Repetitive Transcranial Magnetic Stimulation as a possible new treatment strategy to improve social skills in Autism Spectrum Disorder

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Abstract

Autism spectrum disorder (ASD) is one of the most common child psychiatric disorders. Despite the long history of research on ASD, not much is known yet about the exact biological causes and how the disorder can be effectively treated. Behavioral interventions and pharmacological treatments aim to reduce symptoms. These treatments are often non-specific and the effectiveness is limited. It is therefore of great importance to search for alternative treatment strategies. Several studies have suggested that social skill deficits might lie at the core of other symptoms in ASD. Furthermore, neuroimaging studies have shown that social skill deficits in ASD are associated with hypoactivation of in particular the frontal lobes. Repetitive transcranial magnetic stimulation (rTMS) is a technique that is capable of directly influencing neural excitability in a relative focal fashion and might provide a minimally invasive somatic treatment strategy. Increasing excitability in the frontal lobe with rTMS may improve social skills in ASD. The aim of the present review is to examine whether there is a theoretical basis for applying rTMS to improve social skills in ASD. Meta-analyses have shown that rTMS treatments are effective in some disorders, such as depression and schizophrenia. However, safety limits and ethical considerations make it challenging to conduct rTMS treatment in children with ASD. Currently, there is not enough evidence to conclusively support rTMS treatment in children with ASD and further research is needed. To this end, this review proposes a protocol for a pilot study which could provide proof of principle.

Keywords: Autism, Transcranial magnetic stimulation, Treatment, Social skills

Introduction

Autism spectrum disorder (ASD) is one of the most common child psychiatric disorders, with a prevalence estimated at 1.1% of the population (Center of Disease Control and Prevention, 2012). Children diagnosed with ASD differ from typically developing children on many cognitive and behavioral dimensions, and therefore the term 'spectrum' is used to emphasize its full scope. The spectrum consists of a heterogeneous group of disorders, including Autism, Asperger's Syndrome, Pervasive Developmental Disorder- Not otherwise specified (PDD-NOS), Childhood Disintegrative Disorder, and Rett syndrome (American Psychiatric Association, 2000). ASD significantly impairs social interactions. For example, individuals with ASD are often unable to understand and interpret (non)verbal behaviors in others, which can result in a failure to develop peer relationships (Cotugno, 2009).

Several twin studies have demonstrated that ASD is heritable. Monozygotic twins have a higher concordance rate than dizygotic twins, 90% and 10%, respectively (Faras, Al Ateeqi & Tidmarsh, 2010). However, the exact etiology is unknown, and it is likely that a combination of multiple genetic and environmental factors could result in ASD (Oberman, Rotenberg & Pascual-Leone, 2013). Thus, despite a long history of research on ASD, not much is known yet about the biological causes and how the disorder can be treated. This is partly due to the heterogeneity of the disease and the diversity of observed symptoms. At present, there is no cure for the core symptoms of ASD. Treatment strategies, such as behavioral interventions and pharmacological treatments, are aimed to reduce symptoms. Pharmacological treatments are effective in treating comorbid features of ASD, such as catatonia and depression, but currently there is no pharmacotherapy that has shown to be effective in treating the core symptoms of ASD (Oberman, 2012). Most families turn to pharmacological treatment after behavioral interventions have failed to improve the symptoms of their autistic child. Finding the right medicine often comes down to trial and error: trying a certain medication for some period of time (e.g., weeks or months) and if that drug fails to be effective, treatment with another drug is tested (Arky, 2012). Furthermore, treatments such as behavioral and pharmacological interventions are nonspecific. To date, there are no treatment strategies that aim at a specific symptom or specific dysfunctioning brain area. Several studies have suggested that social skill deficits might lie at the heart of other symptoms in ASD (Gutstein & Whitney, 2002; Howlin et al., 2004). A broad range of neuroimaging studies have suggested that these deficits in social skills are associated with hypoactivation of in particular the frontal cortex (Castelli et al., 2002; Murphy et al., 2002;

Dapretto et al., 2006; Gilbert et al., 2009; Grezes et al., 2009; Bastiaanse et al., 2011; Yang et al., 2011). Stimulating these specific brain regions might result in a more balanced activation pattern and could improve social skills in ASD.

The relatively new technique of repetitive transcranial magnetic stimulation (rTMS) is a technique that is capable of stimulating brain regions very focally and might provide a more specific treatment strategy. The aim of the present review is to examine whether there is a theoretical basis for applying rTMS to improve social skills in ASD. To this end, this review will integrate the literature on the neural basis of ASD and the knowledge of rTMS. The benefits of rTMS and its downsides will be discussed and ultimately, directions for further research are proposed.

Core symptoms and social skill deficits

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; American Psychiatric Association, 2000) is the most widely used instrument for diagnosing ASD along three core symptoms: (1) qualitative impairments in social communication, (2) qualitative impairments in social interaction, and (3) restricted repetitive and stereotyped patterns of behavior, interests and activities. In addition, sensory abnormalities, including hyposensitivity and hypersensitivity are also common (Charman, 2008). Furthermore 70% of the children with ASD show a varying degree of learning disability ranging from problems studying in school (low grades because they are incapable of keeping up with their peers) to difficulties in learning how to wash themselves or prepare a meal (Zoghbi & Bear, 2012).

In particular, the impairments in social interactions are considered to have major implications for the prognosis of ASD. Social skills can be defined as the ability to interpret social situations, perceive and process emotional signals and the use of verbal and non-verbal behaviors that result in positive social interactions (Rao, Beidel & Murray, 2008). Making eye contact and smiling during conversations, asking questions and showing interest in other individuals, and the ability of feeling empathy for the misery of others are all examples of social skills. As a matter of fact, every skill that facilitates interactions and communication with others can be seen as a social skill. Social skills deficits that are often observed in individuals with ASD include: difficulty interpreting verbal and non-verbal social cues; a lack of eye contact; inadequate response towards a social stimulus; less interest or enjoyment in social interactions; lack of empathy to other's distress; and inappropriate emotional responses

to social cues (Gutstein & Whitney, 2002). Good social skills during childhood have been positively associated with parent-child relationships, mental health and even academic achievement (Hartup, 1989). Unfortunately, because children with ASD often show deficits in social skills, they experience difficulties with these factors, often persisting throughout adulthood (Howlin & Goode, 2000). Deficits in social skills are not something a child with ASD will simply overgrow. In fact, the majority of children with ASD remains within the spectrum as an adult and continue to experience social skills deficits, resulting in problems with independent living, social relations and employment (Howlin et al., 2004). Treatment strategies for ASD are therefore commonly maintenance therapies, meaning that treatment must be continued for very long times in order to retain positive effects.

Social difficulties experienced by children with ASD can become more troublesome as children become older. In middle- and high school, social complexity and social pressure increase and the child might become more self-aware of his or her social disabilities (Tantam, 2003). This, in turn, could lead to secondary mood and anxiety problems. Indeed, several studies have shown that there is a high prevalence of anxiety disorders co-occurring in individuals with ASD. A recent review of anxiety studies in children with ASD found that between 11% and 84% of the children with ASD experience anxiety (White et al., 2009). Children with ASD who are aware of their social skill deficits may experience anxiety related to misinterpretation of social cues and/ or be afraid to fail in social interactions. This might result in social avoidance and in turn further limits the child's opportunities to practice appropriate social skills in everyday life. In a study of White and Roberson-Nay (2009) children with ASD (aged 7-14) with self-reported increased levels of anxiety reported greater feelings of social loneliness. Furthermore, this study also reported a significant relationship between parent-reported child withdrawal and the level of social disability. Moreover, a study comparing adolescents with ASD, adolescents with anxiety disorder and typically developing controls reported that the ASD group scored highest on anxiety (Farrugia & Hudson, 2006).

Additionally, ASD shares overlapping symptoms with major depression- and dysthymic disorder, such as social withdrawal and sleep disturbance. A review of the literature has indicated that depressed mood was frequently reported in individuals with ASD (Stewart et al., 2006). Other symptoms of depression, e.g. feelings of worthlessness and guilt, were less often reported. However, the authors noted that these subjective feelings may be more difficult to assess in children with ASD. The above-mentioned findings indicate that social skill deficits have a major impact on the wellbeing of children with ASD. It is therefore of great importance to understand how these deficits arise and how social skills may be

further improved in individuals with ASD. Neuroimaging studies have already shown that brain development follows different trajectories in children with ASD as compared to typically developing children (TDC). Several of these neuroimaging studies have identified abnormal development of brain regions that are implicated in social skills. These findings might serve as a starting point in finding new strategies to promote social skills in ASD.

Brain development in ASD

Brain development in ASD is characterized by an early brain overgrowth of both gray and white matter in the first years of life, followed by an abnormally slowed growth. An MRI study of Courchesne and colleagues (2001) showed that children with ASD (2 to 4 years old) have abnormally larger whole brain volumes than TDC. This brain enlargement was most evident in the children aged 2-3 years, where 37% of the children with ASD had whole brain volumes two standard deviations higher than the mean volume of TDC. Head circumference measurements at birth were normal for most of the ASD patients in this study, suggesting that a postnatal factor may cause the increased total brain volume seen in young patients with ASD. At older ages (5-16 year), whole brain volumes of ASD were slightly larger than in TDC, but this difference was no longer significant.

In addition, this study showed that 2-3 year old children with ASD had an 18% increase of cerebral white matter. However, the increase of white matter with age was smaller than in TDC. In TDC the increase of white matter volume from 2-3 years of age to adolescence (12-16) was 59%, whereas in children with ASD, this increase was only 10%. So, in the children with ASD, compared to TDC, more white matter volume was observed at young age, but less white matter volume at adolescence. The same pattern was found in the development of cerebral cortical grey matter. At the age of

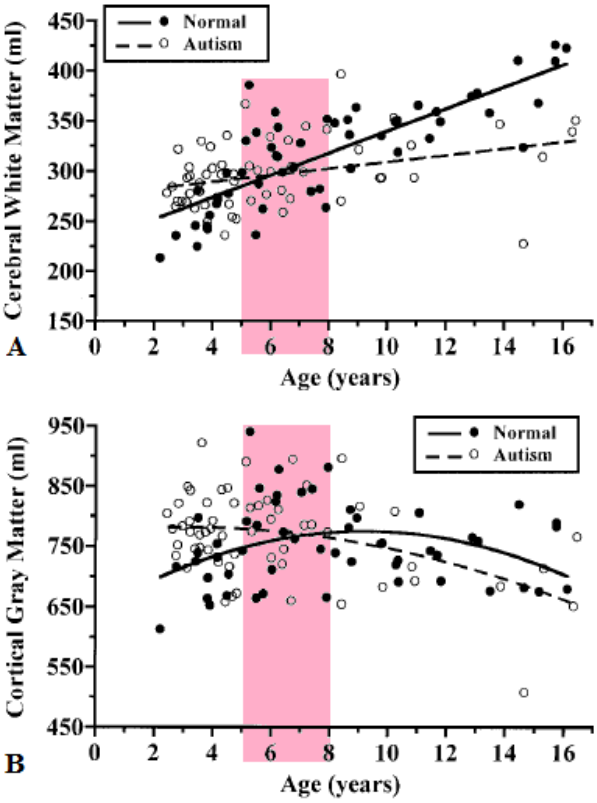

Figure 1. *Cerebral volumes by age. A: volumes of cerebral white matter. B: volumes of cortical gray matter. The pink boxes indicated the critical period in which treatment might have the most beneficial effects. (Adjusted from Courchesne et al. 2001)*

2-3 years, the children with ASD show 12% more grey matter than in TDC. However, where grey matter increased with 12% from 2-3 years to 6-9 years in TDC, there was a slight decrease of grey matter (2%) found in the children with ASD during this time. Furthermore, the initial early biological differences most likely modify brain maturation across the whole lifespan, since studies have also shown that brain aging in adults with ASD is significantly different from controls (McAlonan et al., 2002).

As illustrated in figure 1, these findings suggest that the brain growth of children with ASD is most typical compared to TDC around the age of 5-8. This could indicate a critical period in which treatment might have the most beneficial effects. Treatment during the critical period might prevent the start of abnormal slow brain maturation that is usually observed in children with ASD. In this way, the treatment might induce the brain maturation of children with ASD to remain comparable to that of typically developing children throughout adolescence and adulthood.

In addition to differences in grey and white matter across the whole brain, some specific brain regions are implicated in particular, including the frontal cortex, the cerebellum, the corpus callosum, the limbic system and temporal lobes, and the fusiform face area (FFA). Several of these brain regions are also implicated in social skills and it is very likely that abnormalities in these regions are linked to the social skill deficits observed in ASD. For example, cerebellar damage can cause behavioral symptoms resembling those seen in ASD, such as impaired executive skills, deficits in social behavior and flattening of affect (Schmahmann & Sherman, 1998). Nowadays, the cerebellum is no longer seen as an exclusively motor functioning brain structure and is increasingly being recognized as a structure that is also involved in higher order emotional, social and cognitive processing (Fatemi et al., 2012). The limbic system, on the other hand, has been associated with emotions for almost a decade. Back in the thirties, Papez (1937) already referred to the limbic system as the 'emotion system', a system particularly important in the generation of emotions. However, structural neuroimaging studies on the limbic system in children with ASD have been inconsistent, with some studies showing increased volumes of the limbic system compared to TDC, some showing decreased volumes and some even observed no differences. Neuroimaging studies have, however, consistently found differences in activity of the frontal lobes of individuals with ASD. The frontal lobes have been associated with visual attentiveness, executive functioning and theory-of-mind skills (the ability to understand the intentions and feelings of others). In addition, lesion studies have shown that damage to the frontal cortex leads to significant changes in personality, emotion regulation and social

functioning (Eslinger, Flaherty-Craig & Benton, 2004). Social skills tend to rely strongly on the frontal regions, which continue to develop throughout childhood and into early adulthood (Beauchamp & Anderson, 2010). Several studies point towards the direction that social skill deficits observed in individuals with ASD arise at least in part from frontal lobe dysfunction.

Frontal lobe dysfunction in ASD

Single-photon emission computed tomography (SPECT) studies have reported differences in frontal brain activation in individuals with ASD (Sasaki et al., 2010; Yang et al., 2010). SPECT is used to measure regional cerebral blood flow (rCBF), which is suggested to reflect changes in synaptic functional activities. Yang et al. (2011) observed significant decreases of rCBF in the bilateral frontal poles (the anterior end of the hemispheres) in children with ASD. They also found a significant difference in the symmetry of hemispheric perfusion between the control group and the ASD group. The ASD group showed greater right rCBF in the inferior temporal gyrus, and the interior - and middle frontal gyrus, compared to TDC. The asymmetry of hemispheric perfusion might posse a different neural base in ASD, possibly resulting in impairments of social skills (Yang et al., 2010). Furthermore, MR spectroscopy imaging can be used to qualify neuronal integrity. Neuronal integrity refers to the brain tissue being intact. It has been shown that individuals with ASD have significant abnormalities in prefrontal lobe neuronal integrity and that this is related to the severity of behavioral symptoms (Murphy et al., 2002). In particular, increased concentrations of choline, a biochemical marker for demyelination, in prefrontal regions have been significantly correlated with social dysfunction, measured by the communication domain of the Autism Diagnostic Interview (ADI-R).

Numerous functional neuroimaging studies have shown alterations in activity of the frontal regions in patients with ASD during tasks such as processing social stimuli, story comprehension and visual search for embedded figures. Hypoactivation of the medial prefrontal cortex (mPFC) during an fMRI mentalizing task has been reported in individuals with ASD (Castelli et al., 2002). A study of Gilbert et al. (2009), on the other hand, did not show group differences in BOLD activity in the mPFC between adults with high functioning ASD and typical adults (mean age 32). However, by using multi-voxel similarity analyses the researchers also examined the functional specialization (i.e., the distribution of activity across voxels) of the mPFC and with this approach, they found significant group differences. In the control group, the distribution of activity over the mPFC showed a significant positive

relationship between tasks that had the same function (both attention-related or both mentalizing-related). On the other hand, when the distribution of activity between two unrelated tasks was analyzed (attention vs. mentalizing), the control group showed a negative relationship. This distinctive pattern was not observed in the ASD group. The authors concluded that the functional organization of the mPFC is different in individuals with ASD. Even though high functioning individuals with ASD may perform similar to control participants on many tasks, it is likely that they use atypical, compensatory mechanisms during these tasks. The mPFC has been associated with attending to theory-of-mind-related cognition, one's own mental state and the mental state of others (Van Overwalle et al., 2011). It has been suggested that the mPFC is an important node of the brain's network associated with understanding of other minds (Castelli et al., 2002). Other fMRI studies have reported hypoactivation of the inferior frontal gyrus during perception and imitation of emotional facial expression (Schultz & Robins, 2005). Hypoactivation of the inferior frontal gyrus during the perception of facial expressions has been interpreted by several researchers as evidence for a deficit of the mirror neuron system in children with autism.

Mirror neurons, the inferior frontal gyrus and social skills

An influential, yet controversial theory states that the core social impairments in ASD originate from a dysfunction of the mirror neuron system (MNS; Dapretto & Iacoboni, 2006). Single-cell recordings in macaques have shown that these so called mirror neurons fire when the monkeys perform an action, but also when they observe a similar action being performed by another monkey (Fuji, Hihara & Iriki, 2008). Neuroimaging studies have reported that a similar MNS exist in humans. In healthy individuals, perceiving emotional facial expressions increases activity in the pre-central motor face area, which is associated with facial mimicry. The perceived emotion is unconsciously mimicked and by the activation of motor representation, motivations and intentions associated with the facial expression are also activated. In addition to understanding the goals of the other person, typically controls are also able to experience their intentions and emotions when they watch someone else (Kaplan & Iacoboni, 2006). This mimicking of emotional expressions is taken as an important aspect involving empathy. Activity in the inferior frontal gyrus (IFG, Brodmann areas 44, 45 and 47, see figure 2) has been suggested to confirm interaction between emotion perception and motor stimulation. In typically developing children, the activity of the IFG during the observation and imitation of emotional faces correlates with empathy scores of those children (Pfeifer et

al., 2008). The authors suggested that the neural mirroring of the emotions expressed by others may play an important role in, not only understanding the emotional states of others, but also to feel what others feel.

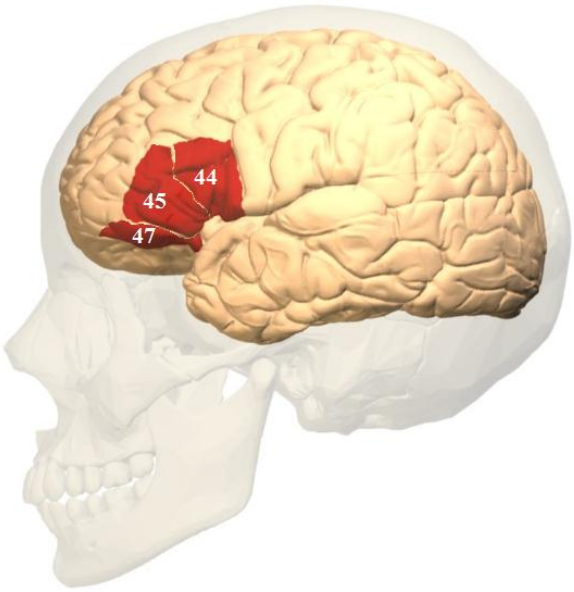

Figure 2. *Illustration of the inferior frontal gyrus consisting of Brodmann area's 44, 45 and 47. Modified from Body Parts 3D/ Anatomography website, the content of this website is published under the Creative Commons Attribution 2.1 Japan license.*

A recent review on the MNS concluded that there is little evidence for a global dysfunction of mirror neurons in ASD (Hamilton, 2012). However, several studies have shown differences in the activation of the IFG between individuals with ASD and typically controls. Grezes and colleagues (2009) reported that both typical and ASD participants engaged MNS in response to movies of neutral body actions. However, when viewing emotional, fearful body actions, the typical controls showed more activation of the IFG than the participants with ASD. This group difference was not due to differences in the amount of attention given to the task, since performance level in both groups indicated that the subjects were indeed attending to the stimuli. Furthermore, in a study of Dapretto et al. (2006) a group of children with ASD did not show any significant activation of the IFG during the observation of emotional facial expressions, whereas in TDC there was significant activation of the IFG. The lack of significant activation of the IFG was not due to gaze behavior, since there were no group differences in the amount of time spent fixating on the face and eye region. In addition, this study also reported that there was a significant negative correlation between IFG activity and social skill deficits in children with ASD. In addition, Bastiaanse et al. (2011) examined whether the dysfunction of the IFG persisted in adulthood. They found that activity in the IFG during the observation of facial expressions increased with age in individuals with ASD, but not in control subjects. This age-related increase of IFG activity was associated with improvement of social functioning. However, this study did not control for gazing behavior and differences in the amount of attention for the task might have confounded the results.

Table 1 provides a summary of the main results from studies discussed in relation to frontal lobe dysfunctions in ASD. The studies of Dapretto et al. (2006) and Bastiaanse et al.

(2011) demonstrate that, despite of the ongoing debate whether or not there is a MNS dysfunction in ASD, there is indeed a relation between hypoactivation of the IFG and social skill deficits in ASD. More importantly, the findings of Bastiaaanse et al. (2011) indicate that the dysfunction of the IFG is not necessarily a fixed state and that changing IFG functioning may have beneficiary effects. Thus, a treatment strategy that specifically aims at normalizing brain activity in the IFG might cause improvement of social skills in ASD. However, such specific treatment strategies are not yet available. In fact, current therapies used in ASD are often non-specific as these therapies do not target a specific symptom or brain region.

Table 1. *Main findings of studies that examined frontal lobe dysfunctions in ASD.*

Study	Main result
Castelli *et al.* 2002	- Hypoactiviton of mPFC during a mentalizing task in ASD, compared to TDC
Murphy *et al.* 2002	- Significant abnormalities in prefrontal lobe neuronal integrity in ASD - Abnormalities are related to the severity of behavioral symptoms
Dapretto *et al.* 2006	- No significant activation of the IFG when observing emotional facial expression in ASD - Differences not due to differences in gaze behavior. - Significant negative correlation between IFG activity and social skill deficits in ASD
Gilbert *et al.* 2009	- Differences in functional organization of the mPFC between ASD and TDC
Grezes *et al.* 2009	- Hypoactivation of the IFG when viewing emotional body actions in ASD, compared to TDC - No differences in IFG activity when viewing neutral body actions - Differences are not due to attention differences
Bastiaanse *et al.* 2011	- Activity of IFG increases with age in ASD, but not in TDC - Age related increase of IFG in ASD are associated with improvement of social functioning - Differences might be due to attention differences
Yang *et al.* 2011	- Less rCBF in the bilateral frontal poles in ASD, compared to TDC - Significant difference in the symmetry of hemispheric perfusion: greater right rCBF in the IFG, and the interior - and middle frontal gyrus in ASD, compared to TDC

Abbreviations: medial Prefrontal Cortex (mPFC); Autism Spectrum Disorder (ASD); Typically developing control (TDC); Inferior Frontal Gyrus (IFG); regional Cerebral Blood Flow (rCBF)

Current treatment strategies in ASD

Current treatments strategies in ASD involve behavioral interventions and forms of medication treatment. Both strategies can produce significant improvements in communication and social skills that maintain both over time and across settings (Bodfish, 2004). Research has shown that the most effective therapy for ASD is early intensive behavioral interventions (Dawson & Osterling, 1997). These interventions focus on developing language and communication skills, social responsiveness, academic achievement

and appropriate behaviors. Examples of these behavioral therapies include Applied Behavior Analysis (ABA; Jensen & Sinclair, 2002) and Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH; Panerai, Ferrante & Zingale, 2002). In a review of important principles and components of effective early childhood intervention, Myers and Johnson (2007) concluded that these treatments are very intensive, often requiring active engagement of the child for at least 25 hours a week, 12 months per year. Furthermore, they state that for a good therapy outcome, as indicated by significant reductions in core symptoms, it is important to include a family component, such as parent training. Moreover, a high degree of structure and routine needs to be implemented in the child's home situation.

In addition to behavioral interventions, pharmacological interventions, for example the prescription of selective serotonin reuptake inhibitors (SSRI's), have been used to treat maladaptive behaviors such as aggression, hyperactivity, self-injurious behavior, repetitive behavior, sleep disturbance, and anxiety. In case of a comorbid disorder, for instance anxiety disorder, the patient is treated with medications that are useful for treating this comorbid disorder specifically. As mentioned before, there is a high rate of co-occurrence between anxiety disorders and ASD. Some studies have suggested that specific features of ASD are consequences of the anxiety by the difficulty of comprehending the social environment (Howlin, 1998; Thomas et al., 1998). As discussed earlier in this review, children with ASD might experience anxiety related to misinterpretation of social cues. Stereotypical and repetitive behavior, such as twirling and hand flapping, often increases when children are distressed. These behaviors might serve as mechanisms to cope with the anxiety in children with ASD (Gillott, Furniss & Walter, 2005). In this context, treating the anxiety disorder can result in a decrease of symptoms of repetitive and stereotypical behavior. A review of the efficiency of SSRI's in autism indeed found that most studies demonstrated significant improvement in global functioning and in symptoms associated with anxiety and repetitive behaviors (Kolevzon, Mathewson & Hollander, 2006).

Pharmacological treatment is also used in the absence of a clear comorbid diagnosis, by a target-symptom approach (Hollander, Phillips & Yeh, 2003; Myers, 2007), where different symptoms of ASD are treated. For example, risperidone, an atypical antipsychotic agents, have been shown to decrease aggressive- and self-injurious behavior in children and adolescents with ASD (Arnold et al., 2003; McCracken et al., 2000; Shea et al., 2004). Psychostimulants, e.g. methylphenidate and dextroamphetamine, can reduce symptoms of hyperactivity and impulsivity (Handen et al., 2000; Quintana et al., 1995). Furthermore, the

SSRI's fluoxetine and fluovoxamine are used to minimize repetitive behaviors and obsessive-compulsive behaviors in ASD (Hollander et al., 2005; McDougle et al., 1996). However, these medications have adverse effects that include weight gain, fatigue, hypomania, apathy and alteration of sleep (Myers & Johnson, 2007). In addition, finding the right medicine and the right doses takes time and often requires a trial-and-error approach (Hu, 2011). There is some evidence to suggest that individuals with ASD may be overmedicated, or at least medicated with more powerful substances when less toxic substances would also suffice (Schall, 2002). Furthermore, when the right medicine is found, the treatment can only be effective when the correct doses of medication is taken at specific intervals. Practical problems can arise when parents forget to give their child their medication and the risk of this incorrect use medication increases when the amount of intervals and/or different medications increases (Claxton, Cramer & Pierce, 2001). A study on the psychotropic medication use in 2007-2008 of 5,181 children with ASD reported that 35.3% of the children were using at least one psychotropic medicine and 9% of the children was using 3 or more concurrent psychotropic medications (Rosenberg et al., 2010).

Both the behavioral interventions as the pharmacological treatments have significant disadvantages in the fact that they both ask a lot of time and effort from parents. In addition, both treatments are rather nonspecific as they do not target a specific core symptom. As several studies have shown that social skill deficits might lie at the core of other symptoms in ASD, it might be more preferable to focus on this specific disabling symptom. It might be argued that "deficits in social skills' is still a relatively broad and non-specific symptom. However, studies have shown that these deficits are associated with very specific brain regions, such as the inferior frontal gyrus. By specifically targeting this brain region, a very specific treatment strategy could possibly be realized. Transcranial magnetic stimulation is a technique that is able to non-invasively stimulate the frontal lobe. In recent years, it has been explored and used in the treatment of various psychiatric disorders and several researchers have suggested that it might be a candidate tool to improve symptoms of ASD (Tsai, 2004; Hoppenbrouwers et al., 2008; Sokhadz et al., 2012).

Repetitive transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique and can be used to study the causal relationships between neuropsychology and behavior. TMS is based on Faraday's law of electromagnetic induction. A coil that consists

of copper wires is placed over the scalp and a large but brief electrical current flows through this coil (figure 3). This generates a strong, but short (~200 microseconds) magnetic field, which runs perpendicular to the plane of the coil. This magnetic field will cause a secondary, weaker, electric current in the superficial parts of the brain that is able to excite the underlying nerve tissue (Bohning, 2000).

The magnitude of the electric current that is needed to excite nerve tissue depends on the scalp-cortex distance and physiological properties of the stimulated tissue (Schutter, 2012). The intensity of TMS stimulation is taken as a percentage of the individual motor threshold (MT). The MT is the amount of stimulation over the primary motor cortex (M1) that is needed to excite motor neurons causing activation of the corticospinal tract and finger movement. Suprathreshold stimulation intensities (e.g., 110% MT) result in relatively spread activation pattern, whereas subthreshold stimulation (90% MT) produce more local effects (Strens et al., 2002). The strength of the magnetic field decays exponentially with distance, therefore only the first few centimeters of the cortex can be directly stimulated by TMS (Hallet, 2007). However, more distal regions can be stimulated indirectly by TMS because of signal propagation in brain networks (Schutter, 2012). The depth of the stimulation also depends on the type of coil that is used. Round coils are relatively powerful, but figure-of-eight shaped coils have a more precise magnetic field, because the electric current summate at the intersection of the two round segments (Hallet, 2007). The iron core coil, a modified eight-shaped coil wired around soft iron instead of air, allows greater strength and depth of penetration (Epstein & Davey, 2002) and is more focal due to the iron core. This allows for treatment strategies that target more specific brain regions.

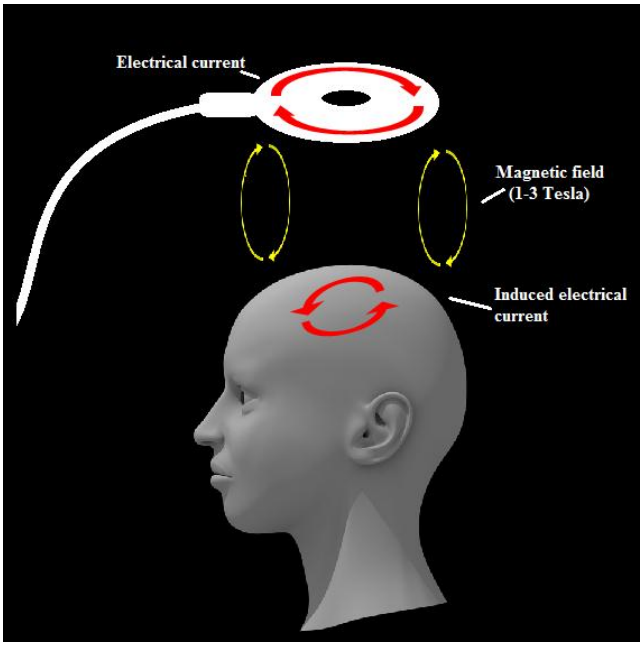

Figure 3. *Illustration of electrical currents and magnetic fields generated in the TMS procedure.*

The duration of the effects of single TMS pulse is usually very short. Nevertheless, when single pulses are applied in repetitive fashion in a particular frequency for a longer period (>10 min) the effects can outlast the stimulation period (Schutter, 2012), and may even

induce long term changes (Helfrich, 2012). So called repetitive TMS (rTMS) involves a train of magnetic pulse that can increase or decrease cortical excitability (Helfrich et al., 2012). High frequency rTMS, which is repetitive TMS at low frequencies (0-1 Hz) typically decreases cortical excitability whereas rTMS at higher frequencies (> 5 Hz) increase cortical excitability (Schutter, 2012). Because the effects of rTMS remain for a longer time window, rTMS provides a possible means for treating psychiatric and neurological diseases (Di Lazzaro et al., 2002; George et al., 1999).

The effectiveness of rTMS

RTMS protocols involve the clinical treatment of neuropsychiatric disorders such as migraines, strokes, Parkinson's disease and psychiatric conditions, mainly depression (Croarkin, Wall & Lee, 2011). Treatment with rTMS predominantly consists of multiple sessions of rTMS stimulation spread out over a certain amount of days or weeks. Therapy for depression has generally been directed to excitatory stimulation of the left dorsolateral prefrontal cortex (DLPFC), since neuroimaging studies have shown hypometabolism in that brain region in depressed patients (Hallett, 2007). A meta-analyses of 30 double-blind sham-controlled treatment trials reported a significant overall mean effect size of 0.39 (p<0.0001) for active treatment of the left DLPFC (Schutter, 2009). Most studies (50%) used a frequency of 10 Hz, but frequencies of 20 Hz were also common (33%). In the majority of studies (70%), the rTMS stimulation was administered at ten sessions. The meta-analysis showed that fast-frequency rTMS was superior to sham control TMS and might even be as effective as some of the available antidepressant medications. Correspondingly, a recent meta-analyses of Slotema et al. (2010) also observed a significant mean effect size (0.53; p<.001) for rTMS applied at the left DLPFC, compared to sham TMS. These effect sizes are reasonably high compared to the effect sizes reported for pharmacotherapy in depression, which range from 0.17-0.46 (Slotema et al., 2010). More importantly, these effect sizes indicate that rTMS is indeed capable of increasing cortical excitability in hypoactive brain regions, thereby reducing symptoms of depression (Croakin et al., 2010).

The finding that rTMS can increase cortical excitability has also been found in schizophrenia patients. A recent study on the association between schizophrenia and ASD has shown that there are moderate to large correlations (ranging from 0.30 to 0.50) between schizoid personality symptoms and ASD social deficits (Gadow, 2013). Therefore, findings from rTMS treatment in schizophrenia patients might also give insight in rTMS treatment

possibilities in individuals with ASD. Several neuroimaging studies have shown that the left temporal-parietal cortex (auditory cortex) is active during auditory verbal hallucinations in right handed schizophrenia patients (Shergill et al., 2000). Most rTMS protocols in schizophrenia therefore target this area with slow rTMS in order to reduce this activation. A meta-analyses on the effectiveness of rTMS on auditory verbal hallucinations (7 trials, 189 patients in total), reported a mean effect size of 0.54 ($p<.001$), indicating a moderate effect (Slotema et al., 2010). This finding corresponds to an earlier meta-analyses of Aleman, Sommer and Kahn (2007) that also reported moderate effect sizes. These results show that rTMS is a very promising technique in restoring altered brain activation and can be used as a treatment for some disorders.

In addition to improving specific symptoms of depression and schizophrenia, rTMS has also been suggested to enhance cognition in neuropsychiatric disorders (Demirtas-Tatlidede, Vahabzadeh-Hagh & Pascual-Leone, 2013). Recently, Schutter et al. (2010) reported significantly higher sensitivity for recognizing angry facial expressions after slow rTMS over the right parietal cortex, compared to sham rTMS, in patients with depression. Improvement of cognitive functions have also been reported in patients with schizophrenia. After 10 daily sessions of rTMS to the left DLPFC, Mogg et al. (2007) observed a beneficial effects on cognitive function, specifically on delayed recall, and a trend towards improvement on executive function, measured by the Stroop test. Interestingly, a study of inhibitory rTMS over the bilateral DLPFC on patients with high functioning ASD has also shown improvement in executive functioning, specifically in error monitoring and correction (Sokhade et al., 2012). Furthermore, a very recent double blind controlled study reported that bilateral deep rTMS over the DLPFC resulted in a significant improvement of social relatedness in adults with ASD (Enticott et al. in press). This study also showed a nearly significant reduction in social relating symptoms between measurements prior to the rTMS treatment and measurements after a one month follow up.

These findings indicate that rTMS can be a very useful technique in stimulating disrupted brain regions and thereby improve the symptoms that might result from these altered brain responses. In addition it has been proven to have beneficial effects on cognitive functioning. Therefore, rTMS might also be a valuable technique in treating the social skill deficits observed in ASD, by specifically targeting the IFG. The IFG is a brain region in the cortex and close to the scalp, making it a suitable candidate for targeting with TMS. High frequency rTMS stimulation over the IFG might result in an increase of cortical excitability. This in turn could result in more activation of the IFG and a better recognition of others'

emotions and thus improve social skills. Nevertheless, before jumping to conclusions on whether or not rTMS should be explored as a possible treatment strategy in ASD, there are several limitations, ethical considerations and safety issues that need to be taken into account.

Limitations, ethical considerations and safety issues

The first limitation of rTMS studies and trials is the blindness of these studies. In double-blind placebo controlled trials, the patients and clinical raters are blind to the stimulation condition. The physician that applies the stimulation, however, does know whether the patient is in the real rTMS trial or the sham rTMS trial. Although the interaction between physicians and patients is normally kept to a minimum, this may have influenced the outcome of treatments (Schutter, 2010). The attitude of the physician might reveal that the patient is in the active rTMS session and this knowledge could influence the expectations of the participant. In addition, participants could also be aware of the experimental condition if they have participated in previous rTMS studies and have been debriefed in the meantime. They might observe the difference between active rTMS and sham rTMS. This is of particular influence when the outcome measurements are self-reportage questionnaires. The participant might exaggerate his improvement, because he is aware that an improvement is expected in the active rTMS condition or vice versa, ignore improvements when they were in the sham condition.

A second and related limitation is the fact that good sham control conditions are difficult to establish. Some sham TMS conditions can also produce cortical stimulation (for an overview, see Lisanby et al. (2001)), making the interpretation of results of clinical trials more difficult. This also depends on whether or not the blinding of the study has been successful. Several studies have actually checked whether patients had remained blind during the treatment. Most participants were unsuccessful in guessing in which condition they were (Schutter et al., 2009). However, Mogg et al. (2008) reported that patients in the active rTMS condition were significantly better in determining in which experimental condition they were participating. These participants knew they were part of the active rTMS group, because their symptoms were improving. Of course, this problem exists not solely in TMS studies, since pharmacological trials can also improve symptoms and thereby reveal the experimental condition. Nevertheless, these factors, in combination with the fact that ideal sham conditions are difficult to establish makes it challenging for researchers to create a successful double blind study. Fortunately, several researchers are working on refining of sham control

conditions and with more sophisticated techniques being developed, this might be a problem of less concern in the future (Schutter, 2009). For example, George et al. (2010) developed a sham rTMS condition that consist of a similar coil with a metal inserted that blocks the magnetic field and with scalp electrodes that delivered matched somatosensory sensations. This sham condition was very successful since the clinical raters, patients and even the physician remained blind during the treatment trial.

The third limitation has to do with the duration of rTMS effects. Although it is clear that the effects of rTMS can outlast the stimulation period, there is no consensus about the duration of effects. The number of studies that conduct follow-up measurements after weeks or months is small. There are several studies that do find effects of rTMS treatment after a month (Bortolomasi et al., 2006) or even after 4.5 months (Bentwich et al. (2011)). However, to my knowledge, there are no meta-analyses or reviews that focus on the long term effects of rTMS.

In addition to these limitations, several safety and ethical considerations must be taken into account when examining rTMS as a potential treatment strategy. Over the past decade, numerous healthy subjects and patients with various neurological and psychiatric diseases have undergone TMS allowing for a better assessment of relative risks. The safety of TMS is supported by recent meta-analyses (for an example, see Janicak et al. (2008)). The most severe adverse effect of rTMS is the induction of seizures. Nevertheless, considering the large number of subjects and patients who have undergone rTMS studies and the small number of seizures, the risk of rTMS to induce seizures is certainly very low, less than 1% in typical controls. The risk of inducing seizures in epileptic patients, however, is slightly higher (1.4%, Bae et al., 2007) and this is also relevant for TMS treatment in individuals with ASD, since the comorbidity of epilepsy and ASD is estimated at 25-30%. When an individual with ASD has a comorbid diagnosis of epilepsy this does not necessarily mean rTMS treatment is unsafe. The potential benefits of rTMS treatment (i.e., improvement of social skills) might outweigh the downsides (inducing an insult) of such a treatment. However, the Safety of TMS Consensus Group has recommended rigorous monitored during rTMS trials for these patients (Rossi et al., 2009). For example, EEG monitoring for spread of excitation should be encountered, along with video recording of the TMS session to be able to analyze in detail the characteristics of a spell.

Caution must be taken especially in the combination of drugs and medication with TMS stimulation. Active central nervous system drugs can lower the seizure threshold. Intake of frequently prescribed medications in ASD, such as fluoxetine, fluvoxamine, reboxetine and

risperidone, form a relative hazard for application of rTMS due to their significant seizure threshold lowering potential (Rossi et al., 2009). RTMS treatment can be applied when participants are taking these types of medication, although monitoring (i.e., EEG during the TMS off-period to track epileptogenic activity) is of great importance. Intake of antipsychotic drugs such as clozapine and chlorpromazine and some of the tricyclic antidepressants, such as nortriptyline and doxepine, however form a strong potential risk when combined with rTMS. These drugs have a highly significant seizure threshold lowering potential and thereby increase the risk of seizures induced by rTMS (Rossi et al., 2009). In case an individual with ASD is using these latter drugs, it might be better to either stop taking these medicines when undergoing rTMS, or not go through with rTMS treatment at all.

Another potential side effect of rTMS treatment is damage to the auditory system (Rossi et al., 2009). When the TMS stimulating coil is energized, it can produce intense acoustic artifacts which can, depending on the type of TMS machine that is used, exceed 140 dB of sound pressure level (Counter & Borg, 1992). This is of special concern for children, since their canal resonance is different from adults and their smaller head size results in the TMS coil being closer to the ear. However, the majority of studies in which hearing protection, such as earplugs, is used report no change in hearing after TMS.

The most frequently reported side effects of rTMS applied in non-motor cortical areas are headaches (site pain) and neck pain. It has not been exactly clear what causes the headaches but it might be due to myalgia of the head muscles, since TMS induces muscle contraction. The pressure of the coil on the head and stimulation of the meninges could also result in site pain. The reported neck pain is probably due to the often uncomfortable positions the participant has to take during the rTMS treatment. Stimulating the IFG with TMS can produce contractions of facial muscles, which can be discomforting. Nevertheless, in the clinical trials of rTMS to date, only a small percentage (less than 2%) has dropped out of therapy due to this discomfort. Some studies have used a local injection of 1% lidocaine to reduce the painfulness (Bockart et al., 2008). This resulted in an overall reduction in pain intensity of 50%, but also resulted in hypersensitivity in some subjects. In addition, aspirin and acetaminophen are very effective in ameliorating pain associated with undergoing rTMS treatment.

In the case of children, special considerations need to be made. After all, ASD is a developmental disorder and positive outcome is associated with early intervention. Developmental changes in the central nervous system may affect susceptibility to adverse effects of TMS treatment. Developmental processes that have been suggested to play a role in

pediatric TMS safety are the maturation of the cerebral cortex, closure of the fontanels and growth of the external auditory canal (Rossi et al., 2009). These factors are of particularly interest in children younger than two years and the risk of adverse effects is suggested to decrease with age. However, in the absence of a large amount of data on the potential adverse effects of rTMS in children, the Safety of TMS Consensus Group maintains the previous guidelines (from the consensus conference of 1996, see Wassermann (1998)) that children should not be used as subjects for rTMS without compelling clinical reasons. Nevertheless, children with ASD suffer from severe social skill deficits and since there are no effective treatment strategies for these deficits, rTMS stimulation in children with ASD could be justified. RTMS stimulation might improve the social skills of children with ASD, which in turn could result in a better quality of life for children with ASD and their loved ones. The potential benefits of rTMS might outweigh the downsides of such treatment. It is therefore of great importance to conduct a pilot study that can give proof of principle.

Proposition rTMS pilot study protocol for improving social skills in ASD

Ideally, effects of rTMS treatment should be demonstrated in a small pilot study with a sample of children with ASD aged between 5 and 8, since this review has shown that there might be a critical period during these ages. These children should have no comorbid diagnosis with epilepsy, near use any active central nervous system drugs. Children participating in such a study must be patients with severe social skill deficits, so severe that they will almost certainly not benefit from regular therapies. The rTMS treatment will consist of local stimulation of the inferior frontal gyrus, thereby decreasing the hypoactivation of these region. By using stimulus intensities of 90% MT, the rTMS stimulation will be relatively focal and allows to specifically target the IFG (Strens et al., 2002).

As mentioned earlier, stimulation with frequencies of 10 Hz is safe and the most commonly used frequency in rTMS treatments. Furthermore, this frequency has been proven to have therapeutic effects (Schutter, 2010) and therefore might also be a favorable frequency for this pilot study. There has been consensus that the maximum safe duration of a single train of rTMS at 90%MT with a frequency of 10 Hz is 5 seconds (see table 4 in Rossi et al. 2009 (p. 2023)). A single train in this rTMS treatment will therefore consist of 5 s. on and 25 s. off. This consensus is obtained mostly from adult rTMS studies. This pilot study, however, is based on children, and to be absolutely sure that this stimulation train is safe, epileptogenic activity will be monitored with EEG during the 25s. off-period condition. Furthermore, the

rTMS treatment will consist of 30 trains, and one session will last for 15 minutes (total number of pulses: 1500 pulses). During treatment sessions, the left IFG will be stimulated first, and after a break of 2 hours, the right IFG will be stimulated by the same parameters. This session will be repeated for 10 sessions in total, (Schutter, 2010). Treatment sessions will be scheduled daily, therefore the intervention period will take 10 days. In an effort to succeed the blinding of the pilot study, the sham rTMS condition of George et al. (2008) that was discussed earlier in this review will be used.

Furthermore, reliable symptom rating scales such as the Social Responsiveness Scale (SRS) and the Autism Diagnostic Observation Scale (ADOS) need to be implemented before and after the study to measure whether social skills change after TMS. As an additional and more objective outcome measurement, the child version of 'reading the mind in the eyes' test (eyes-C; Chapman et al., 2006) will also be used. The 'reading the mind in the eyes' test is developed to measure subtle differences in social skills and is therefore a perfect outcome measurement for a small pilot study (Baron-Cohen & Jolliffe, 1997; Baron-Cohen et al., 2001). Ideally, this test will be performed as an fMRI task before and after the treatment and additionally at a two month follow up. In this way, information can be obtained on whether or not social skills improve, but also whether this is associated with increased activation of the IFG, and ultimately whether these changes consist over time. Figure 4 provides a schematic overview of the proposed pilot study protocol.

Pre-measurement (t=0)	Intervention 10 days	Post-measurement (t=1)	2 month follow up (t=2)
- Social responsiveness scale - ADOS - Eyes-C fMRI task	- Treatment days scheduled every day, making a total of 10 sessions - Treatment days consist of: - 15 minutes rTMS at the left IFG - 2 hour break - 15 minutes rTMS at the right IFG	- Social responsiveness scale - ADOS - Eyes-C fMRI task	- Social responsiveness scale - ADOS - Eyes-C fMRI task

Active rTMS: 10 Hz, 90% MT, 30 trains, 5 s. on/25 s. off (EEG monitoring)
Sham rTMS: sham condition developed by George et al. (2008)

Figure 4: *Schematic overview of the proposed pilot study protocol. Such a pilot study could provide proof of principle whether or not rTMS is applicable in the treatment of autism spectrum disorder. Abbreviations: ADOS: Autism diagnostic observation scale; Eyes-C: Child version of the reading the mind in the eyes test; IFG: inferior frontal gyrus; rTMS: repetitive transcranial magnetic stimulation.*

Conclusion

ASD is a life disabling disorder characterized by severe deficits in social skills. These deficits can have major implications for the quality of life of individuals with ASD and for their loved ones. Several neuroimaging studies have focused on social skills and social skill deficits have been associated with hypoactivation of the frontal lobes. In particular activation

of the IFG seems to be altered in children with ASD. The aim of this review was to reveal whether there is a theoretical basis for applying rTMS to improve social skills in ASD. Effect sizes show that rTMS treatment is successful in depression, as well as schizophrenia. This review has demonstrated that rTMS is a very promising technique and has potential in developing a more specific treatment strategy in ASD. For example, by stimulating the IFG with rTMS, the activation of this region might normalize, potentially resulting in an improvement of social skills. Such a specific treatment strategy might be more beneficial than the nonspecific therapies that are currently used in ASD. Although the duration of the effects of rTMS are not yet clear, rTMS treatment could certainly serve as an alternative maintenance therapy. An approach with rTMS would ask less time and effort of the parents and especially in children where medication does not seem to help, rTMS treatment could provide a possible alternative.

However, this review also discussed several limitations, ethical considerations and safety limits. Since there is not much known about the duration of the effects of rTMS, further research should include more follow-up measurements. Moreover, the risk of rTMS inducing seizures is slightly higher in patients with epilepsy and the prevalence of epilepsy in individuals with ASD is 25-30%. Furthermore, most individuals with ASD use medication which may increase the risk of seizure when treated with rTMS. However, the potential benefits of rTMS might outweigh these downsides. This review has therefore proposed a pilot study that could provide proof of principle.

In conclusion, the aim of the present review was to examine whether there is a theoretical basis for applying TMS to improve social skills in ASD. Although rTMS is proven effective in some disorders, more research is needed before rTMS can be considered a possible somatic treatment of ASD.

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