 2012).***

Pharmacological treatments are at times effective in treating secondary and co morbid features of ASD, such as aggression or hyperactivity and attention deficit, or epilepsy, but there is currently no pharmacotherapy shown to effectively treat the core symptoms of ASD ***(Hampson et al., 2012).***

One way that may be accomplished is with transcranial magnetic stimulation (TMS), a noninvasive method for cortical excitability modulation that may avail to the field a physiologic biomarker to aid with ASD diagnosis and perhaps obtain deeper insight into ASD physiology. As well, TMS may have therapeutic prospects as well ***(Obermann et al., 2015).***

Transcranial magnetic stimulation (TMS) was introduced in 1985 as a technique to stimulate the cerebral cortex non-invasively. A TMS device generates a strong magnetic field, inducing an electric current in a specific area, and this in turn induces intracerebral currents in associated neural circuits ***(Ruhe et al., 2012).***

The physical principles of TMS were discovered in 1881 by English physicist Michael Faraday, who observed that a pulse of electric current passing through a wire coil generates a magnetic field. The rate of change of this magnetic field determines the induction of a secondary

current in a nearby conductor. During TMS, the stimulating coil is held over a subject's head and produces an electric current in the subject's brain via electro-magnetic induction. This current in turn depolarizes neurons and can generate various physiological and behavioral effects depending on the targeted brain area. Because magnetic fields can pass the skull with almost no resistance, TMS can induce relatively large currents in targeted cortical areas ***(Horvath et al., 2011)***.

One neuro scientific tool that has become widely used, safe and non- invasive way to probe aberrant neuroplasticity is transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS).

TMS mechanism of action at the synaptic level the fine balance between excitation mediated by glutamate and inhibition mediated by GABA could be crucial for optimal level of neuroplasticity ***(Baroncelli et al., 2011).*** It has been suggested that the excitation / inhibition imbalance could be the key determinant in neuroplasticity abnormalities in neuro developmental disorders such ASD ***(Rajji et al., 2013)*** and a deficit in inhibitory neurotransmission has been implicated in the pathogenesis of the ASD. It is believed that such deficit could develop during neuronal maturation ***(Baroncelli, et al., 2011).***

Studies that used rTMS for therapeutic purposes to improve either symptoms or physiological and cognitive indices have focused on four areas of ASD brain: the dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (mPFC) supplementary motor area, and right pars triangularis and pars opercularis ***(Obermann et al., 2014).***

About rTMS safety data available indicate that when it is applied within established safety guidelines, is well tolerated and safe in both adult and pediatric ASD populations ***(Oberman et al., 2015)***.

Aim of the Study

To study the potential therapeutic effect of transcranial Magnetic Stimulation (rTMS) in patients diagnosed with Atism Spectrum disorder (ASD).

Chapter (I): Autism Spectrum Disorders (ASD)

Autism Spectrum Disorders are organic neurodevelopmental disorders caused by genetic or neurobiological factors rather than by psychological or environmental ones ***(Kim, 2015).*** Autism spectrum disorder (ASD) is defined a wide continuum of associated cognitive and neurobehavioral persistent deficits in social communication and social interaction across multiple contexts, as manifested by deficits in social emotional reciprocity, deficits in nonverbal communicative behaviors used for social interaction, or deficits in developing, maintaining and understanding relationships with restricted and repetitive patterns of behavior ***(American Psychiatry Association APA, 2013).***

Historical background:

Kanner (1943) first documented a syndrome of "autistic disturbances" in 11 children who shared previously unreported patterns of behavior, including poor social interaction, obsessiveness, stereotypic movement, and echolalia. Before Kanner's report, the behavior was generally known as childhood schizophrenia. Infantile Autism, first described in medical literature as serious psychiatric disturbance of childhood which dooms a

majority of its victims to lifetime disability manifesting early in life. The term autism (Greek for "self-ism") refers to their self-absorption and withdrawal from social transactions. Some such children remain totally mute while others fail to develop communicative speech ***(quoted from Kanner, 1943).***

Concurrent with Kanner's report and observations were those of Asperger in 1944. However, Asperger's report, in a German language journal, was not brought to the forefront until the 1980s. The children described by Asperger had milder forms than descried by Kanner ***(quoted from Asperger, 1944).***

According to O'Gorman an autistic child shows these essential features:

1) Withdrawal from or failure to become involved with reality; in particular, failure to form normal relationships with people.

2) Serious intellectual retardation with islets of normal, near normal or exceptional intellectual function or skills.

3) Failure to acquire speech, or to maintain or improve on speech already learned, or to use what speech has been acquired for communication.

4) Abnormal response to one or more types of sensory stimulus (usually sound).

5) Gross and sustained exhibition of mannerisms or peculiarities of movement, including immobility and hyperkinesis and excluding tics.

6) Pathological resistance to change. This may be shown by:

   a) Insisting on observance of rituals in the patient's own behavior or in those around him.

   b) Pathological attachment to the same surroundings, equipment and toys, and people (even though the relationship with the person involved may be purely mechanical and emotionally empty).

   c) Excessive preoccupation with peculiar objects or certain characteristics of them without regard to their accepted functions.

   d) Severe anger or terror or excitement, or increased withdrawal, when the sameness of the environment is threatened (e.g. by strangers) ***(quoted from O'Gorman, 1967)***.

Till 1970 available research strongly supported inclusion of autism as a new condition in DSM-III, which had adopted research diagnostic criteria approach. In DSM-III autism was included in a class of conditions called pervasive developmental disorder (PDD). The DSM-III definition was very focused on infantile autism and developmental change was only cursorily addressed, although other categories for late-onset autism were also included (although without much justification). In DSM-III-R (1987) there was a major attempt to address the lack of developmental orientation. A single disorder and a subthreshold category were described (the name of the latter was changed from atypical PDD to pervasive developmental disorder not otherwise specified (PDD-NOS). The criteria set was more extensive than in DSM-III and included a polythetic definition with symptoms chosen from social, communication, and resistance to change categories. Although a field trial was conducted it was limited in some ways and, in retrospect, DSM-III-R appeared to over diagnose autism in individuals with greater cognitive disability while, to some extent, underdiagnosing at the other end of the IQ range ***(Volkmar and Klin, 2005).***

The *Diagnostic and Statistical Manual of Mental Disorders, fourth edition* (DSM-IV; 1994) and the DSM-IV-TR (text revision; 2000) included five possible diagnoses under the pervasive Developmental disordrs PPD: autistic disorder, Asperger disorder, childhood disintegrative disorder, Rett's syndrome, and PDD-not otherwise specified (NOS). Of these conditions, the definition of Asperger's proved most problematic (the text was radically changes at the time DSM-IV-TR (2000) appeared but the criteria could not be changed at that point). As a result the concept has been used inconsistently although research on it has increased dramatically. Rett's disorder was included because it appeared to be a very interesting condition that might have a specific neurobiological basis and the PDDs seemed the best place for it ***(Rutter, 1994)*** subsequently, a gene has been discovered for this condition and it is often no longer regarded as an autism spectrum disorder, although DSM-5 have included it as a specifier. Childhood disintegrative disorder was of great interest, despite its rarity, in that a child would develop typically to 4 years, 5 years, or even 6 years of age before having a rapid and dramatic regression followed by a more classic autism presentation ***(Volkmar et al., 1994; Michael Rutter, 2011).***

A revision of the Autism Spectrum Disorders (ASDs) was proposed in the DSM5. The autism spectrum describes a range of conditions classified as neurodevelopmental disorders in the fifth edition of the DSM. The new diagnosis encompasses the previous diagnostic criteria for autistic disorder, Asperger syndrome, childhood disintegrative disorder, and Pervasive Developmental Disorder not otherwise specified (PDD-NOS). It is believed that individuals with ASDs are best represented as a single diagnostic category because they show similar types of symptoms and are better differentiated by clinical specifiers (i.e., dimensions of severity) and associated features (i.e., known genetic disorders, epilepsy, and intellectual disability). An additional change to the DSM-5 includes synthesizing the social and communication deficits section into one domain ***(Kim, 2015).***

Epidemiology:

The prevalence of autism has increased dramatically, and it has been currently recognized as one of the most common developmental disorders. For many years after autism was first described in the 1940s, its prevalence was considered to be two to four cases per 10,000 children ***(Wing & Potter, 2002)***.

The Centers for Disease Control and Prevention (CDC) estimates that 1 in 68 children (or 14.7 per 1,000 eight-year-olds) children (1 in 54 boys and 1 in 252 girls.) in multiple communities in the United States has been identified with ASD. This is more children than are affected by diabetes, AIDS, cancer, cerebral palsy, cystic fibrosis, muscular dystrophy and Down syndrome combined. Providing a systematic review of epidemiological surveys of autistic disorder and pervasive developmental disorders (PDDs) worldwide, the median of prevalence estimates of autism spectrum disorders was 62/10 000 ***(Elsabbagh et al., 2012; Centers for Disease Control and Prevention, 2014).***

The increase of ASD prevalence cannot be fully explained by advances in diagnostics or sudden genetic shifts (only about 50% of the observed increase in autism incidence can be accounted for by changes in diagnostic criteria, public awareness or other non-causal parameters). There is a growing consensus among scientists and clinicians that ASDs ensue from an interaction between biological vulnerability factors and environmental or iatrogenic insults ***(Gillberg, 2009).***

There is also a co diagnosis with known medical disorders such as fragile X syndrome, Tourette syndrome, and Down syndrome. Additionally, the growing public awareness among parents and teachers in developing countries has led to earlier diagnoses. Other factors include the increased availability of services and the ability to diagnose children at younger ages ***(Nassar et al., 2009)***.

Diagnosis of Autism from Kanner to DSM5:

Kanner's initial report on autism in 1943 listed 10 characteristics of autistic children and their families:

1. The primary and most noted sign is the child's inability to relate to others.
2. Mothers of these children report that the children did not show an anticipatory posture before being picked up.
3. Eight of the 11 children began speaking either on time or afterward. In some speech developed normally and was then lost with the onset of the autism.
4. Typically, the children had excellent memories.
5. The children demonstrated echolalia (repetition of particular sounds).
6. Words were interpreted literally.
7. Personal pronouns were used inaccurately.
8. The children had unusual reactions to sensory stimuli.
9. The children had the desire to keep the world around them constant.