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Low-frequency repetitive transcranial magnetic stimulation modulates evoked-gamma power, event-related potentials, and behavior in autism spectrum disorders.

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LOW-FREQUENCY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION MODULATES EVOKED-GAMMA POWER, EVENT-RELATED POTENTIALS, AND BEHAVIOR IN AUTISM SPECTRUM DISORDERS

By

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B.A. University of Kansas, 2005

M.S. University of Louisville, 2009

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A Dissertation Approved on

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DEDICATION

I would like to dedicate this dissertation to my parents who from a young age instilled in me the everlasting value of education. I am eternally grateful for their love and support.

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I would like to thank Dr. Manuel Casanova for his mentorship and support throughout my training. I am forever indebted to Dr. Casanova's expertise and foresight in making my training a truly rewarding and productive experience.

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ABSTRACT

LOW-FREQUENCY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION MODULATES EVOKED-GAMMA POWER, EVENT-RELATED POTENTIALS, AND BEHAVIOR IN AUTISM SPECTRUM DISORDERS

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Evidence suggests that cortical minicolumns are reduced in size and increased in number in individuals with autism spectrum disorder (ASD), especially in the dorsolateral prefrontal cortex (DLPFC). More specifically minicolumns in individuals with ASD are narrower and contain less peripheral, neuropil space; this may cause an increase in the ratio of cortical excitation to inhibition and adversely affect the functional distinctiveness of minicolumnar activation. A lack of cortical inhibition may cause signal/sensory amplification which can impair functioning, raise physiological stress, and adversely affect social interaction in patients with ASD. Additionally, the DLPFC forms a circuit interconnected with many areas of cortex (e.g., anterior cingulate, orbitofrontal) and is involved in selecting a possible range of responses while suppressing inappropriate ones. Low-frequency (≤1Hz) repetitive transcranial magnetic stimulation (rTMS) has

been shown to increase inhibition of stimulated cortex by the activation of inhibitory circuits.

The baseline hypothesis was that individuals with ASD would show electroencephalopgrahic (EEG) and event-related potential (ERP) evidence of amplified cortical activity at early and late stages of visual processing as well as impaired indices of selective attention. The second hypothesis was that low-frequency rTMS would reduce augmented cortical responses at early stage and late stages of visual processing and improve selective attention and behavior in ASD.

The baseline findings indicate both ERP and evoked gamma activity are amplified and indiscriminative in ASD at early stages of visual processing which may reflect decreased 'signal to noise' due to decreased cortical inhibitory processing. Additionally, individuals with ASD showed evidence of compromised selective attention, and had a significantly higher rate of motor response errors. After low-frequency rTMS individuals with ASD showed significant reductions in augmented ERP responses at very early stages of visual processing and showed significant improvement in discriminatory EEG gamma activity. There was also evidence of improved ERP indices of selective attention and significant reductions in irritability and repetitive behavior. TMS has the potential to become an important therapeutic tool in ASD treatment and has shown significant benefits in treating core symptoms of ASD with few, if any side effects.

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CHAPTER 1: INTRODUCTION

Symptomatology

Autism was first described by Kanner (1943) and now is considered to be an etiologically heterogeneous and biologically determined developmental disorder characterized by severe disturbances in reciprocal social relations, impaired development of language and communication skills and by a limited repertoire of behavioral patterns with a restricted ability of abstraction (American Psychiatric Association, 2000; [DSM–IV–TR] 4th ed., text rev.). The term autism spectrum disorder (ASD) is used to encompass three conditions sharing a similar core symptomatology: Autism, Asperger syndrome, and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). Charman (2008) explains that all individuals with ASD share common behavioral characteristics: First, they have qualitative impairments in social interaction. These impairments are manifested by the use of nonverbal behaviors to regulate social interaction, a failure to develop peer relationships, a deficiency in the spontaneous sharing of interests and a lack of emotional reciprocity. Secondly, ASD patients show qualitative impairments in social communication. These deficits are generally indicated by delayed language development without nonverbal compensation, problems starting and sustaining conversations, stereotyped language, and a lack of imagination in their play. Thirdly, individuals with ASD show a limited compilation of interests, behaviors,

and activities. Impairments of this nature manifest themselves by an abnormal overfocus on certain topics, adhering to nonfunctional routines, the display of stereotyped motor mannerisms and a preoccupation with object parts rather than the complete whole. Finally, it has been reported that individuals with ASD have abnormal reactions to the sensory environment (Charman, 2008) and visuo-perceptual abnormalities (Happe′, 1999). Aversive reactions to visual, auditory, and tactile stimuli have been commonly recorded in autistic individuals (Casanova, Buxhoeveden, & Gomez, 2003). These are generally indicated by hyposensitivity or hypersensitivity and an extraordinary interest in certain sensations. In fact, according to Gomes, Pedroso, and Wagner (2008) sensory–perceptual abnormalities affect 90% of individuals with Autism.

Epidemiology

According to Blaxill (2004) the rates of autism spectrum disorder were reported to be <3 per 10,000 children in the 1970s and rose to >30 per 10,000 in the 1990s. The Centers for Disease Control and Prevention (CDC, 2006) summarized data from several studies on the prevalence rates of ASD ranging from 1 in 500 to 1 in 166, making it the sixth most common disability classification in the United States. In fact, the CDC (2007) suggested a prevalence of 1 in 150 (Coben, Clarke, Hudspeth, & Barry, 2008). Recently a study by Kogan *et al.*, (2009) estimated the prevalence of ASD to be 1 in 91 American children. ASD is four to seven times more likely to occur in boys than girls (CDC, 2002); among identical twins, if one child has an ASD, then the other will be affected about 60-96% of the time (Boyle & Alexander, 2005). The median age of ASD diagnosis is

currently between 4.5 and 5.5 years, but there is evidence that ASDs can often be identified at around 18 months (CDC, 2002).

Augmentation of Prefrontal White Matter

One of the most consistent gross anatomical findings in ASD has been an abnormal increase in brain volume. According to Courchesne, Carper, and Akshoomoff (2003) the autistic brain undergoes accelerated growth during the early postnatal period, and this is then followed by a period of deceleration in age-related growth. Amaral, Schumann, and Nordahl (2008) allude to four MRI studies indicating that children with autism between the ages of 18 months and four years have a 5%-10% abnormal enlargement of total brain volume (Hazlett *et al.*, 2005; Courchesne, *et al.*, 2001; Sparks, *et al.*, 2002; Ayland, Minshew, Field, Sparks, & Singh, 2002). Redcay and Courchesne (2005) recently reviewed past and present literature on abnormalities in head circumference, as well as recent developmental MRI studies of brain growth in autism; they found that the most rapid rates of increased deviation from normal brain size was within the first year of life and the greatest rates of decrease in deviation from normal were during middle and late childhood (Figure 1).

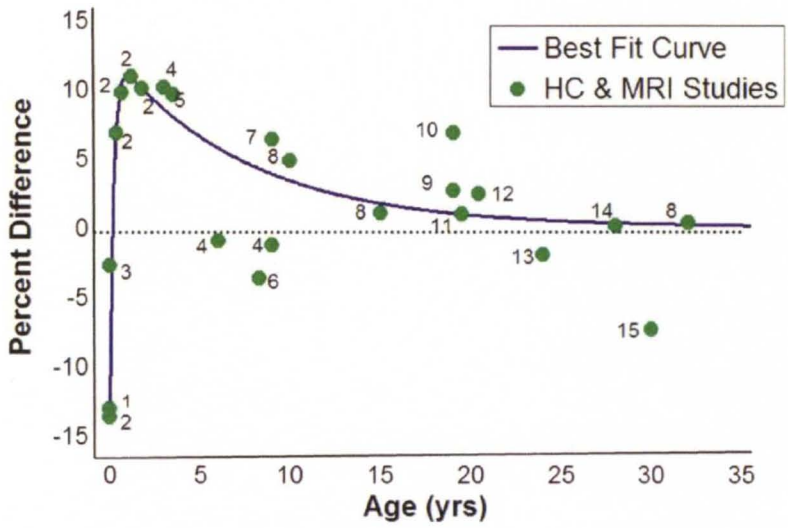

Figure 1: This figure illustrates a best fitted curve from 15 studies of head circumference (HC) and MRI percent difference (%Diff) from normal by age in Autism. % Diff values from all HC and MRI studies are plotted by the mean age of the study. The best fitted curve shows the most rapid rates of increased deviation from normal brain size in autism within the first year of life and the greatest rates of decrease in deviation from normal during middle and late childhood (Redcay & Courchesne, 2005).

Infants and toddlers with this disorder may suffer from a period of excessive brain growth that occurs during the first years of life, a period of time that coincides with the onset of autism symptoms. Further, this period of overgrowth is followed by an abnormally reduced rate of brain growth (Courchesne, 2004). According to Amaral *et al.* (2008) regional enlargements have been described in the frontal, temporal, and parietal lobes, but the largest and most consistent augmentations have been accounted for in the frontal lobes (Palmen *et al.*, 2005; Hazlett, Poe, Gerig, Smith, & Piven, 2006; Carper, Moses, Tigue, & Courchesne, 2002; Herbert *et al.* 2004). In their 2005 review Courchesne and Pierce (2005) report that brain volume is enlarged among autistic 2-4 year-old children especially in the dorsolateral subregion of the frontal cortex (Figure 2).

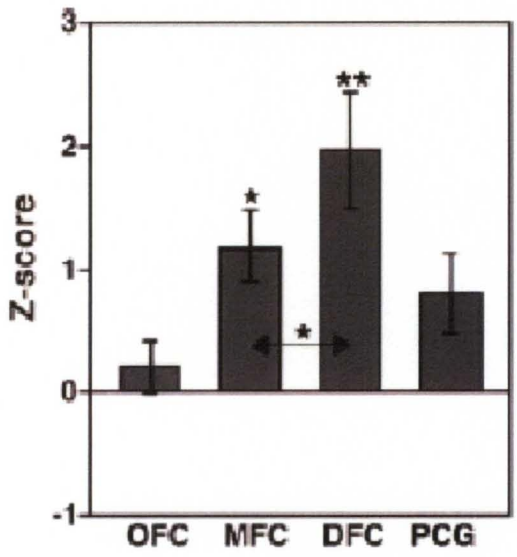

Figure 2: This figure shows abnormal enlargement of the dorsolateral frontal cortex and medial frontal cortex in 2-4-year-old autistic children. Volumes of each frontal region were converted to z-scores based on the means and standard deviations of normal children in the same age range. Z-scores therefore represent relative degree of deviation from normal. The mean is defined as 0 with a standard deviation of 1. $*p \leq 0.05$; $**p \leq 0.005$. OFC, orbitofrontal cortex; MFC, medial frontal cortex; DFC, dorsolateral prefrontal cortex; PCG, precentral gyrus (Courchesne & Pierece, 2005 from Carper & Courchesne, 2005)

Several studies have indicated that abnormal brain growth is due to disproportional increases in white matter as compared to gray matter (Herbert *et al.*, 2003; Hazlett *et al.*, 2005; Courchesne, *et al.*, 2001). Herbert et al. (2004) report that increased brain volume in autistics is primarily due to an augmentation of the prefrontal white matter, which contains mostly short corticocortical connections (Herbert et al., 2004; Jäncke, Staiger, Schlaug, Huang, & Steinmetz, 1997; Casanova, 2004). In their 2005 review Courchesne and Pierce report significantly increased frontal white matter volumes among autistic 2-4 year-old children (Figures 3).

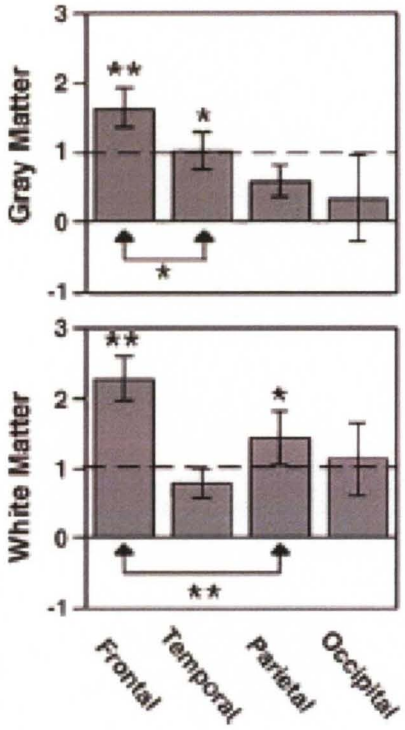

Figure 3: In autistic 2-4-year-old children frontal lobes have the most abnormal enlargement. For each white and gray matter region volumes were converted to z-scores for each autistic child based on means and standard deviations of the same age. '0' on the y-axis indicates the normal mean. Frontal and parietal white matter volumes were found to be significantly larger (asterisks) than normal among autistic 2-4-year-old children. Error bars are standard error of the mean for autistic children (Courchesne and Pierece, 2005)

Casanova (2007) suggests that additional white matter in autism is the result of an increased amount of short range association fibers which are required by an increased number of cortical minicolumns, and Courchesne and Peierce (2005) believe that this expansion of prefrontal white matter is connected to an overall reduction in long-range frontal-posterior reciprocal connections. Also there is evidence that interhemispheric connections may be compromised as Goldberg, Szatmari, and Nahmias (1999) have found a decreased size of the posterior corpus callosum is autism. Casanova et al. (2009) found that autistic patients manifested a significant reduction in the aperture for afferent/efferent cortical connections (i.e., gyral window), and the size of the gyral window directly correlated to the size of the corpus callosum. A reduced gyral window constrains the possible size of projection fibers and biases connectivity towards shorter corticocortical fibers at the expense of longer association/commisural fibers (Casanova et

al., 2009). There may be a bias in connectivity emphasizing shorter-range association fibers required by an increased number of cortical minicolumns, and this may be at the expense of longer commissural pathways, such as the corpus callosum (Casanova, 2007; Casanova, 2004).

In other words, it appears that the increased white matter in the frontal lobes of autistic individuals is correlated with an increase in short corticocortical connections (Herbert et al., 2004; Jäncke et al., 1997) and an increased number of cortical minicolumns (Casanova, 2007; Casanova, 2004). In addition, the increase in short corticocortical connections seems to be evident in autism at the expense of long range connectivity to complimentary brain regions (Casanova, 2007; Casanova et al., 2009). This disparity in connectivity is commonly believed to be the anatomical basis for the extraordinary, savant-like discriminative and calculative abilities of some individuals with ASD.

The Cortical Minicolumn

As discussed earlier, the augmentation of frontal lobe white matter in autism is associated with an increased number of cortical minicolumns. Mountcastle (2003) describes minicolumns as the basic anatomical and physiological unit of the cerebral cortex essentially correlating to small processing units. Minicolums consisist of vertical strands of perikarya forming a linear arrangement of single-cell columns orientated perpindicluar to the pial surface between layers VI and II (Buxhoeveden, Switala, Roy, &

Casanova, 2000); the core of the column and its immediate surroundings appear to contain most of the neurons, apical dendrites, cortical efferents, and corticocortical fibers, as well as unmyelinated axons and synapses (Peters & Setharis, 1996). A cell-poor area, or peripheral neuropil space, surrounds the linearly aggregated cells and is rich in unmyelinated axon fibers, dendritic arborizations, and synapses (Seldon, 1981). Myelinated axon bundles presumably are cortical efferents originating in pyramidal cells in layers II and III, and descend toward the white matter, lying within or adjacent to the cellular core of a column (Casanova, Buxhoeveden, Switala, & Roy, 2002b). Apical dendrites originating in layer V pyramidal cells ascend in bundles through or adjacent to the cell column core (Peters & Walsh, 1972). Patterns of lateral inhibition in the surrounding neuropil of the column maintain the vertical arrangement of cortical neurons into discrete units of function (i.e., minicolumns). (Seldon, 1981; Buxhoevedan et al., 2000); this neuropil space consists of several species of inhibitory interneuron cell bodies (i.e., double-bouquet, basket, and chandelier cells) as well as their projections and surround the stacking of the neuronal soma (Seldon, 1981; Mountcastle, 1997) (Figure 4).

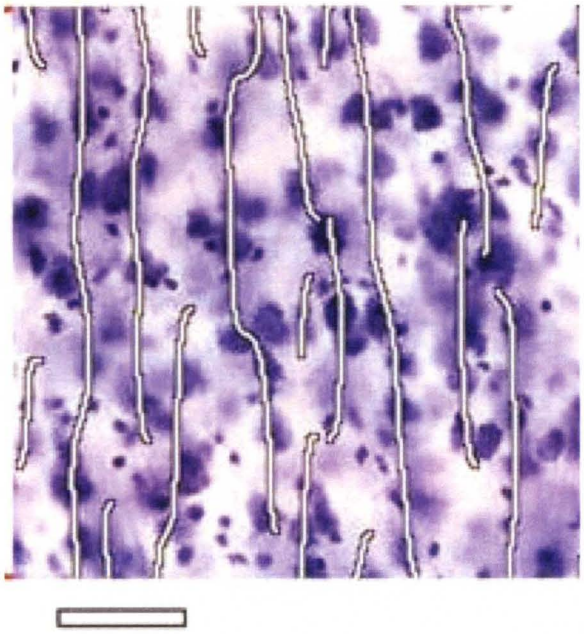

Figure 4: The minicolumn may be viewed as vertically-oriented aggregates of cell bodies interspersed by cell-poor areas, or neuropil space. This figure using Gallocyanin-stain illustrates minicolumns in Brodmann area 4, lamina III. The cores of the column are highlighted, and the scale bar measures 50 μm (Casanova et al., 2006b). By definition the minicolumn includes the peripheral neuropil space (Seldon, 1981).

The double bouquet cells are present in all layers of cortex and have axons that terminate upon both pyramidal cells and inhibitory inerneurons (Moutcastle, 1997); they impose a strong vertically directed stream of inhibition, and may also exert a vertically directed disinhibition of those pyramidal cells upon which those other inhibitory interneurons project (Moutcastle, 1997). The narrow vertical distribution of the double bouquet axons is so specific and restricted that it creates a narrow vertical cylinder of inhibition running geometrically perpendicular to the pial surface (Moutcastle, 1997; Douglas & Martin, 2004). Basket cells exert inhibitory control over pyramidal cell bodies while chandelier cells exert inhibitory control over initial axon segments (Moutcastle, 1997); unlike the double bouquet cells neither basket nor chandelier inhibitory interneurons maintain any constant cortical orientation (Douglas & Martin, 2004) (Figure 5).

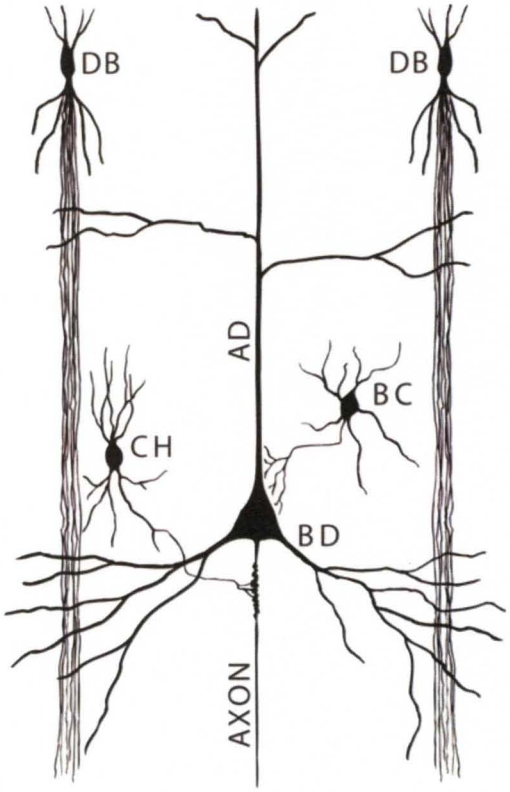

Figure 5: Illustration of inhibitory cells within columnar arrangements. Basket (BC) and Chandelier (CH) inhibitory interneurons do not maintain constant cortical organization within the neuropil of the cortical mincolumn. Double-bouquet (DB) inhibitory interneurons provide a vertical stream of inhibition (Mountcastle, 1997, 2003) surrounding the minicolumnar core and maintain a geometrically exact orientation perpendicular to the pial surface (Douglas & Martin, 2004; Mountcastle, 1997).

Minicolumnar inhibitory interneurons use gamma-aminobutyric acid (GABA) as a neurotransmitter and contribute to a circumferential zone of inhibitory and disinhibitory activity gating communication of the central minicolumnar core with surrounding areas (Casanova & Tillquist, 2008). While the minicolumn is a fixed anatomical structure and functional unit, it is not isolated. The minicolumn interacts with other columns, whether immediate neighbors or distant locations, forming larger units of function (Buxhoedevan et al., 2000; Mountcastle, 1997). The small groups of cells within columns may be activated as a subunit of the column, and the functional activity of columns may be studied at many levels including their structure as groups of oscillating neuronal activity (e.g., electroencephalography) (Buxhoedevan et al., 2000).

Within the context of autism there has been an increasing interest in the alteration of minicolumnar architecture in the cortex. In a 2002 post-mortem study Casanova et al. analyzed the minicolmnar morphometry of nine individuals with autism and nine age-matched controls in layer III of Brodmann areas (BA) 9, 21, and 22, which correlate respectively to the dorsolateral prefrontal cortex, middle temporal gyrus and the caudal two thirds of the superior temporal gyrus (Casanova et al., 2002b). In the photomicrographs of autistic individuals Casanova et al. (2002b) found a significantly narrower (P=0.034) minicolumnar width compared to controls and most of the decrease was due to a significant reduction of the peripheral neuropil space (P=0.007); the peripheral neuropil space was found by subtracting the width of the column core (defined as that part of the column that contains 90% of the cell bodies) from the center-to-center distance between adjacent columns (Casanova et al., 2002b). In addition, the number of minicolumns per image area was increased in autistic subjects relative to controls, and this corresponds to a greater gray level index or greater overall cell density (Casanova et al., 2002b). There was also an area by diagnosis interaction with the greatest minicolumnar width reduction appearing in the dorsolateral prefrontal cortex or BA 9 (Casanova et al., 2002b).

Also, in two 2006 post-mortem studies Casanova et al. examined the peripheral neruopil space in the minicolumns of six individuals with autism and six age matched controls in the following Brodmann's areas: 10 (frontopolar cortex), 11 (orbitofrontal cortex), 9 (dorsolateral prefrontal cortex), 4 (primary motor cortex; M1), 3b (primary sensory cortex; S1), 43 (frontoinsular cortex), 44 (ventrolateral cortex), 24 (anterior cingulate cortex), S1 (primary somatosensory cortex), and 17 (primary visual cortex; V1)

(Casanova et al., 2006ab). Both studies were consistent with prior results by finding reduced neuropil space in the dorsolateral prefrontal cortex (BA 9) (Casanova et al., 2006ab). For photomicrograph comparisons of lamina III of the right DLPFC in an autistic male and age-matched male without autism see figure 6. For an example of photomicrographs with minicolumnar cores highlighted in an autistic patient and an age-matched control see figure 7.

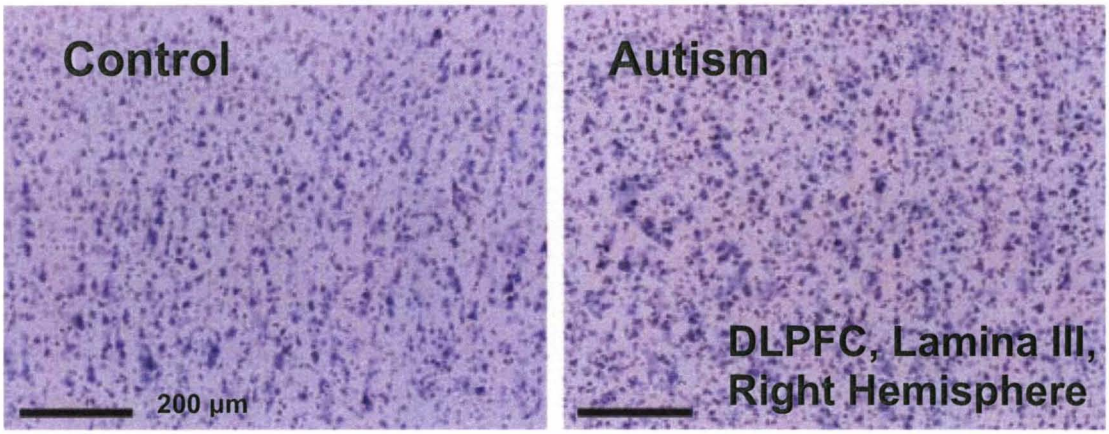

Figure 6: Nissel stained micrographs of lamina III of the right dorsolateral prefrontal cortex (DLPFC) in autism and control. Left: cortical area 9, right hemisphere, lamina III from a 25-year-old man without autism Right: the same region from a 24-year-old autistic man. In the micrograph of the autistic individual there are more minicolumns per image area and there is less space between columns. Scale bars measure 200µm. (Casanova, 2007).

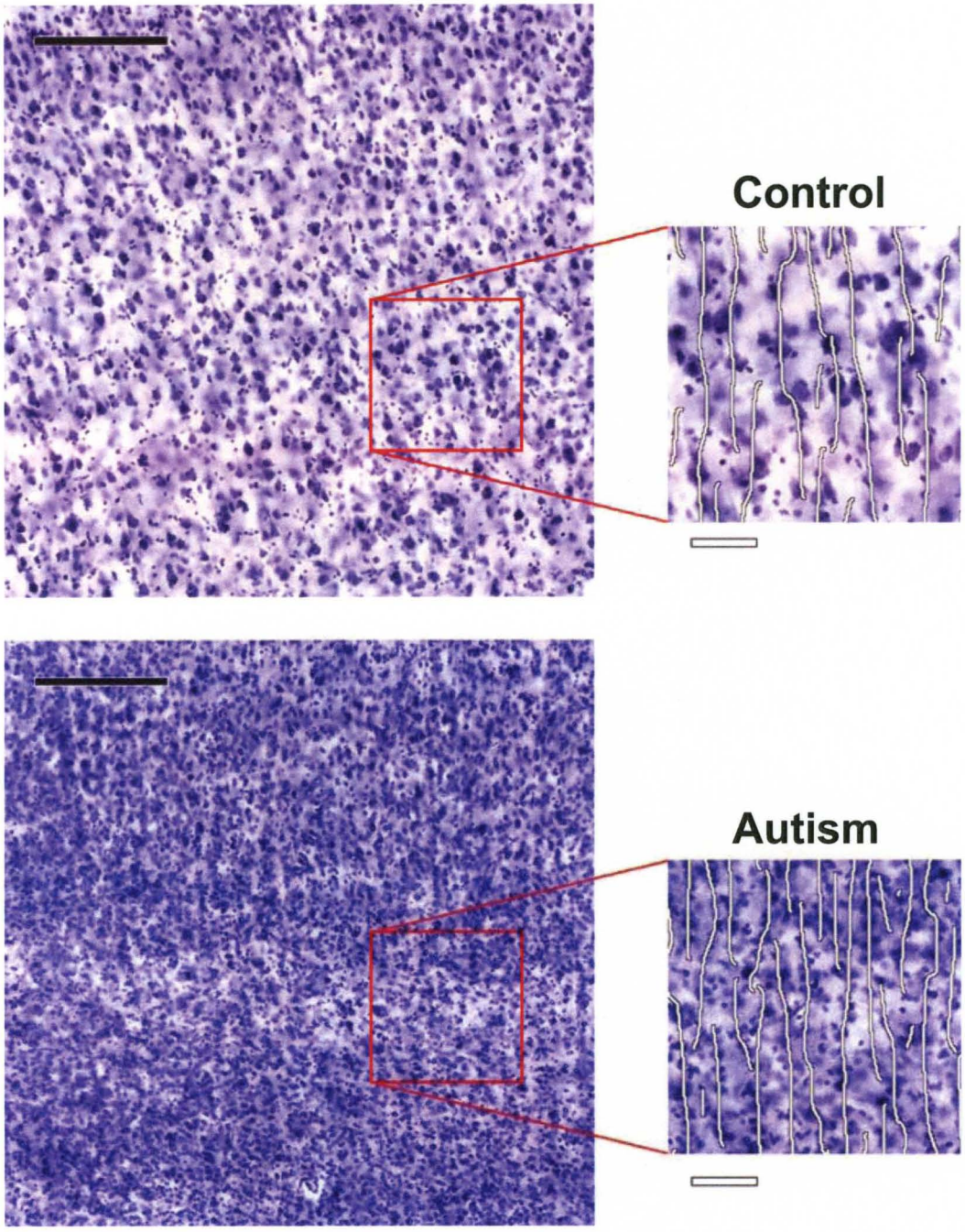

Figure 7: Gallocyanin-stain micrographs of minicolumns in Brodmann area 4, lamina III, in an autistic patient (bottom) and an age-matched control (top). Insets highlight the cores of minicolumn illustrating the reduction in minicolumnar width. Scale bars measure 200 μm on left and 50 μm on right. (Casanova et al., 2006b).

Function and Connectivity of the Dorsolateral Prefrontal Cortex

The dorsolateral prefrontal cortex (DLPFC) lies on the anterior part of the frontal lobe on the lateral side of the prefrontal region; it includes Brodmann's areas 9 and part of 46 (Figure 8). Historically, damage to the DLPFC resembled the effect of lesions to many subcortical areas, and this discovery along with the examination of neuronal connections lead to the discovery of the dorsolateral prefrontal circuit (Tekin & Cummings, 2002).

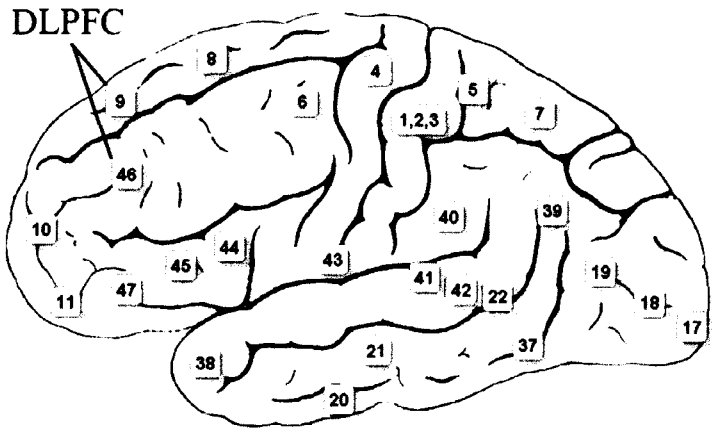

Figure 8: The doroslateral prefrontal cortex (DLPFC) (BA 9 & BA 46) lies on the lateral side of the prefrontal region directly in front of motor (BA 4), premotor (BA 6), and frontal eye field (BA 8) areas. BA=Broadmann's Area

The DLPFC circuit originates in the DLPFC and projects to a part of the striatum called the dorsolateral head of caudate nucleus. From this region neurons project to the lateral mediodorsal part of the globus pallidus interna and to the rostrolateral part of the substantia nigra. The neurons then move on to the parvocellular portions of the ventral anterior and mediodorsal thalamus and finally project back to the DLPFC (for a summary, see Tekin & Cummings, 2002). This sequence represents one of five circuits: The other circuits are the lateral orbitofrontal circuit, the anterior cingulate circuit, the

motor circuit, and the oculomotor circuit. All of these circuits project from the DLPFC and then traverse to the striatum, to the globus pallidus and substantia nigra, and then to the thalamus before returning to the DLPFC (Alexander, DeLong, & Strick, 1986). Figure 9 shows an example of the anatomy of the dorsolateral prefrontal circuit and its connectivity to the lateral orbitofrontal circuit (Figure 9).

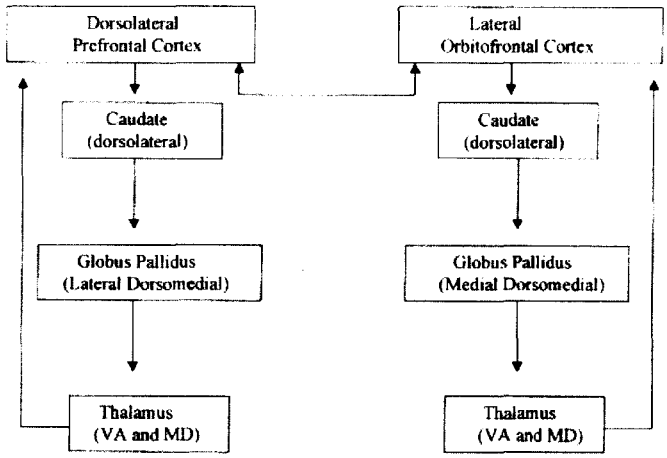

Figure 9: The anatomy of the dorsolateral prefrontal circuit and its connectivity to the lateral orbitofrontal circuit. The other circuits of the DLPFC (i.e., anterior cingulate, motor, and oculomotor) are analogous. VA= ventral anterior; MD= mediodorsal. (Tekin & Cummings, 2002)

The fibers in each circuit originating from the DLPFC are mediated by excitatory glutamatergic neurotransmission and project to the striatum. Projections from the striatum to the globus pallidus and substantia nigra are mediated by GABA and are inhibitory. Projections from these regions to the thalamus are also mediated by GABA and are inhibitory. Finally, projections from the thalamus to the frontal cortex are excitatory, and are mediated by glutamate (see Tekin & Cummings, 2002).

According to Ward (2006) the left DLPFC is involved in selecting a possible range of responses while suppressing inappropriate ones as well as manipulating the contents of working memory. The right DLPFC is involved in vigilance, sustained attention, and

monitoring information held in mind in conditions of uncertainty (Ward, 2006). Gray, Chabris, and Braver (2003) suggest the DLPFC processes attentional components of working memory, oversees decisions, and directs attention in a controlled manner (i.e., selective attention): Selective attention can be defined as the ability to focus on task-relevant goals while excluding salient distracters (Matzel & Kolata, 2009). Gehring and Knight (2002) propose that one of the perceptual benefits afforded by the DLPFC is an inhibition of stimulations occurring on task irrelevant perceptual channels.

According to Casanova et al. (2002ab, 2006ab) the DLPFC in autism contains an increased amount of cortical minicolumns and these minicolumns have a significantly reduced amount of peripheral neuropil space. A lack of appropriate neuropil space and associated lateral inhibition (Seldon, 1981; Mountcastle, 1997) may adversely affect the functional distinctiveness of minicolumnar activation and could result in enhanced localized activation in the context of a lack of associated inhibition (Rippon, Brock, Brown, & Boucher, 2007). In other words, an alteration in the balance between cortical excitation and inhibition at the level of the cortical minicolumn may amplify and distort cortical activation patterns leading to an increase in cortical 'noise'. In such over-wired networks signal is insufficiently differentiated from noise or task-irrelevant information, and as a result information capacity is drastically reduced (Belmonte & Yurgelun-Todd, 2004; Rubenstein & Merzenich, 2003).

Higher-than-normal noise in cortical processes also affects normal development of differentiated representations, because cortical response selectivity in space and time is a product of balanced inhibitory and excitatory processes (Casanova, 2006a). Such over-representations by non-differentiated systems could plausibly account, for example, for

the strong aversive reactions to auditory, tactile, and visual stimuli that are commonly recorded in autistic individuals (Casanova, 2006a). Behaviorally speaking signal/sensory amplification may impair functioning, raise physiological stress, and adversely affect social interaction in patients with ASD (Ratey, 1997).

Although interneurons are at the periphery of the minicolumn they play a prominent role in finely tuning cortical information processing (Levitt, Eagleson, & Powell, 2004; Casanova & Tillquist, 2008). For example, in mice targeted mutations reducing the number of GABAergic cells manifested seizures and complex behavioral disturbances (Levitt et al., 2004). The phenotypic spectrum of these targeted mutations suggests a connection between GABAergic abnormalities and the pathophysiology of autism and other neurodevelopmental disorders (Levitt et al., 2004; Casanova & Tillquist, 2008). Specifically within the prefrontal cortex disturbances in information processing provide for a brain which is less equipped to use learning as an adaptive strategy and has diminished resources (plasticity) to handle social interaction/behaviors (Duffy & Cambell, 1994; Casanova et al., 2006a). In fact, it has been shown that the prefrontal cortex interconnects with every distinct functional unit of the brain (Nauta, 1972) and the widely distributed network of connectivity accounts for the phenomenon of frontal lobe diaschisis, i.e., executive cognitive deficits in lesions distant to the anterior cortical region (Mesulam, 2002; Casanova et al., 2006a). The many connections of the prefrontal cortex are essential for 'dissociating appearance from, significance, grasping changes of context, shifting from one mental set to another, assuming multiple perspectives, and comparing potential outcomes of contemplated actions' (Mesulam, 2000, p. 48; Casanova et al., 2006a).

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) allows scientists to stimulate the brain noninvasively in alert, awake patients. The first TMS device that could stimulate focal regions of the brain was developed in Sheffield, England by A.T. Barker and colleagues in 1985 (Barker, Jalinous, & Freeston, 1985). TMS operates based on Faraday's law of electromagnetic induction (1831) which describes the process by which electrical energy is converted into magnetic fields and vice versa. The TMS apparatus achieves the induction of a magnetic field by using a power supply to charge capacitors which are then discharged through the TMS coil, and this creates a magnetic field pulse. The principle of electromagnetic induction proposes that a changing magnetic field induces the flow of electric current in a nearby conductor--in this case the neurons below the stimulation site. Typically TMS coils are designed to produce magnetic fields in the range of 1 tesla (T) which is powerful enough to cause neuronal depolarization: If the resting membrane potential (RMP) of a neuron, about -70mV, is depolarized to about -40mV, NA^+ channels open initiating an action potential (George & Belmaker, 2007). The focal point of stimulation is about 1 cm^2 in area, and maximal induction is proposed at 90 degrees to the magnetic field. In body tissue the magnetic field induces a perpendicularly orientated electric field, or voltage difference, and charge is moved across an excitable cellular membrane creating a transmembrane potential (see George & Belmaker, 2007). We theorize that contrary to other inhibitory cells (i.e., basket and chandelier), whose projections keep no constant relation to the surface of the cortex, the geometrically exact

orientation of double-bouquet cells and their location at the periphery of the minicolumn (inhibitory surround) makes them an appropriate candidate for induction by a magnetic field applied parallel to cortex (Baruth et al., 2010a) (Figure 10).

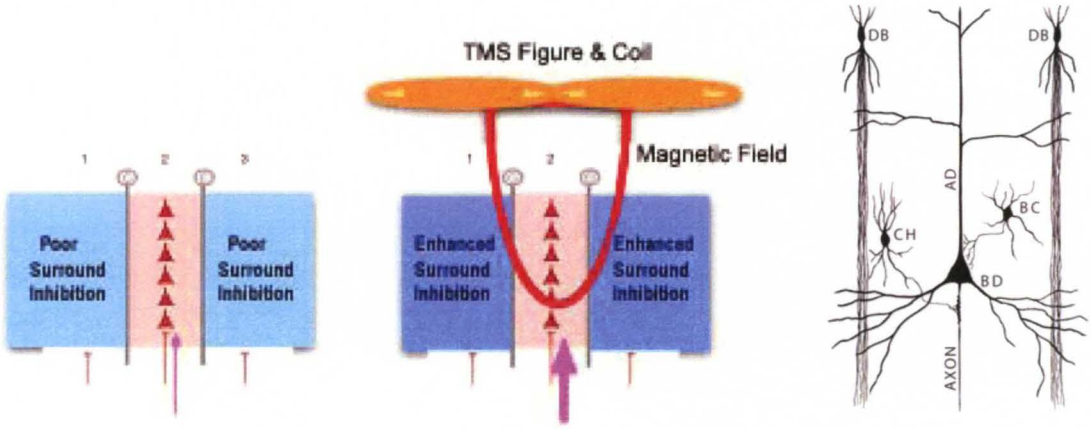

Figure 10: We theorize that contrary to other inhibitory cells (i.e., basket and chandelier), whose projections keep no constant relation to the surface of the cortex, the geometrically exact orientation of double-bouquet cells and their location at the periphery of the minicolumn (inhibitory surround) makes them an appropriate candidate for induction by a magnetic field applied parallel to cortex. CH=Chandelier; BC=Basket; DB= Double-Bouquet

TMS can be administered in a single-pulse manner where single or paired pulses are delivered non-rhythmically and not more than once every few seconds or repetitively (rTMS) where pulses are delivered at specific frequencies in trains with precise inter-train intervals (ITI). Generally, single-pulse TMS is used for physiological research or diagnostic purposes while rTMS is used to alter the excitability and function of targeted areas of cortex. rTMS can be divided into low-frequency rTMS (≤1Hz) and high-frequency rTMS (>1Hz), which categorically affect cortical excitability in different ways. Studies have shown that low-frequency or 'slow' rTMS (≤1Hz) increases inhibition of

stimulated cortex (e.g., Boroojerdi et al., 2000; Chen et al., 1997; Maeda et al., 2000; Muellbacher et al., 2000; Ziemann, 2004), whereas high-frequency rTMS (>1Hz) increases excitability of stimulated cortex (e.g., Di Lazzaro et al., 2002; Maeda et al. 2000; Pascual-Leone et al., 1994; Ziemann, 2004). For example, Chen et al. (1997) reported that there was a 19.5% decrease in motor-evoked potential amplitude (MEP) following 15 minutes of low-frequency rTMS application (0.9Hz) to the primary motor cortex, and this lasted for at least 15 minutes in healthy volunteers. Furthermore, Maeda et al. (2000) reported significant inhibition of MEPs immediately following 1 Hz rTMS stimulation of the primary motor cortex ($P<0.001$) and significant facilitation of MEPs immediately following 20 Hz rTMS stimulation of the primary motor cortex ($P<0.001$) in healthy volunteers.

rTMS is a simple outpatient procedure lasting approximately 30 minutes. Patients are seated in comfortable, reclining chair and are fitted with a swim cap to outline the TMS coil position and aid in its placement for each session. Before the procedure begins the 'motor threshold' is determined in each patient. 'Motor threshold' is the intensity of the pulse delivered over the motor cortex that produces a noticeable motor response (George & Belmaker, 2007). Sensors are applied to the hand muscle (i.e., the first dorsal interosseous) opposite the site of stimulation and motor responses are monitored with physiological monitoring tools. The output of the machine is gradually increased by 5% until a 50μV deflection of the electromyograph or a visible twitch of the muscle is observed (George & Belmaker, 2007). Once the patient's 'motor threshold' is determined the coil is moved to the site of stimulation (e.g., the DLPFC) and the pulse intensity is

adjusted relative to the patient's 'motor threshold'. Common dosing schedules include one to two visits per week.

TMS is generally regarded as safe without lasting side effects. Reported side effects include a mild, transient tension-type headache on the day of stimulation and mild discomfort due to the sound of the pulses (Ward, 2006); earplugs are recommended especially at higher frequencies of stimulation. Given the modulatory effect of rTMS on cortical excitability, there is a very small risk of inducing a seizure with rTMS (see Wasserman, 1996). Given this risk, participants with epilepsy or a family history of epilepsy are generally excluded of rTMS studies, and as a safety precaution, most rTMS studies adjust the stimulation intensity below the participants 'motor threshold' (e.g., 90% of motor threshold). rTMS is generally considered safe for use in pediatric populations, as no significant adverse effects or seizures have been reported (see Quintana, 2005 for review)

Putative Mechanisms of Low-Frequency rTMS

As stated earlier, a number of studies, mainly on the primary motor cortex, have indicated that low-frequency or 'slow' rTMS (≤1Hz) increases inhibition of stimulated cortex (e.g., Boroojerdi et al., 2000; Chen et al., 1997; Maeda et al., 2000; Muellbacher et al., 2000; Ziemann 2004), whereas high-frequency rTMS (>1Hz) increases excitability of stimulated cortex (e.g., Di Lazzaro et al., 2002; Maeda et al. 2000; Pascual-Leone et al., 1994; Ziemann, 2004).

The parameter of frequency in direct electrical stimulation has been shown to parallel the effects of frequency in rTMS stimulation (Post et al., 1997, 1999). Higher – frequency direct electrical stimulation (>10 Hz) of neural tissue has been shown to produce long-term potentiation of transsynaptic signal propagation as well as the kindling of seizures. In contrast low- frequency direct electrical stimulation (1-5 Hz) has been shown to curtail synaptic transmission and is called long-term depression (see Hoffmann and Cavus, 2002). For example, in human neocortical slices long-term depression can be induced with low-frequency (1Hz) 15-minute stimulation of layer IV afferents, and long-term potentiation can be induced with high-frequency stimulation (40-100Hz) (Hoffmann and Cavus, 2002).

Low-frequency direct stimulation has also been shown to reverse high-frequency induced potentiated synaptic responses; this is a phenomenon referred to as 'depotentiation,' whereby synaptic weights are 'reset' to baseline levels; this has been proposed as the most relevant model for understanding the inhibitory effect of low-frequency rTMS (Hoffmann and Cavus, 2002). For example, in slices of human temporal cortex 1-Hz electrical stimulation has been shown to depotentiate already potentiated synapses (Chen et al., 1996). Also, low-frequency electrical stimulation has been shown to depotentiate hippocampal long-term potentiation in rodent in vivo models (Kulla, Reyman, & Mahan-Vaughan, 1999; Staubli & Scafidi, 1999).

Furthermore, it has been shown that both direct electrical stimulation and rTMS can contribute to naturally occurring neuroplasticity. Bliss and Gardner-Medwin (1973) showed that hippocampal long-term potentiation can endure over many weeks in unanesthetized rabbits with repeated stimulation trains. A number of more recent studies

have indicated that long-term depression is inducible with direct 1 Hz stimulation in the hippocampus and cortex of freely moving rats that can last for several days (Heynen, Abraham, & Bear, 1996; Manahan-Vaughan & Braunewell, 1999; Froc, Chapam, Trepel, & Racine, 2000). In awake cats 1-Hz stimulation of the amygdala has been shown to cause depotentiation that lasted for several days with synaptic efficacy returning to a potentiated state roughly 70 days later (Adamec, 1999). Also, daily 1-Hz electrical stimulation of the amygdala for 15 minutes over a week succeeded in suppressing kindled seizures in this brain region for 21 days (Weiss, Xiu-Li, Rosen, Li, Heynen, & Post, 1995). Similiarily in TMS Chen et al. (1997) showed that the suppressive effects of low-frequency rTMS on motor evoked potentials lasted up to 30 minutes after stimulation and Speer et al. (2000) found reduced cortical activation 3 days after a protocol of 1-Hz rTMS in depressed patients.

Additionally a number of studies have indicated that both low frequency direct electrical stimulation and low frequency transcranial magnetic stimulation not only modulate regions proximal to stimulation but can induce transsynaptic effects presumably by functional connections. For example, low frequency rTMS of the left primary cortex reduces motor evoked potentials elicited by single-pulse TMS administered to the right primary motor cortex, which was putatively mediated by transcallosal projections (Wasserman, Wedegaertner, Ziemann, George, & Chen, 1998). Also, low-frequency rTMS application to the premotor cortex was shown to reduce motor evoked potentials elicited by the primary motor cortex (Gerschlager, Siebner, & Rothwell, 2001) and Bohning et al. (1999) demonstrated increased activation both locally and in distant sites by using functional magnetic resonance imaging (fMRI) interleaved with 1-Hz rTMS of

the motor cortex. As is evident low-frequency rTMS is analogous to low-frequency direct electrical stimulation in many respects. It may putatively be inferred that rTMS may operate by selectively depotentiating enhanced synaptic weights associated with pathological conditions and is capable of modulating functionally interconnected regions.

At the level of the single neuron as well as at subcellular and molecular levels relatively little is known about the inhibitory mechanism of action of low-frequency rTMS (George & Belmaker, 2007). However, it has been proposed that the effect of 'slow' rTMS arises from increases in the activation of GABA-dependent inhibitory interneuronal circuits (Pascual-Leone, Walsh, & Rothwell, 2000), and there is some speculative evidence this inhibitory activity may be mediated by GABA-B receptors. Gamma- aminobutyric acid (GABA) mediates synaptic inhibition in the brain and is modulated by a powerful uptake system that limits the spatial diffusion of GABA and the duration of inhibitory postsynaptic potentials (IPSPs) (Isaacson, Solís, & Nicoll, 1993). GABA-A receptors mediate a short-lasting Cl^- dependent component of stimulation induced inhibitory IPSP whereas GABA-B receptors mediate a longer-lasting K^+ dependent component (McCormick, 1992).

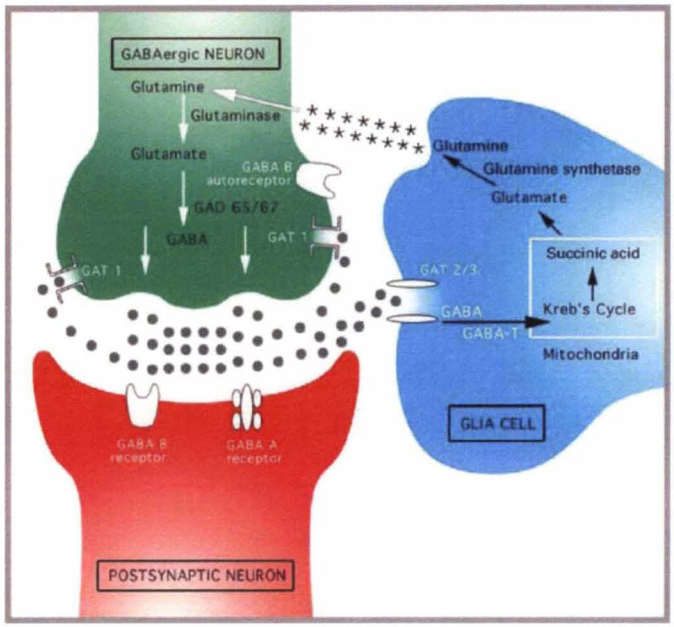

Figure 11: Little is known about the inhibitory mechanism of low-frequency rTMS. However, it has been proposed that the effect of 'slow' rTMS arises from increases in the activation of GABA-dependent inhibitory interneuronal circuits (Pascual-Leone et al., 2000), and there is some speculative evidence this inhibitory activity may be mediated by GABA-B receptors (George & Belmaker, 2007) (Figure from Brambilla et al., 2003)

A conditioning cortical magnetic pulse (S1) either inhibits or facilitates the amplitude of a motor evoked potential (MEP) following a test stimulus (S2) depending on the interstimulus interval (Kujirai, et al. 1993). It has been shown that at very short interstimulus intervals (e.g., 40 ms) the test MEP is facilitated by S1 whereas at longer interstimulus intervals the MEP is inhibited (Claus, Weis, Jahnke, Plewe, & Brunhölzl, 1992; Valls-Solé, Pascual-Leone, Wassermann, & Hallett, 1992); this is termed long-interval intracortical inhibition (LICI). There is evidence that LICI relates to activity at the GABA-B receptor as McDonnell, Orekhov, and Ziemann (2006) observed that intrathecal administration of the GABA-B receptor agonist Baclofen potentiated LICI. It may be plausible to speculate that at higher frequencies rTMS may suppress the inhibitory activity of double-bouquet inhibitory interneurons selectively allowing excitatory drive to pyramidal cell outputs; whereas at lower frequencies (e.g., 1 Hz) inhibitory activity may be expressed in double-bouquet inhibitory interneurons due to the temporal specifics of these intracortical inhibitory mechanisms. However, more studies in

animals are necessary to further elucidate the mechanism of rTMS at the cellular and subcellular levels.

CHAPTER 2: EARLY AND LATE EVENT-RELATED POTENTIALS

Introduction

Research methods measuring brain activity roughly fall into two categories: 'electromagnetic' approaches that measure the activity of the brain directly by recording electromagnetic fields generated by neuronal populations, and 'hemodynamic' approaches that indirectly measure the activity of the brain by recording changes in vascular variables that are linked to changes in neural activity (Handy, 2005). Functional electrophysiology consists of the use of event-related potentials (ERPs), which represent scalp-recorded, transient changes in the electrical activity of the brain in relation to the onset of a stimulus, and provide a neurobiological measure of perceptual and cognitive processing. Compared to other functional imaging methodologies, such as fMRI and PET, ERPs are unique in that they provide the necessary temporal resolution to fully characterize the transient reorganization of coupled neuronal populations on a millisecond timescale (Rippon, et al. 2007). In fact, according to Jeste & Nelson (2009) of neuroimaging tools used to elucidate brain circuitry, functional electrophysiology stands alone in the capacity to characterize early (i.e., in infancy) neural markers and endophenotypes (Jeste & Nelson, 2009), i.e. measures of abnormalities intermediate between genotypic vulnerability and the clinical expression of a disorder (Gottesman & Gould, 2003). Additionally, ERP recording is non-invasive and in some cases may be

acquired without attention or response requirements making them a useful diagnostic implement in young populations (Paavilainen, Tiitinen, Alho, & Näätänen, 1993).

ERPs consist of component waveforms spanning from as early as 50 ms post-stimulus to up to 600-1000 ms post-stimulus. For example, in the components N100 and P200 the letter indicates the polarity and the number indicates the period after onset of the stimulus, i.e. 100 is in the 100-200 ms period (or earlier) and 200 is in the 200-300 ms period (Luck, Heinze, Mangun, & Hillyard, 1990; O'Donnel, Swearer, Smith, Hokama, & Mccarley, 1997). Generally components in the first 50- 200 ms are considered early, exogenous field potentials reflecting 'pre-attentive' processes and the processing of physical attributes of a stimulus (Coles & Rugg, 1995; Herrmann & Knight; 2001) while those after 200 ms represent endogenous field potentials reflecting polymodal associative processing and later stage attentional processes (e.g. sustained attention, perceptual closure) (Pritchard, 1981; Picton, 1992; Polich, 2003).

Inferences may be made concerning the neural sources of ERP components based on the behavior being tested. For example, in a paradigm requiring explicit memory, one may assume that part of the generated ERP component reflects hippocampal function (Jeste & Nelson, 2009). Also, patients with brain lesions can allow researchers to make inferences about ERP source generation by evaluating changes in ERP components when specific brain structures are dysfunctional (Nelson, Collins, & Torres, 1991).

Auditory processing abnormalities have been widely examined in ASD using ERPs (see Bomba & Pang, 2004 for review). Briefly, individuals with ASD have been shown to have normal brainstem auditory evoked potentials (AEPs) (Klin, 1993; Rosenhall, Nordin, Brantberg, & Gillberg, 2003). However, the most consistently

reported auditory ERP abnormality is attenuated amplitude of the centroparietal P300 in various auditory stimulus presentation paradigms in ASD patients of all ages (Bruneau, Garreau, Roux, & Lelord, 1987). Also, the short-latency fronto-central N100 has reliably been found to be attenuated in amplitude and latency during tasks involving target detection and tones of varying frequency and intensity (Lincoln, Courchesne, Harms, & Allen, 1995; Bruneau, Roux, Adrien, & Barthelemy, 1999; Oades, Walker, Geffen, & Stern, 1988; Ferri et al., 2003). Furthermore, the mismatch negativity (MMN), a large negative deflection occurring when frequent stimuli are subtracted from infrequent stimuli, has commonly been found to be prolonged in latency in response to pitch deviants (Seri, Cerquiglini, Pisani, & Curatolo, 1999; Jansson-Verkasalo et al., 2003; Lepistö et al., 2005).

ERP studies of visual processing commonly employ an 'oddball' discrimination task of selective attention in which the participant responds to an infrequent target stimulus among more frequent non-target stimuli (Vohs et al., 2008). Most investigations into visual processing in ASD have focused on higher-level, long-latency ERPs, like the P300 (Courchesne, Courchesne, Hicks, & Lincoln, 1985a; Courchesne, Lincoln, Kilman, & Galambos, 1985b; Courchesne, Lincoln, Yeung-Courchesne, Elmasian, & Grillon, 1989; Verbaten, Roelofs, van Engeland, Kenemans, & Slangen, 1991; Kemner, van der Gaag, Verbaten, & van Engeland , 1999; Towensend et al., 2001; Hoeksma, Kemner, Kenemans, & van Engeland, 2006). The P300 can be divided into the attention-orienting frontal P3a component and the sustained-attention centro-parietal P3b component (Katayama & Polich, 1998; Polich, 2003). Briefly the centro-parietal P300 amplitude (i.e., P3b) has been found to be similar (Courchesne, et al. 1985ab, 1989; Hoeksma et al.,

2006) reduced (Verbaten et al., 1991; Towensend et al., 2001) and augmented (Kemner et al., 1999) in ASD patients to target stimuli compared to controls. There have been fewer studies on early-stage (i.e., 50-200 ms) visual processing (see Jeste & Nelson, 2009 for review) especially in comparison to other psychopathologies like schizophrenia (e.g., Doninger et al., 2000; Foxe, Doninger, & Javitt, 2001; Spencer, Dien, & Donchin, 2001; Butler & Javitt, 2005; Tendolkar, et al., 2005).

Visual processing is based on a core system consisting of occipito-temporal regions in extrastriate visual cortex (Haxby, Hoffman, & Gobbini, 2001) although parietal (Posner & Petersen, 1990) and frontal (Clark, Fan, & Hillyard, 1995) regions also play a role in directing visual attention. The earliest electrical sign of cortical activity observed in humans (commonly referred to the P100) during visual tasks (Mangun, 1995) can occur as early as 50 ms post stimulus (Seeck et al., 1997) to as late as 160 ms depending on topography and visual task and reflects early categorization and recognition processes (Herrmann, Ehlis, Ellgring, & Fallgatter, 2005). The visual P100 likely has posterior generators in the primary visual cortex, extrastriate areas (Tendolkar, et al., 2005) and fusiform gyrus (Heinze et al., 1994), while the anterior P100 likely reflects the activation of frontal generators (Clark et al., 1995). The P100 may reflect early sensory processing of attended stimuli (Haxby et al., 2001) and is generally larger to attended visual stimuli thus giving evidence of orientated attention (Hillyard, Mangun, Woldorff, & Luck, 1995); for this study over parieto-occipital regions of interest this early visual component will be referred to as P50 instead of P100.

The visual N100 directly follows the P100 and is similarly considered an index of stimulus discrimination (Hopf, Vogel, Woodman, Heinze, & Luck, 2002; Vogel & Luck,

2000). The N100 is generally defined within a time window starting as early as 70 ms post stimulus onset (Courchesne et al., 1985b) to as late as 180 ms post stimulus onset (Tendolkar, et al., 2005). Over posterior electrode sites the visual N100 is probably generated by dipoles in lateral extrastriate cortex (Gomez-Gonzales, Clark, Fan, Luck, & Hillyard, 1994) with a contribution from parieto-occipital and occipito-temporal areas (Hopf et al., 2002; Yamazaki et al., 2000); while the visual N100 over frontal electrode sites most likely is reflective of frontal generators (Clark et al., 1995). The visual N100 generally is augmented during attentional stimulus processing, which is also know as the 'N1-effect' (Hillyard, Hink, Schwent, & Picton, 1973), and is larger towards task-relevant target stimuli (Luck et al., 1990; Hillyard et al., 1995).

The visual P200 over frontal electrode sites is generally found in a latency range of 180– 320 ms post-stimulus and has been reported in working memory and attention tasks. Kenemans, Kok, and Smulders (1993) described this frontal positivity as a component that indexes the hierarchical selection of task-relevant features for further processing. Over inferior frontal recording sites source localization places dipoles of this component in the orbito-frontal cortex (Potts, Liotti, Tucker, & Posner, 1996; Potts, Dien, Harty-Speiser, McDougl, & Tucker, 1998). The visual P200 over posterior regions has been less studied but likely is associated with generators in the primary visual cortex and extrastriate areas reflecting visual categorization processes.

The visual N200 is a negative endogenous ERP component directly following the P200; it is mainly found in a latency range of 180-350 ms post-stimulus over centro-parietal scalp locations (Näätänen, Gaillard, & Mäntysalo 1978; Näätänen, Schröger, Karakas, Tervaniemi, & Paavilainen, 1993) but can be isolated over frontal regions as

well. Over centro-parietal scalp locations the visual N200 component is associated with categorization, perceptual closure and attention focusing ultimately signaling that a perceptual representation has been formed (Potts, Patel, & Azzam, 2004); it is enhanced if the presented stimulus contains a perceptual feature or attribute defining the target in the task. Over frontal channels the visual N200 can provide information about processes related to response conflict detection and processing, as well as inappropriate response inhibition (West, Bowry, & McConville, 2004; West, 2003); it is thought to originate from the anterior cingulate cortex (ACC) and prefrontal sources (Donkers & van Boxtel, 2004).

The P300 directly follows the N200 and is one of the most studied ERP components; it is elicited when a subject detects an unexpected (novel, rare) stimulus and consists of two components labeled P3a (fronto-central P300) and P3b (centro-parietal P300). The P3a (sometimes referred to as the novelty P300) is a fronto-central wave occurring within a time window of 300 to 520 ms; it reflects an aspect of the orienting response and has been related to evaluative attentional processes (Hruby & Marsalek, 2003; Polich, 2003). The P3b is a centro-parietal wave occurring between 320 and 560 ms that has been linked to task-relevance and the decision- related character of the eliciting stimulus; it reflects memory-updating processes and/or processing closure (Picton, 1992). Source localization techniques have claimed that multiple brain areas are involved in the generation of the visual P3b: the hippocampus and parahippocampal areas, the insula, the temporal lobe, occipital cortex, and the thalamus (Goto, Brigell, & Parmeggiani, 1996; Herrmann & Knight, 2001; Mecklinger et al., 1998; Rogers, Basile,

Papanicolaou, & Eisenberg, 1993). Most studies agree that the P3b has multiple dipole sources (Halgren, Marinkovic, & Chauvel, 1998; Knight, 1997; Townsend et al., 2001

The present study was designed to evaluate ERP indices of selective attention in individuals with ASD evoked at both early (i.e., 50-200 ms) and later (i.e., 200-600ms) stages of attentional processing using a three-stimuli visual 'oddball' task. The baseline hypothesis is that individuals with ASD will manifest deficits in early stages of visual processing shown by an augmentation of evoked potentials elicited by task-irrelevant distracter stimuli, and this will consequently disrupt stimulus discrimination at later-stages as compared to the control group. Additionally, individuals with ASD will show evidence of compromised selective attention by having significantly different reaction times and error rates in motor responses to target stimuli.

The second hypothesis is that after 6 sessions of low-frequency of 'slow' rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) individuals with ASD will show significant improvement in ERP indices of selective attention as well as an improvement in reaction time and error rate. Mainly, there will be reduced amplitudes and latencies to irrelevant visual stimuli at early stages of visual processing and evidence of better stimulus discrimination at later stages. It may be proposed that that low-frequency rTMS may have increased cortical inhibitory tone in the DLPFC and subsequently improved performance in the novelty processing task. TMS has the potential to become an important therapeutic tool in ASD treatment with few, if any side effects.

Material and Methods

Participants

Participants with ASD were recruited through the University of Louisville Weisskopf Child Evaluation Center. Diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000; [DSM–IV–TR] 4th ed., text rev.) and further ascertained with the Autism Diagnostic Interview–Revised (LeCouteur, Lord, & Rutter, 2003). They also had a medical evaluation by a developmental pediatrician. All participants had normal hearing based on past hearing screens. Participants either had normal vision or wore corrective lenses. Participants with a history of seizure disorder, significant hearing or visual impairment, a brain abnormality conclusive from imaging studies, or an identified genetic disorder were excluded. All participants were assessed for IQ using the Wechsler Intelligence Scale for Children, Fourth Edition (Wechsler, 2003) or the Wechsler Abbreviated Scale of Intelligence (Wechsler, 2004). Controls were recruited through advertisements in the local media. All control participants were free of neurological or significant medical disorders; had normal hearing and vision; and were free of psychiatric, learning, or developmental disorders based on self- and parent reports. Participants were screened for history of psychiatric or neurological diagnosis using the Structured Clinical Interview for DSM–IV Non-Patient Edition (First, Spitzer, Gibbon, & Williams, 2001). Participants within the control and ASD groups were attempted to be matched by age, Full-Scale IQ, and socioeconomic status of their family. Socioeconomic status of ASD and control

groups was compared based on parent education and annual household income. Participants in both groups had similar parent education levels.

Participating individuals and their parents (or legal guardians) were provided with full information about the study including the purpose, requirements, responsibilities, reimbursement, risks, benefits, alternatives, and role of the local Institutional Review Board. The consent and assent forms approved by the Institutional Review Board were reviewed and explained to all individuals who expressed interest to participate. All questions were answered before consent signature was requested. If the individual agreed to participate, she or he signed and dated the consent form and received a copy countersigned by the investigator who obtained consent.

ERP Data Acquisition and Signal Processing

Electroencephalographic (EEG) data were acquired using a 128 channel Electrical Geodesics Inc. (EGI) system (v. 200), consisting of Geodesic Sensor Net electrodes, Net Amps and Net Station software (Electrical Geodesics Inc., Eugene, OR) running on a Macintosh G4 computer. EEG data are sampled at 500 Hz and 0.1–200 Hz analog filtered. Impedances were kept <50 kΩ, and according to the EGI Technical Manual (2003) impedances <50 kΩ are sufficient for recording quality EEG data; Ferree, Luu, Russell, and Tucker (2001) have suggested that modern high input impedance amplifiers and accurate digital filters for power noise provide excellent EEG signals in conjunction with scalp impedances of approximately 40 kΩ.

The Geodesic Sensor Net is a lightweight elastic thread structure containing Ag/AgCl electrodes housed in a synthetic sponge on a pedestal. The sponges are soaked in a KCl solution to render them conductive. EEG data are recorded continuously. EEG channels with high impedance or visually detectable artifacts (e.g., channel drift, gross movement, etc.) were marked in 'on-line' mode using Net Station's event-marker tools and further removal was performed in 'off-line' mode using the Net Station Waveform Tool (NSWT).

Stimulus-locked EEG data are segmented off-line into 1,000 ms epochs spanning 200 ms pre-stimulus to 800 ms post-stimulus around the critical stimulus events resulting in three conditions: (1) rare target, (2) rare non-target distracter (novel), and (3) frequent non-target (standard). Data are digitally screened for artifacts (eye blinks, movements), and contaminated trials are removed using artifact rejection tools. The Net Station Waveform Tools' (NSWT) Artifact Detection module in 'off-line' mode rejects EEG channels if the fast average amplitude exceeds 200 μV, the differential average amplitude exceeds 100 μV, or if the channel has zero variance. Segments are rejected if they contain more than 10 bad channels or if eye blinks or movement are detected (>70 μV). After the detection of 'rejected' channels, the NSWT's 'Bad channel replacement' function is used to replace rejected channel data with data interpolated from the remaining acceptable channels (or segments); this process uses spherical splines (for more information on the interpolation methods used in EGI Net Station systems refer to Fletcher, Kussmaul, & Mangun, 1996; Luu et al. 2001; Perrin, Pernier, Bertrand, Giard, & Echallier, 1987; Srinivasan, Tucker, & Murias, 1998).

The remaining data are digitally filtered using 60 Hz Notch and 0.3–20 Hz bandpass filters and are then segmented by condition and averaged to create ERPs. Averaged ERP data are baseline corrected and re-referenced into an average reference frame. All stimulus presentation and behavioral response collection is controlled by a PC computer running E-prime software (Psychology Software Tools Inc., PA). Visual stimuli are presented on a 15'' display. Manual responses are collected with a 5-button keypad (Serial Box, Psychology Software Tools, Inc, PA).

Three-Stimuli Visual 'Oddball' with Novel Distracters

This test represents a traditional visual three-stimuli oddball task. Stimuli letters 'X', 'O', and novel distracters ('v', '^', '>' and '<' signs) are presented on the screen after a fixation mark '+'. One of the stimuli ('O') is presented on 50% of the trials (frequent standard); the novel stimuli stimulus (e.g., '>') is presented on 25% of the trials (rare distracter), whereas the third ('X') is presented on the remaining 25% of the trials representing the target (Figure 12). Subjects are instructed to press a key when they see the target letter on the screen. Each stimulus is presented for 250 ms, with a 1,100 ms inter-trial interval. There were 240 trials in total, and the complete sequence takes 20 min. Participants with ASD were administered the three-stimuli 'oddball' test before (pre-TMS) and after (post-TMS) treatment. There was also a randomly assigned waiting-list group where individuals with ASD were administered the three-stimuli 'oddball' test twice (with an 8-week interval) to control for the TMS treatment. Control participants were administered the three-stimuli 'oddball' test once.

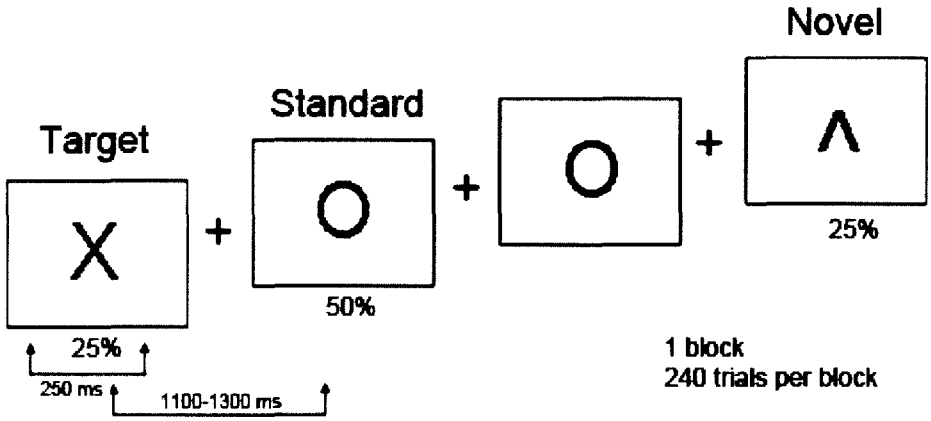

Figure 12: Presented Stimuli of Traditional Visual Three-Stimuli 'Oddball' Task.

Motor Response Measures

Motor response measures were mean reaction time (in ms) and response accuracy (percent of correct hits) to the target stimulus.

Event-Related Potentials (ERP)

ERP dependent measures were: adaptive mean amplitude and latency of the ERP peak (e.g., P3a, P3b) within a temporal window across a region-of-interest (ROI) (Figure 13). ERP dependent variables included stimulus-averaged amplitudes and latencies of frontal ERP components: P100 (40–80 ms post-stimulus), N100 (80–180 ms), P200 (180–320 ms), N200 (220– 350 ms), and P3a (300–520 ms); and posterior ERP components: P50 (40–100 ms), N100 (120–180 ms), P200 (160–250 ms), and centro-parietal N200 (N2b, 180– 320 ms) and P3b (320–560 ms). The frontal ROIs for the P100, N100, N200 and P3a components included the following EGI channels: left ROI—EGI channel 12, F1, F3, FC1; midline ROI—FCz, Fz); right ROI—EGI channel 5, F2, F4,

FC2. The anterior-frontal ROI for the P2a component had more anterior scalp locations, including AF3, AF4, FPz, AFz and 4 neighboring EGI channels: 18, 19, 9, 10. The centro-parietal ROI for N2b and P3b components included the following EGI channels: left ROI—EGI channel 32, CP1, P1, P3, EGI channel 54; midline ROI—CPz, Pz; right ROI—CP2, P2, P4, EGI channels 80 and 81. The early and middle latency ERP components (P50, N100, P200) were analyzed as well for parieto-occipital and occipital ROIs (left—PO7, O1, EGI channels 65, 71; right—PO8, O2, EGI channels 84, 91). Frontal negativities (N100, N200) were analyzed separately for midline frontal and fronto-central ROIs (Fz, FCz, EGI channels 12, 5) and lateral frontal and fronto-central ROIs (left—F1, FC1, FC3, EGI channel 29; right—F2, FC2, FC4, EGI channel 118).

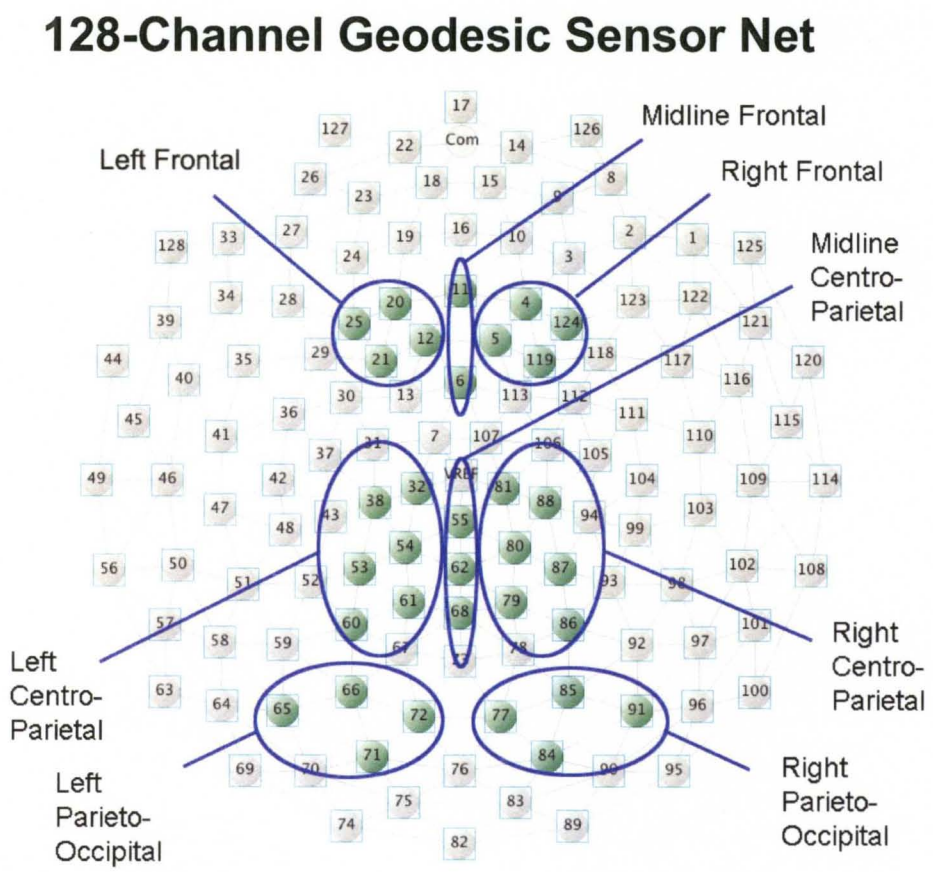

Figure 13: Sensor layout of the 128-channel Geodesic net (EGI, Eugene, Oregon) with selected regions-of-interest (ROI) labeled.

TMS Procedure

A trained electrophysiologist delivered rTMS using a Magstim Rapid (Model 220) instrument (Magstim Corporation, Sheffield, England) with a 70-mm wing span figure-eight coil. Motor threshold (MT) was determined in all individuals by gradually increasing the output of the machine by 5% until a 50 μV deflection or a visible twitch in the first dorsal interosseous (FDI) muscle was identified in two out of three trials of stimulation over the cortical area controlling the contralateral FDI. Electromyographic responses were monitored on a continuous basis with a C-2 J&J Engineering physiological monitor (Poulsbo, WA). Motor-evoked potentials were recorded from the hand contralateral to stimulation using the C2 J&J system with USE-2 Physiodata software applications. Heart rate, heart rate variability, skin conductance, and skin temperature were also recorded. EMG and other physiological recordings were stored for later analysis. Autistic patients were encouraged to visit the laboratory at least once beforehand to get familiar with the TMS procedure.

The TMS treatment course was administered once per week for six weeks (a total of six 1Hz rTMS treatments); the treatments were over the left DLPFC. The site for stimulation was found by placing the coil 5 cm anterior, and in a parasagital plane, to the site of maximal FDI stimulation. The figure-eight coil, with a 70-mm wing diameter was kept flat over the scalp. Participants were wearing a swimming cap on their head. Stimulation was done at 1Hz and 90% MT, with a total of 150 pulses / day (fifteen 10-s trains with a 20- to 30-s interval between the trains). 1Hz was selected as the stimulation frequency as studies have shown that low-frequency rTMS (≤1 Hz) increases inhibition of stimulated cortex (e.g., Boroojerdi et al., 2000); there is also a lower risk for seizures

the lower the rTMS frequency. Selection of 90% of the MT was based on the experience of numerous publications where rTMS was used for the stimulation of DLPFC in different psychiatric and neurological conditions (for reviews, see Daskalakis, Christensen, Fitzgerald, & Chen, 2002; Gershon, Dannon, & Grunhaus, 2003; Greenberg, 2007; Holtzheimer, Russo, & Avery, 2001; Loo & Mitchell, 2005; Rosenberg et al., 2002; Wassermann & Lisanby, 2001). The stimulation power was also kept below MT as an extra safety precaution due to the increased risk of seizure within this study population. The minimal number of TMS pulses during a TMS session has varied from 30 to 2,000 pulses on a once-per-week over 8 weeks to twice-a-day basis over 10 days (Daskalakis et al., 2002). It has been concluded that less than 100 pulses per session is not very promising in terms of therapeutic efficacy (see Helmich, Siebner, Bakker, Munchau, & Bloem, 2006, for review).

Statistical Analysis

Statistical analyses were performed on subject-averaged ERP and motor response data with subject averages being observations. The primary analysis model was the repeated measures ANOVA, with dependent variables being reaction time (RT), error rate and specific ERP components' amplitudes and latencies at selected ROIs. The data of each ERP dependent variable for each relevant ROI was analyzed using ANOVA with the following factors (all within participants): Stimulus (Target, Novel, Standard) and Hemisphere (Left, Right). The between-subject factors included the following group comparisons: baseline (ASD vs. controls), treatment (ASD pre-TMS vs. ASD post-TMS),

and wait-list (ASD Pre- WTL vs. ASD Post-WTL; i.e., no TMS). Post-hoc analyses were conducted where appropriate. A-priori hypotheses were tested with Student's t-tests. In all ANOVAs Greenhouse-Geisser corrected P-values were employed where appropriate. SPSS v.14 and Sigma Stat 3.1 packages were used for statistical analysis.

Results

Participant Characteristics

Twenty-eight autistic patients (ASD group) were enrolled, 25 male and 3 female, with a mean age of 12.9 ± 3.8 years. Eighteen of them were randomly assigned to active 1.0 Hz TMS treatment (TMS group), whereas 10 were randomly assigned to the waiting-list group (WTL group) (Figure 14). Mean age of participants in the TMS group was 12.8 ± 2.4 years and 13.5 ± 2.1 years in the waiting-list group. Twenty-five control participants were recruited (CNT group), 19 male and 6 female (*M* age = 13.3 ± 4.4 years) for a baseline comparison with 25 of the ASD group. There were no statistically significant age or IQ differences between the groups.

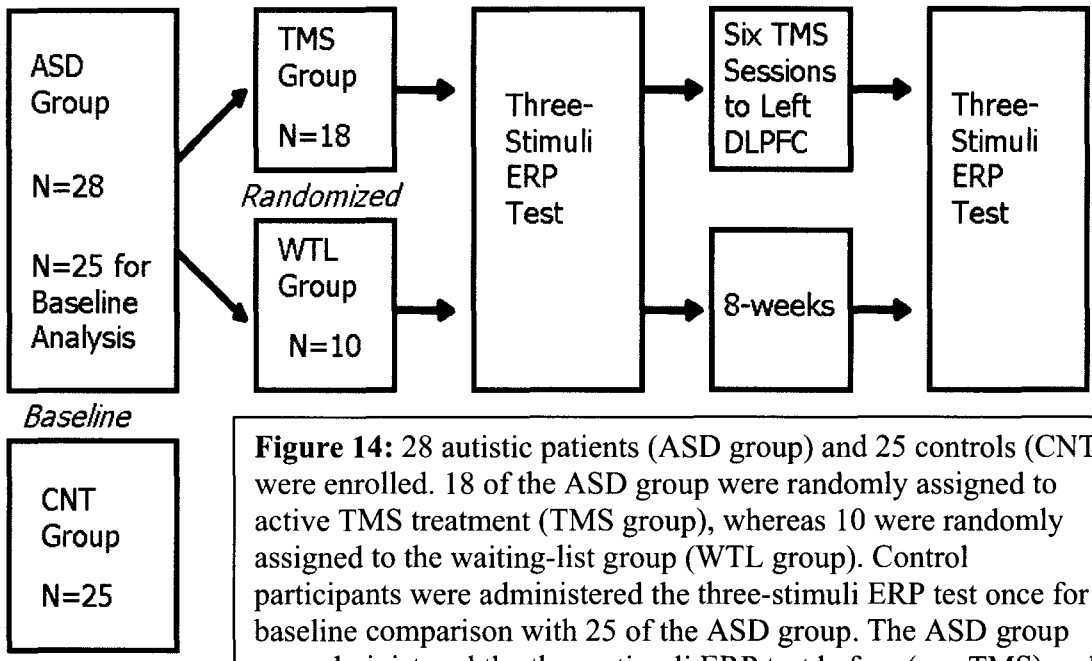

Figure 14: 28 autistic patients (ASD group) and 25 controls (CNT) were enrolled. 18 of the ASD group were randomly assigned to active TMS treatment (TMS group), whereas 10 were randomly assigned to the waiting-list group (WTL group). Control participants were administered the three-stimuli ERP test once for a baseline comparison with 25 of the ASD group. The ASD group was administered the three-stimuli ERP test before (pre-TMS) and after (post-TMS) treatment, and the WTL group was administered the test before and after an 8-week interval to control for the TMS.

Baseline (Pre-TMS) Group Differences

Parieto-occipital ERPs

P50. Amplitude of the parieto-occipital P50 was significantly more positive in the ASD group to all stimuli especially over right ROI (Target, 2.30 ± 2.83 vs. 0.37 ± 1.31 μV, F=9.19, P=0.004; Standard, 1.96 ± 1.98 vs. 0.82 ± 1.79 μV, F=4.44, P=0.040; Novel, 2.54 ± 2.82 vs. 0.56 ± 2.03 μV, F=8.02, P=0.007) (Figures 15 & 16). Latency of the parieto-occipital P50 was bilaterally reduced in the ASD group compared to controls to both target and novel stimuli (Target, 65.8 ± 25.9 vs. 81.4 ± 18.3 ms, F=5.86, P=0.019; Novel, 60.3 ± 28.9 vs. 83.9 ± 17.3 ms, F=12.192, P=0.001).

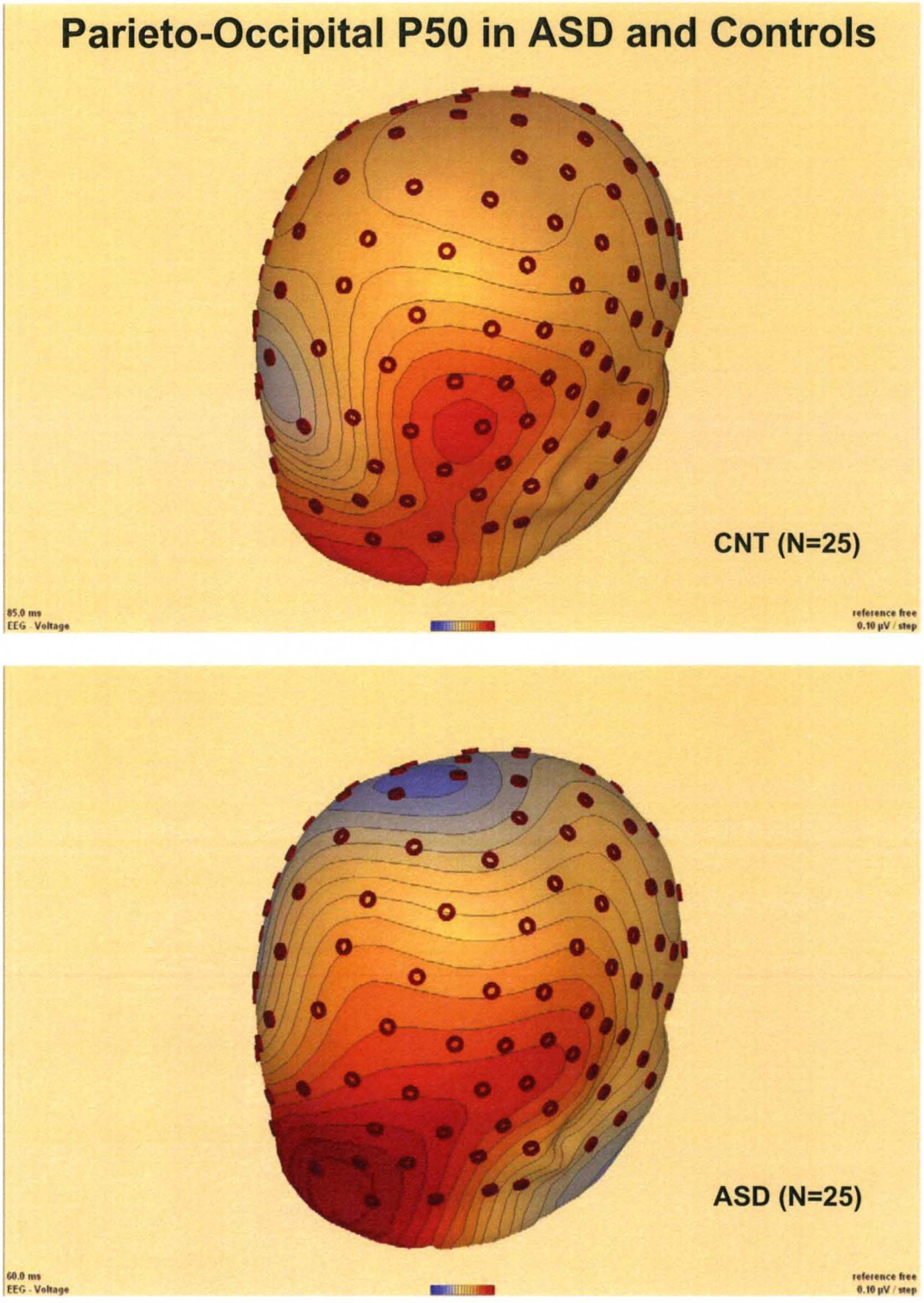

Figure 15: Brain Electrical Source Software (BESA) 3D map of P50 amplitude and latency differences between ASD (N=25) and CNT (N=25) groups to novel stimuli. Notice P50 peak amplitude is more pronounced and latency is reduced in ASD compared to controls.

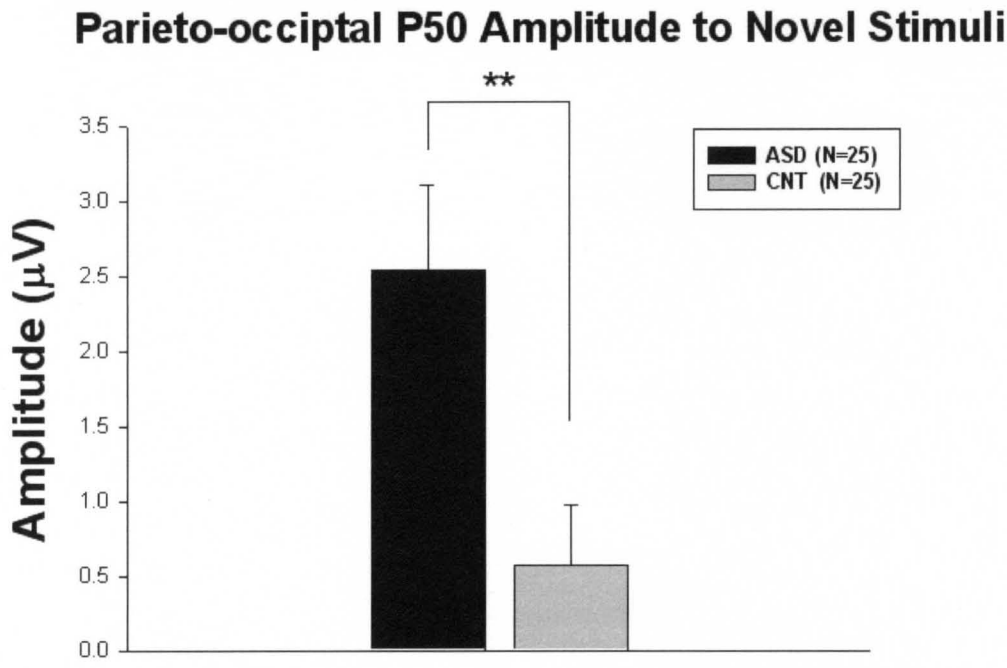

Figure 16: Parieto-occipital P50 amplitude is significantly augmented to all stimuli in ASD group especially over right hemisphere (Novels, F=8.02, P=0.007).

Frontal ERPs

P100. A *Stimulus* (Target, Standard) X *Group* (ASD, CNT) interaction reached significance over the right hemisphere and can be described as a prolonged latency to target stimuli compared to standards in the ASD group while controls showed a relatively prolonged latency to standards compared to targets (F =5.10, P=0.028).

P200. P200 (P2a) latency was bilaterally prolonged to all stimuli in the ASD group compared to controls (Target, 241.1 ± 48.6 vs. 214.2 ± 33.3 ms, F=5.20, P=0.027; Standard, 238.9 ± 47.7 vs. 205.6 ± 23.5 ms, F=9.801, P=0.003; Novel, 235.9 ± 44.3 vs. 209.9 ± 27.6 ms, F=6.173, P=0.017) (Figure 17).

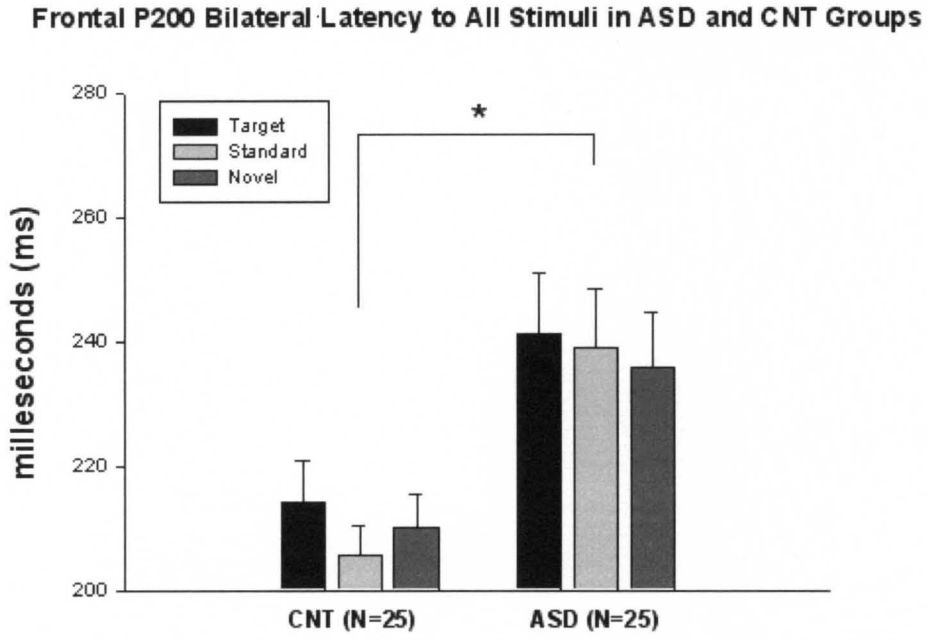

Figure 17: Frontal P200 latency is significantly delayed to all stimuli in the ASD group bilaterally (Target, F=5.20, P=0.027; Standard, F=9.801, P=0.003; Novels, F=6.173, P=0.017).

N200. Amplitude of the N200 (N2a) was significantly less negative to novel stimuli in the ASD group compared to controls over the left hemisphere (-1.01 ± 3.24 vs. -3.11 ± 3.06 μV, F=5.15, P=0.028). Repeated measures analysis revealed a *Stimulus* (Target, Standard, Novel) X *Group* (ASD, CNT) interaction which can be described as a

significantly more negative N2a amplitude to targets in the ASD group compared to controls with a relatively less negative amplitude to standards and novels (F=3.35, P=0.039) (Figure 18); the ASD group showed minimal amplitude differences between standards and novels as compared to controls. N2a latency was bilaterally reduced to all stimuli in the ASD group compared to controls (Target, 283.5 ± 35.8 vs. 315.5 ± 39.0 ms, F=8.56, P=0.005; Standard, 281.2 ± 29.1 vs. 315.3 ± 41.4 ms, F=10.842, P=0.002; Novel, 289.0 ± 34.9 vs. 318.1 ± 42.3 ms, F=6.67, P=0.013).

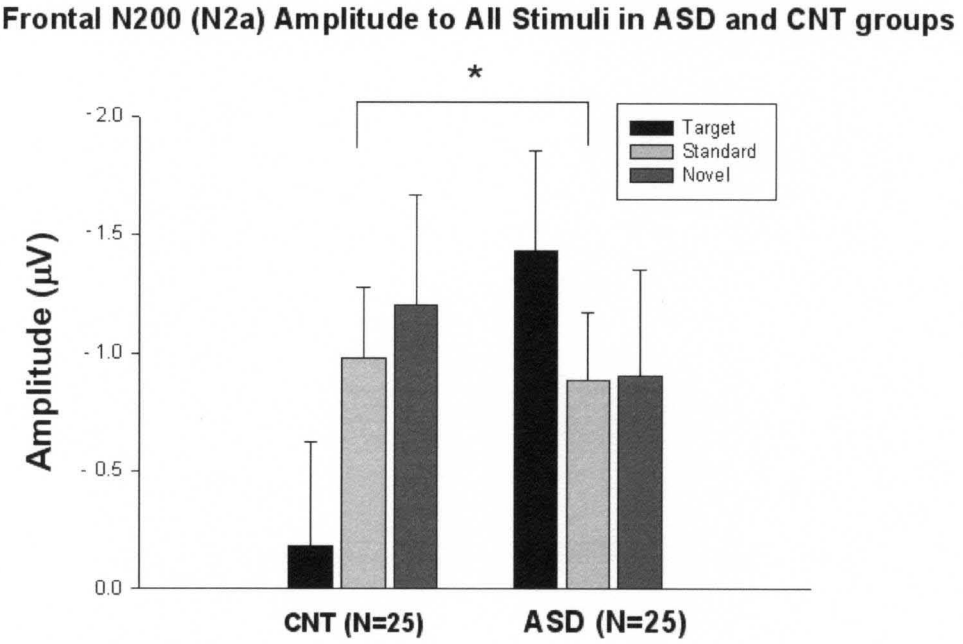

Figure 18: Repeated measures analysis revealed a *Stimulus* (Target, Standard, Novel) X *Group* (ASD, CNT) interaction which can be described as a significantly more negative N2a amplitude to targets in the ASD group compared to controls with a relatively less negative amplitude to standards and novels (F=3.35, P=0.039); this implies augmented response (N2a) conflict to targets and decreased inappropriate response inhibition to standards and novels relative to controls.

P300. P300 (P3a) latency was bilaterally reduced to all stimuli in the ASD group compared to controls (Target, 408.0 ± 49.6 vs. 458.5 ± 59.1 ms, F=10.70, P=0.002; Standard, 409.9 ± 38.8 vs. 462.2 ± 64.3 ms, F=12.12, P=0.001; Novel, 422.8 ± 46.9 vs. 471.8 ± 45.0 ms, F=14.16, $P \leq 0.001$). Repeated measures analysis revealed a *Stimulus* (Target, Novel) X *Group* (ASD, CNT) interaction over the right hemisphere which can be described as reduced latency to novels relative to targets in the control group with a minimal latency difference between target and novel stimuli in the ASD group (F=6.99, P=0.011) (Figure 19).

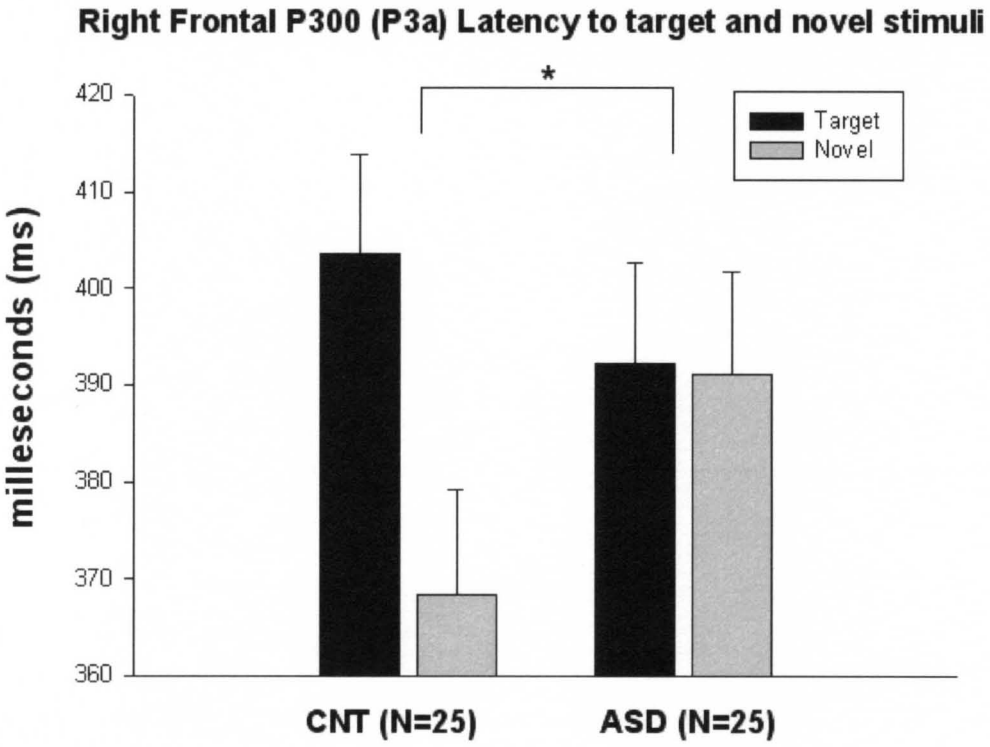

Figure 19: Repeated measures analysis revealed a *Stimulus* (Target, Novel) X *Group* (ASD, CNT) interaction over the right hemisphere which can be described as reduced latency to novels relative to targets in the control group with a minimal latency difference between target and novel stimuli in the ASD group (F=6.99, P=0.011) Minimal P3a latency differences between target and novel stimuli in the ASD group implies evidence of a lack of stimulus discrimination.

Centro-Parietal ERPs

There were no statistically significant ($P \leq 0.05$) N200 (N2b) or P300 (P3b) amplitude or latency baseline differences elucidated between the ASD and control groups.

Baseline (Pre-TMS) Motor Responses

Reaction time (RT) between the ASD and control groups was not significantly different (M=459.3 ± SD 107.1 ms in ASD vs. 479.5 ± 90.6 ms in controls). However, the ASD group made significantly more errors compared to controls (8.50 ± 11.87% vs. 2.6 ± 2.27%, F=4.66, P=.036), and this was mainly due to commission errors (6.0 ± 10.5% in ASD vs. 1.34 ± 1.14% in controls) (Figure 20).

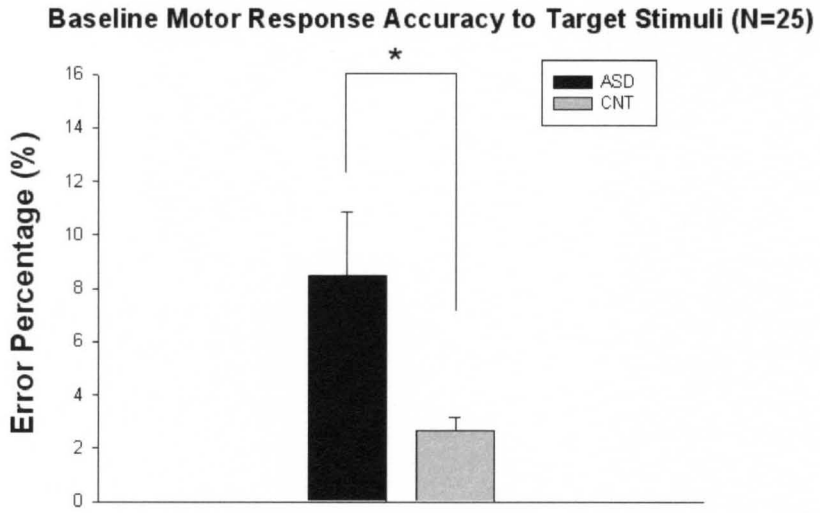

Figure 20: Baseline analysis revealed the ASD group made significantly more errors in motor responses to target stimuli compared to controls (F=4.66, P=.036)

Post-TMS Group Differences

Parieto-occipital ERPs

P50. Amplitude of the parieto-occipital P50 was significantly reduced to novel stimuli over left ROI as a result of TMS (2.87 ± 2.45 vs. 1.24 ± 1.89 μV, F=4.98, P=0.032) (Figure 22). Repeated measures analysis revealed a *Stimulus* (Target, Novel) X *Group* (Pre-TMS, Post-TMS) interaction over the left hemisphere indicating a significant increase in P50 amplitude to target stimuli with a decrease to novels as a result of TMS (F=7.47, P=0.010) (Figure 21).

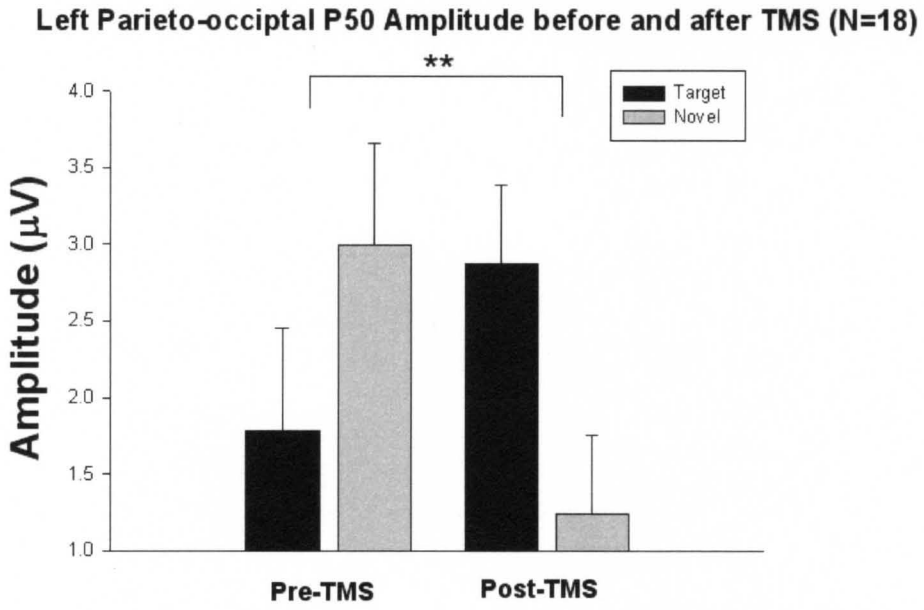

Figure 21: Repeated measures analysis revealed a *Stimulus* (Target, Novel) X *Group* (Pre-TMS, Post-TMS) interaction over the left hemisphere indicating a significant increase in P50 amplitude to target stimuli with a decrease to novels as a result of TMS (F=7.47, P=0.010); TMS minimized early cortical responses to irrelevant stimuli and improved discriminative perceptual processing.

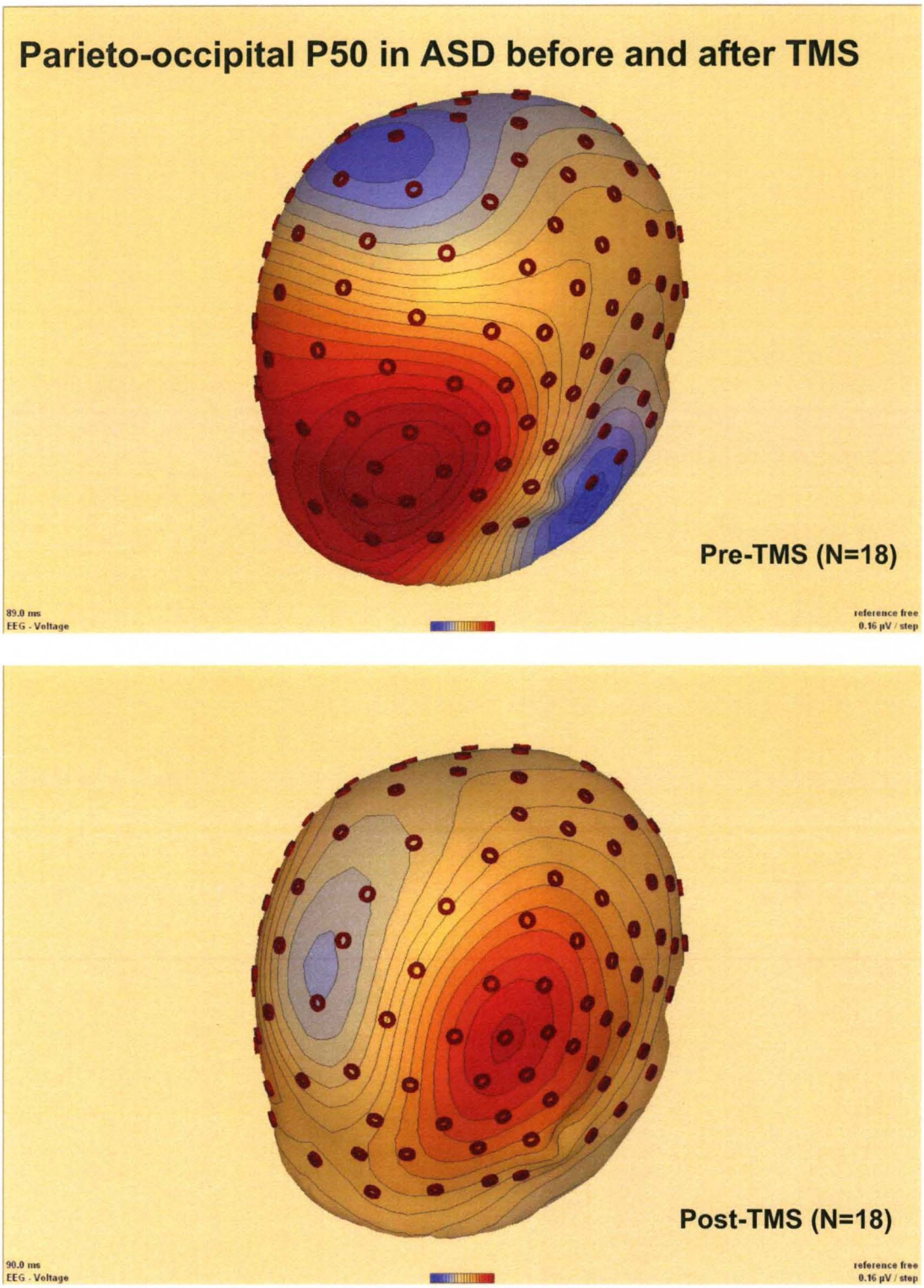

Figure 22: Brain Electrical Source Software (BESA) grand average 3D Map of P50 amplitude differences to novel stimuli before and after TMS. Notice P50 peak amplitude is less pronounced to novel stimuli after TMS.

P200. A *Stimulus* (Target, Standard) X *Group* (Pre-TMS, Post-TMS) interaction revealed a significant increase in P200 (P2b) amplitude to target stimuli with a decrease to standards bilaterally as a result of TMS (F=4.22, P=0.048) (Figure 23).

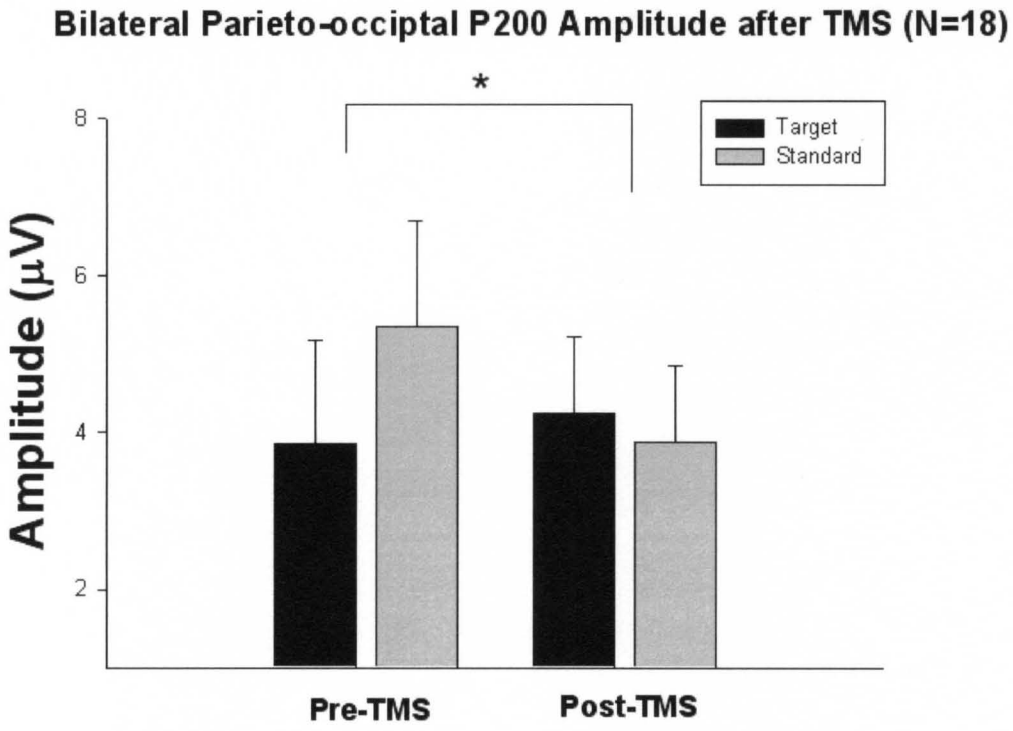

Figure 23: A *Stimulus* (Target, Standard) X *Group* (Pre-TMS, Post-TMS) interaction revealed a significant increase in P200 (P2b) amplitude to target stimuli with a decrease to standards bilaterally as a result of TMS (F=4.22, P=0.048); TMS minimized cortical responses to irrelevant stimuli at the stage of the P200 (P2b) improving stimulus discrimination.

Frontal ERPs

P100. Amplitude of P100 was significantly more positive to target stimuli over the right hemisphere as a result of TMS (2.39 ± 3.34 vs. 4.93 ± 3.74 μV, F=4.60, P=0.039) (Figure 24). Latency of P100 significantly increased to target stimuli over the right hemisphere as a result of TMS (86.3 ± 27.0 vs. 105.2 ± 25.6 ms, F=4.61, P=0.039).

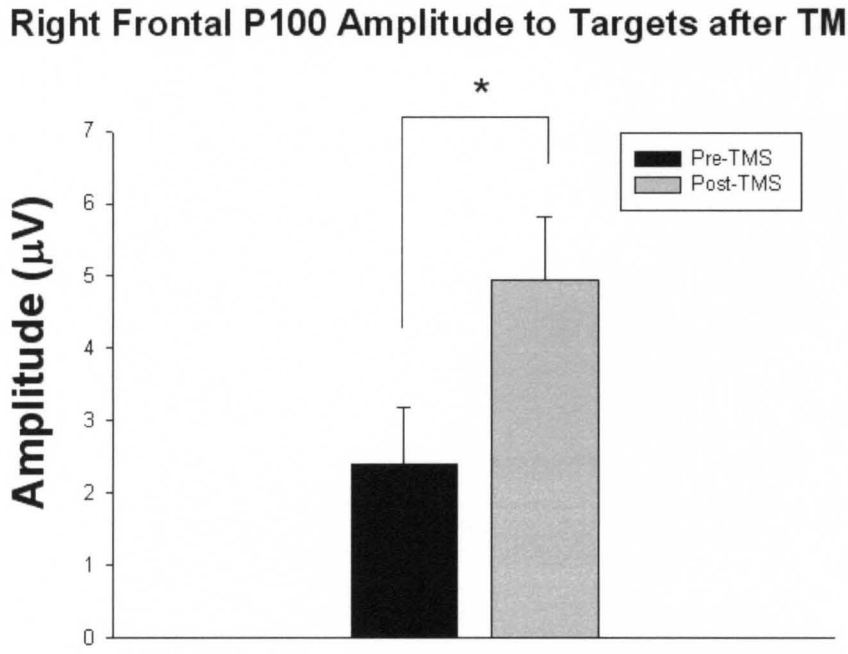

Figure 24: Amplitude of P100 was significantly more positive to target stimuli over the right hemisphere as a result of TMS (2.39 ± 3.34 vs. 4.93 ± 3.74 μV, F=4.60, P=0.039); this implies better orientation to targets and improved stimulus discrimination.

N100. A *Stimulus* (Target, Novel) X *Group* (Pre-TMS, Post-TMS) interaction revealed a significantly more negative amplitude to target stimuli with a less negative amplitude to novels bilaterally as a result of TMS (F=4.13, P=0.05); this interaction was especially significant over the right hemisphere (F=6.22, P=0.018) (Figure 25 & 26).

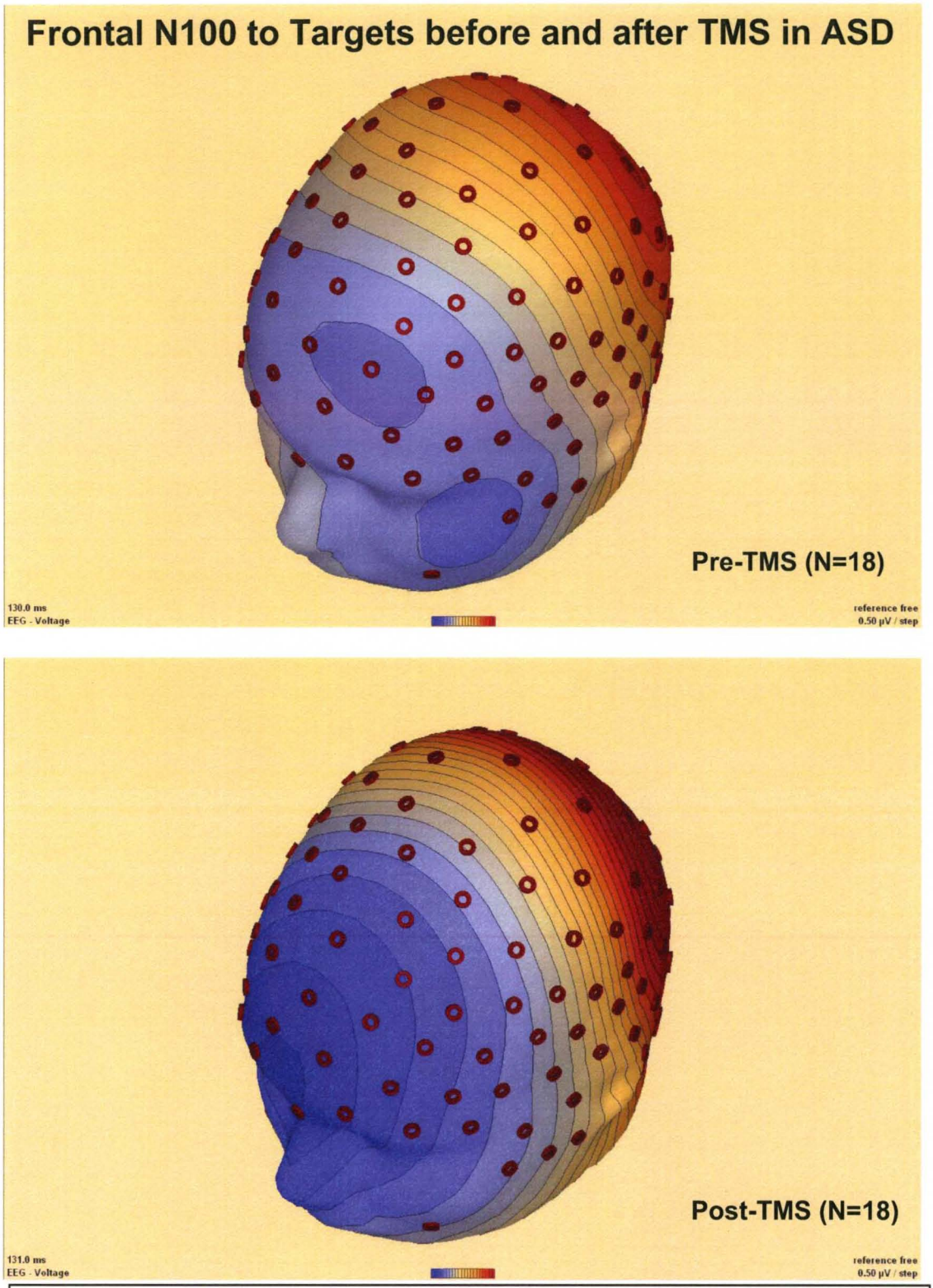

Figure 25: Brain Electrical Source Software (BESA) grand average 3D Map of N100 amplitude differences to target stimuli as a result of TMS. Notice N100 peak amplitude is more negative to target stimuli after TMS.

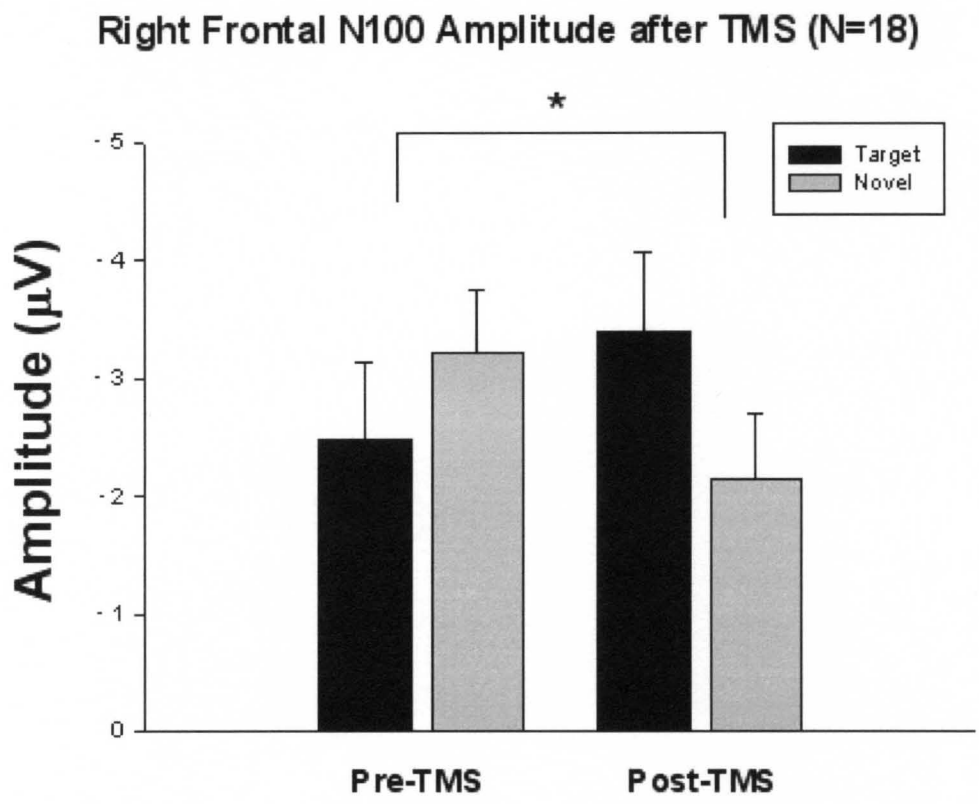

Figure 26: A *Stimulus* (Target, Novel) X *Group* (Pre-TMS, Post-TMS) interaction revealed a significantly more negative amplitude to target stimuli with a less negative amplitude to novels bilaterally as a result of TMS (F=4.13, P=0.05); this interaction was especially significant over the right hemisphere (F=6.22, P=0.018); this implies better orientation to targets and improved stimulus discrimination.

N200. Latency of N200 (N2a) significantly increased over the right hemisphere to standards as a result of TMS (271.3 ± 28.8 vs. 307.9 ± 45.8 ms, F=8.08, P=0.008).

P300. P300 (P3a) latency bilaterally increased to all stimuli as a result of TMS (Target, 402.1 ± 52.6 vs. 472.0 ± 36.5 ms, F=21.43, $P \leq 0.001$; Standard, 409.8 ± 42.8 vs. 451.2 ± 64.1 ms, F=5.096, P=0.031; Novel, 424.4 ± 49.3 vs. 466.7 ± 48.2 ms, F=6.76, $P \leq 0.014$) (Figure 27).

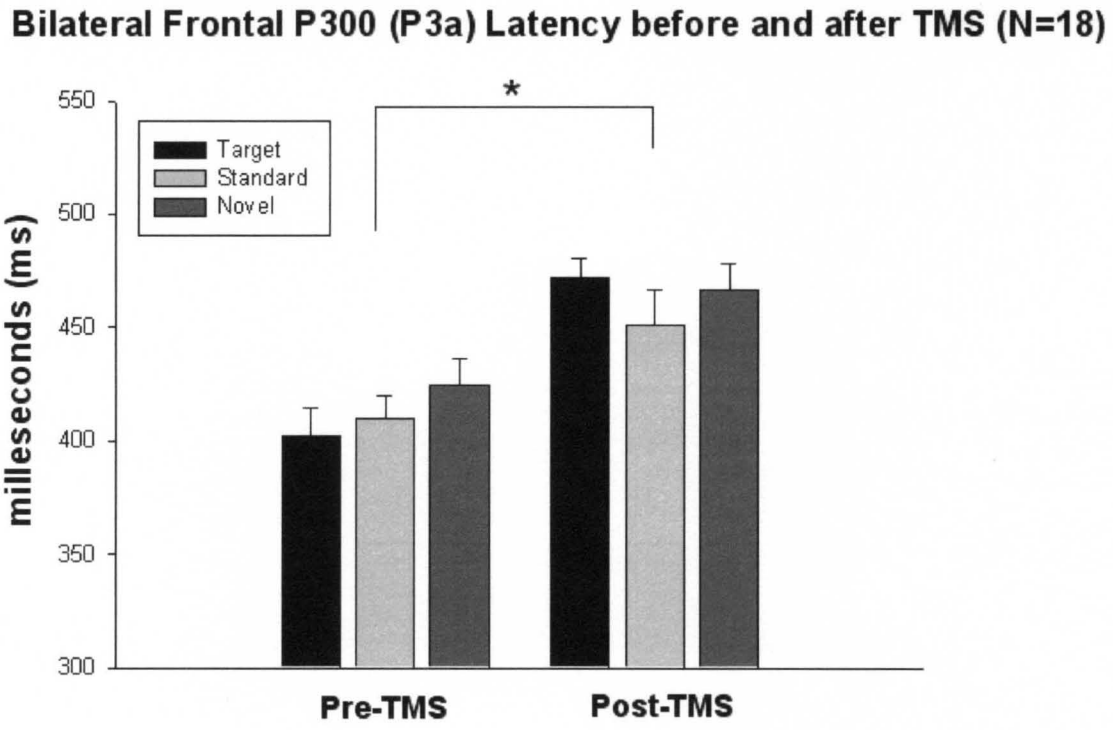

Figure 27: P300 (P3a) latency bilaterally increased to all stimuli as a result of TMS (Target, F=21.43, $P \leq 0.001$; Standard, F=5.096, P=0.031; Novel, F=6.76, $P \leq 0.014$); prolonged P3a latency may imply improvement in conscientious attention and evaluative accuracy.

Centro-Parietal ERPs

There were no statistically significant ($P \leq 0.05$) N200 (N2b) or P300 (P3b) amplitude or latency changes elucidated as a result of TMS.

Post-TMS Motor Responses

RT between the ASD Pre-TMS (N=18) and ASD Post-TMS (N=18) groups was not significantly different following rTMS (471.9 ± 109.4 ms in pre-ASD vs. 472.8 ± 78.3 ms in post-ASD). There was an improvement in response accuracy following rTMS treatment, but the difference did not reach significance (5.44 ± 7.4% before rTMS vs. 2.2 ± 1.5% after rTMS, F=3.30, P=.078). The waiting-list group did not show any differences in RT and accuracy with repeated tests (422.3 ± 89.1 ms in ASD pre- WTL vs. 444.8 ± 103.4 ms in ASD post-WTL, F=0.272, P=0.609, 7.04 ± 12.71% in ASD pre-WTL vs. 7.9 ± 13.06% in ASD post-WTL, F=0.022, P=.883) (Figure 28).

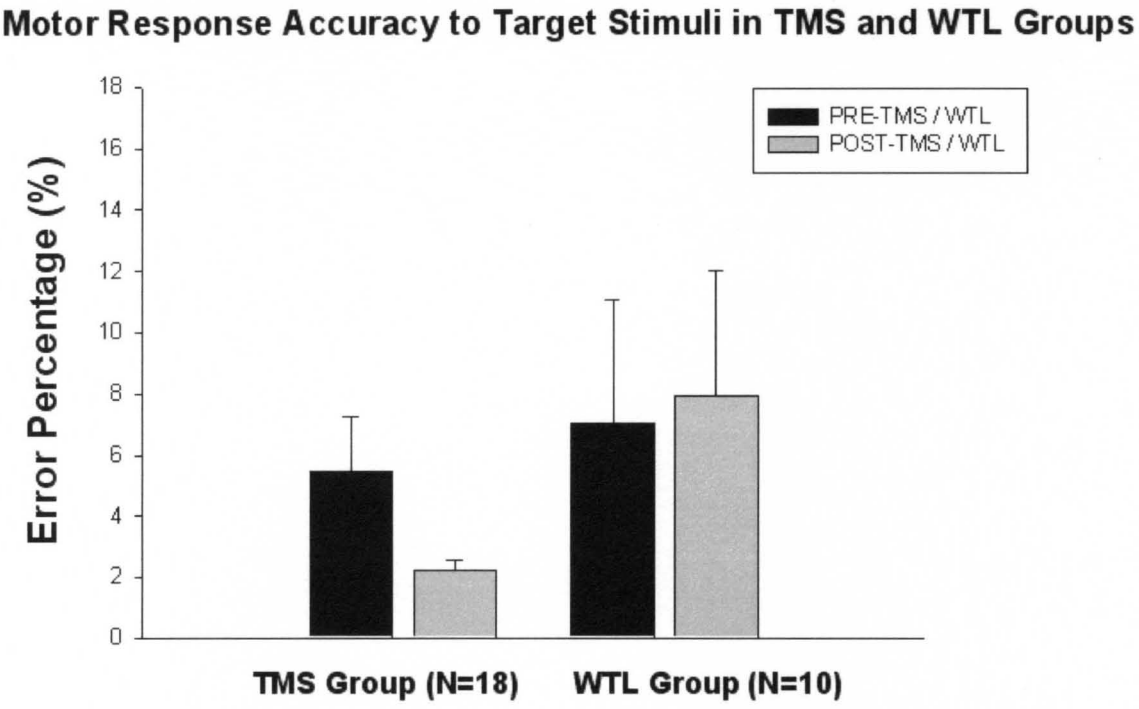

Figure 28: There was an improvement in response accuracy following rTMS treatment; however, the difference did not reach significance (F=3.30, P=.078). The waiting-list did not show any significant changes in response accuracy following the waiting period (F=0.022, P=.883); in fact, there was a slight increase in error percentage.

Discussion

The baseline hypothesis was that individuals with ASD would manifest deficits in early stages of visual processing shown by an augmentation of evoked potentials elicited by task-irrelevant distracter stimuli, and this will consequently disrupt later-stage stimulus discrimination as compared to the control group. Additionally, individuals with

ASD would show evidence of compromised selective attention by having significantly different reaction times and error rates in motor responses to target stimuli. The second hypothesis was that after 6 sessions of low-frequency of 'slow' rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) individuals with ASD will show significant improvement in ERP indices of selective attention as well as an improvement in reaction time and error rate. Mainly, there will be reduced amplitudes and latencies to irrelevant visual stimuli at early stages of visual processing and evidence of better stimulus discrimination at later stages.

The baseline findings indicate that parieto-occipital P50 amplitude was significantly more positive in the ASD group to all stimuli compared to controls especially over right ROI, and the latency of the parieto-occipital P50 was bilaterally reduced in the ASD group compared to controls to target and novel stimuli. The early P50 potential in visual tasks is associated with the sensory processing of attended stimuli and is generally larger to attended stimuli (Hillyard et al., 1995). These results may point to sensory over reactivity in individuals with ASD in early stages of visual processing with a lack of stimulus discrimination. The finding of over reactivity to all stimuli in this study may reflect deficits in cortical inhibitory processes where no pattern can emerge to dominate and constrain perceptual processing. Also, these results likely reflect the findings of altered inhibitory control of sensory intake (Khalfa et al., 2004), sensory overload (Ratey & Johnson, 1997), and hypersensitivity (Charman, 2008) in ASD.

Over frontal ROI there was a prolonged P100 latency to target stimuli compared to standards in the ASD group while controls showed a relatively prolonged latency to standards compared to targets. It may be suggested that ASD patients are abnormally

orientating to task irrelevant stimuli, and this may prolong the processing of targets. Additionally, over frontal ROI P200 latency was bilaterally prolonged to all stimuli in the ASD group compared to controls. The P200 over frontal ROI has been associated with the hierarchal selection of task-relevant features, and in ASD prolonged latencies of this component may reflect a delay in this process. In ASD globally augmented cortical responses at very early stages of visual processing (e.g., parieto-occipital P50) may be complicating stimulus discrimination at later stages of processing, for example at the stage of the P200.

N200 amplitude over frontal ROI was significantly more negative to targets in the ASD group compared to controls with a relatively less negative amplitude to standards and novels. Additionally, the ASD group showed minimal amplitude differences between standards and novels as compared to controls, and N200 latency was bilaterally reduced to all stimuli in the ASD group. The visual N200 over frontal channels can provide information about processes related to response conflict detection and processing, as well as inappropriate response inhibition (West et al. 2004; West, 2003); it is thought to originate in part from the anterior cingulate cortex (ACC). An augmented amplitude of this component to target stimuli in ASD may reflect inappropriate inhibition in response to the salient stimulus as controls appropriately showed an augmentation of this response to irrelevant stimuli (i.e. novels and standards) relative to targets. Minimal amplitude differences between standards and novels and bilaterally reduced latency of the frontal N200 to all stimuli in the ASD group may point to an attenuated and imprecise mode of processing conflicting responses.

P300 latency was bilaterally reduced to all stimuli in the ASD group compared to controls and repeated measures analysis revealed a reduced latency to novels relative to targets in the control group with a minimal latency difference between target and novel stimuli in the ASD group. The frontal P300 (P3a) (sometimes referred to as the novelty P300) is a frontocentral positive wave associated with evaluative attentional processes and orienting to novel stimuli (Hruby & Marsalek 2003; Polich 2003). Reduced P3a latencies and a minimal latency difference between target and novel stimuli in the ASD group may reflect attenuated and impaired evaluative attentional processes as compared to controls.

Baseline reaction times between ASD and control groups were not significantly different. However, the ASD group made significantly more errors compared to controls; this was mainly due to commission errors (i.e., responses to wrong stimulus). Sensory hyperreactivity in individuals with ASD at early stages of visual processing may be consequently disturbing stimulus discrimination at the stage of the motor response.

The baseline results indicate that in ASD cortical responses may be augmented and indiscriminative at early stages of visual processing, and this may result in ineffective later-stage stimulus discriminatory processes; this may be related to an inundation of higher level integrative centers with task-irrelevant information. There were no statistically significant baseline N200 (N2b) or P300 (P3b) amplitude or latency differences detected between the ASD and control groups which may imply minimal group differences at the stage of processing closure; however, this finding confounds with the significantly higher percentage of motor response errors in the ASD group.

After six sessions of low-frequency rTMS to the left DLPFC the amplitude of the parieto-occipital P50 was significantly reduced to novel stimuli over left ROI and repeated measures analysis indicated a significant increased in P50 amplitude to target stimuli with a decrease to novels over the left hemisphere. As the P50 reflects early sensory processing of attended stimuli (Haxby et al., 2001) and is generally larger to attended visual stimuli thus giving evidence of orientated attention (Hillyard et al., 1995), six sessions of low-frequency rTMS may have reduced sensory over reactivity and improved discriminative perceptual processing. Also over parietal-occipital ROI there was a significant increase in P200 (P2b) amplitude to target stimuli with a decrease to standards bilaterally as a result of TMS. A reduction in augmented cortical responses at very early stages of visual processing (i.e., P50) may have consequently improved stimulus discrimination at the stage of the P200 as well.

Over frontal ROI P100 amplitude and latency significantly increased to target stimuli over the right hemisphere as a result of TMS. Also, N100 amplitude was significantly more negative to target stimuli and less negative to novels bilaterally over frontal ROI as a result of TMS. As both the P100 and N100 over frontal ROI are generally larger to task-relevant target stimuli (Hillyard et al., 1995; Luck et al., 1990) thus giving evidence of orientated attention, TMS may have improved early cortical responses to relevant stimuli while minimizing responses to irrelevant stimuli leading to improved selective attention.

Latency of N200 (N2a) significantly increased over right frontal ROI to standards and P300 (P3a) latency bilaterally increased to all stimuli over frontal ROI as a result of TMS. While latencies of both the N200 and P300 over frontal ROI were significantly

reduced to all stimuli in the ASD group relative to controls in the baseline comparison, TMS may have prolonged evaluative attentional processes thereby leading to improved accuracy and a more conscientious process of stimulus discrimination.

There was an improvement in response accuracy following rTMS treatment, but the difference did not reach significance (i.e., P=.078); the waiting-list group actually had a slightly higher percentage of errors following the waiting period. The improvement in response accuracy approaches statistical significance as a result of TMS, but a larger sample size in future studies may be needed to detect this effect.

Overall, the results indicate that in ASD cortical responses may be augmented and indiscriminative at early stages of visual processing, and this may result in ineffective later-stage stimulus discriminatory processes. Six sessions of low-frequency rTMS may have reduced augmented cortical responses at very early stages of visual processing (i.e., P50) and subsequently improved stimulus discrimination and evaluative attentional processes at later stages (e.g., P2b, P3a).

It has been proposed that neural systems in the brains of individuals with ASD are often inappropriately activated (e.g., Belmonte & Yurgelin-Todd, 2003), and there is a disruption in the ratio between cortical excitation and inhibition (Casanova et al., 2002ab; Casanova, 2006ab; Rubenstein & Merzenich, 2003). Higher than normal cortical 'noise,' and a lack of cortical inhibitory tone may explain in part the findings of amplified and indiscriminative cortical activity at early stages of visual processing. Low-frequency rTMS may have putatively altered the disrupted ratio of cortical excitation and inhibition in ASD and subsequently minimized amplified early-stage cortical activity. As the DLPFC is involved in selecting a possible range of responses while suppressing

inappropriate ones, manipulating the contents of working memory (Ward, 2006), and directing attention in a controlled manner (Gray et al., 2003), low-frequency rTMS may have subsequently depotentiated enhanced synaptic weights in this area of cortex thereby improving selective attention and executive function within in this population.

CHAPTER 3: EVOKED AND INDUCED GAMMA OSCILLATION POWER

Introduction

Electroencephalography (EEG) is the measurement of the summation of postsynaptic currents via scalp electrodes, and the oscillatory frequency ranges of the postsynaptic currents can be divided into delta (0-4Hz), theta (4-8Hz), alpha (8-12Hz), beta (12-30Hz) and gamma (30-80Hz) frequencies (Handy, 2005). Electroencephalography is directly related to the postsynaptic activity of the neocortex (Murias, Webb, Greenson, & Dawson, 2007), and high-frequency EEG oscillations (12-80Hz) are generated in neuronal networks involving excitatory pyramidal cells and inhibitory GABAergic interneurons (Whittington, Traub, Kopell, Ermentrout, & Buhl, 2000). According to Grothe and Klump (2000) networks of inhibitory interneurons act as GABA-gated pacemakers and are critically involved in generation of gamma EEG oscillations. Specifically, the generation of normal gamma oscillations directly depends on the integrity of the connections of GABAergic interneurons within cortical minicolumns (Whittington et al., 2000). According to Orekhova (2007) high frequency EEG oscillations can be attenuated by the application of GABAergic drugs (e.g. benzodiazepines or barbiturates), which may be attributed to an increase in the GABAergic contribution of minicolumnar inhibitory interneurons.

According to Orekhova (2007) epilepsy is common in individuals with autism, and some studies indicate as high as a 44% comorbidity rate of autism and seizure disorder (Tuchman & Rapin, 2002; Amaral et al., 2008). In fact, Levitt et al. (2004) found that mutations in mice reducing GABAergic interneuron activity manifested seizures and behavioral disturbances. Among individuals with primary generalized epilepsy EEG oscillation in the gamma range exceeds that of healthy individuals by 3 to 10 times (Willoughby et al. 2003). Even autistic individuals lacking seizures are at a higher risk of manifesting epileptiform EEG abnormalities (Baird, Robinson, Boyd, & Charman, 2006; Chez et al., 2006; Lewine et al., 1999; Tuchman & Rapin, 1997). The high concurrence of epileptiform abnormalities and ASD suggest that autistic individuals as well may be susceptible to increased high frequency EEG oscillations, and according to Rubenstein and Merzenich (2003) a higher occurrence of gamma EEG oscillations in children with autism suggests an imbalance in the ratio between cortical excitation and inhibition.

Electrophysiological research has provided evidence that gamma activity is a physiological indicator of the coactivation of cortical cells engaged in processing visual stimuli (Keil, Gruber, & Müller, 2001; Singer & Gray, 1995; Tallon-Baundry & Bertrand, 1999) and integrating different features of a stimulus (Müller, Gruber, & Keil, 2000). The onset of a visual stimulus gives rise to a burst of gamma activity over occipital sites, and when more complex tasks are undertaken, discrete bursts of gamma activity have been identified overlying cortical regions thought to be engaged in those tasks (Brown, Gruber, Boucher, Rippon, & Brock, 2005). For example, tasks involving attention modulation or the top-down integration of features give rise to simultaneous

bursts of gamma over frontal and occipito-parietal regions (Müller et al., 2000; Müller & Gruber, 2001; Rodriguez et al., 1999). Kanizsa illusory figures (Kanizsa, 1976) have been shown to readily produce gamma oscillations during visual cognitive tasks (Hermann, Mecklinger, & Pfeifer, 1999; Tallon-Baundry, Bertrand, Delpuech, & Pernier, 1996): Kanizsa stimuli consist of inducer disks of a shape feature and either constitute an illusory figure (square, triangle) or not (colinearity feature); in nonimpaired individuals, gamma activity has been shown to increase during 'target-present' compared to 'target-absent' trials (Brown et al., 2005; Müller et al., 1996; Tallon- Baundry et al., 1996).

Gamma band activity can be divided into either evoked or induced: Evoked gamma band activity has been identified at a latency of around 100 ms after stimulus onset (Bertrand & Tallon-Baundry, 2000; Herrmann & Mecklinger, 2000) and is highly phase locked to the onset of the stimulus; induced gamma band activity occurs later with a variable onset, although it has been reported to start at around 250 ms (Brown et al., 2005). It has been proposed that evoked gamma band activity reflects the effect of attention on early visual processing and the binding of perceptual information within the same cortical area (i.e., intra-areal), whereas induced gamma band activity reflects the later binding of feed-forward and feed-back processing in a whole network of cortical areas (corticocortical; Brown et al., 2005; Müller et al., 2000; Shibata et al., 1999). Variations of such activity have been termed event-related synchronization and desynchronization (Pfurtscheller & Aranibar, 1977) or Event Related Spectral Perturbations (Makeig, Debener, Onton, & Delorme, 2004) and have been associated with the activation of task-relevant neuronal assemblies (Pfurtscheller & Lopes da Silva, 1999; Rippon et al., 2007).

A number of studies have found abnormal gamma band activity in individuals with ASD. Brown et al. (2005) showed that autistic participants had higher parietal gamma power than controls in an experiment using Kanizsa, visual illusions; in addition, in this study, individuals with ASD showed a very early burst of gamma activity between 80 and 120 ms, and later gamma (around 300 ms) was found to occur earlier and be more powerful in the autistic patients. Grice et al. (2001) compared gamma band activity over frontal regions during a face discrimination task in adults with Autism and controls. The control participants showed clear discriminative increases in frontal gamma activity when the faces were presented upright compared to inverted, whereas in the autistic group the extent of gamma activity did not differ significantly between the upright and inverted faces. These findings suggest that in ASD gamma activity is augmented and indiscriminative. According to Brown et al. (2005) this may reflect decreased 'signal to noise' due to decreased inhibitory processing: Uninhibited gamma activity suggests that none of the circuits in the brain can emerge to dominate and constrain perceptual processing because too many of them are active simultaneously.

Theoretically contrary to other inhibitory cells (i.e., basket and chandelier), whose projections keep no constant relation to the surface of the cortex, the geometrically exact orientation of double-bouquet cells and their location at the periphery of the minicolumn (inhibitory surround) makes them an appropriate candidate for induction by a magnetic field applied parallel to cortex. Over a course of treatment, slow rTMS may selectively depotentiate enhanced synaptic weights associated with pathological conditions, and in the case of ASD it may lower the ratio of cortical excitation to cortical inhibition.

It may therefore be hypothesized that individuals with ASD will show amplified and indiscriminative gamma power in response to illusory figures reflecting 'noisy' and uninhibited cortical activity at early (i.e., evoked) and later (i.e., induced) stages of visual processing. In addition, 12 sessions of bilateral, slow rTMS stimulation applied to the dorsolateral prefrontal cortices (DLPFC) will attenuate amplified gamma activity and improve discriminatory gamma activity between relevant and irrelevant visual stimuli (i.e., target vs. non-target stimuli).

Materials and Methods

Participants

Participants with ASD were recruited through the University of Louisville Weisskopf Child Evaluation Center. Diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000; [DSM–IV–TR] 4th ed., text rev.) and further ascertained with the Autism Diagnostic Interview–Revised (LeCouteur et al., 2003). They also had a medical evaluation by a developmental pediatrician. All participants had normal hearing based on past hearing screens. Participants either had normal vision or wore corrective lenses. Participants with a history of seizure disorder, significant hearing or visual impairment, a brain abnormality conclusive from imaging studies, or an identified genetic disorder were excluded. All participants were assessed for IQ using the Wechsler Intelligence Scale for Children, Fourth Edition (Wechsler, 2003) or the Wechsler Abbreviated Scale of Intelligence (Wechsler, 2004).

Controls were recruited through advertisements in the local media. All control participants were free of neurological or significant medical disorders; had normal hearing and vision; and were free of psychiatric, learning, or developmental disorders based on self- and parent reports. Participants were screened for history of psychiatric or neurological diagnosis using the Structured Clinical Interview for DSM–IV Non-Patient Edition (First et al., 2001). Participants within the control and ASD groups were attempted to be matched by age, Full-Scale IQ, and socioeconomic status of their family. Socioeconomic status of ASD and control groups was compared based on parent education and annual household income. Participants in both groups had similar parent education levels.

Participating individuals and their parents (or legal guardians) were provided with full information about the study including the purpose, requirements, responsibilities, reimbursement, risks, benefits, alternatives, and role of the local Institutional Review Board. The consent and assent forms approved by the Institutional Review Board were reviewed and explained to all individuals who expressed interest to participate. All questions were answered before consent signature was requested. If the individual agreed to participate, she or he signed and dated the consent form and received a copy countersigned by the investigator who obtained consent.

EEG Data Acquisition and Signal Processing

Dependent measures in EEG gamma band were recorded continuously with an EGI (Electrical Geodesics, Inc., Portland, OR) 128-electrode net, referenced to vertex (impedances <50 kohm; sampling rate 500 Hz; 0.1–200 Hz online bandpass). EEG was

segmented to obtain epochs of 0–180 ms for evoked gamma power and 250-450 ms for induced gamma power. Extraction of gamma band power (30–45 Hz) in 30 trials for each stimulus type was performed with Morlet wavelet analysis (Goupillaud, Grossman, & Morlet, 1984) using MATLAB. The following channels were selected: FPz (EGI channels to left (18) and right (15) of FPz) and AFz (16) from the midline prefrontal area, F1 (20), F2 (4), F7 (34), F8 (122) from the frontal area, and P3 (53), P4 (87), P7 (59), P8 (92) from the parietal area (Figure 29); this channel configuration allowed for the analysis of gamma band activity over both hemispheres. All recorded signals were first automatically and then manually inspected for artifacts and rejected if eye movement artifacts, gross movements, or EEG sensor drifts were detected. For automatic detection, the standard in a moving time window and the normalized cross-correlation coefficient between the current recoded signal and previous succeeded trials were computed; the current recorded signal was rejected if thresholds exceeded two standard deviations or exceeded normalized cross correlation. The standard deviation threshold was in the 35–50 μV range, and normalized cross-correlation was approximately 0.5. To accurately find the features that discriminate autistic participants from controls and autistic participants before and after rTMS using recorded EEG signals, relative power of gamma (i.e., 30–45 Hz) within the entire spectrum was calculated.

Kanizsa Illusory Figure Test

In this task participants have to respond with a button-press to rare (25% probability) Kanizsa squares (targets) among Kanizsa triangles (rare nontarget distracters,

25% probability) and non-Kanizsa figures (standards, 50% probability). The stimuli are presented for 250 ms with inter-trial intervals varying in the range of 1,100 to 1,300 ms. A fixation point (cross) was presented during inter-trial intervals. Black figures were displayed on a white background on a flat 19-in. color LCD.

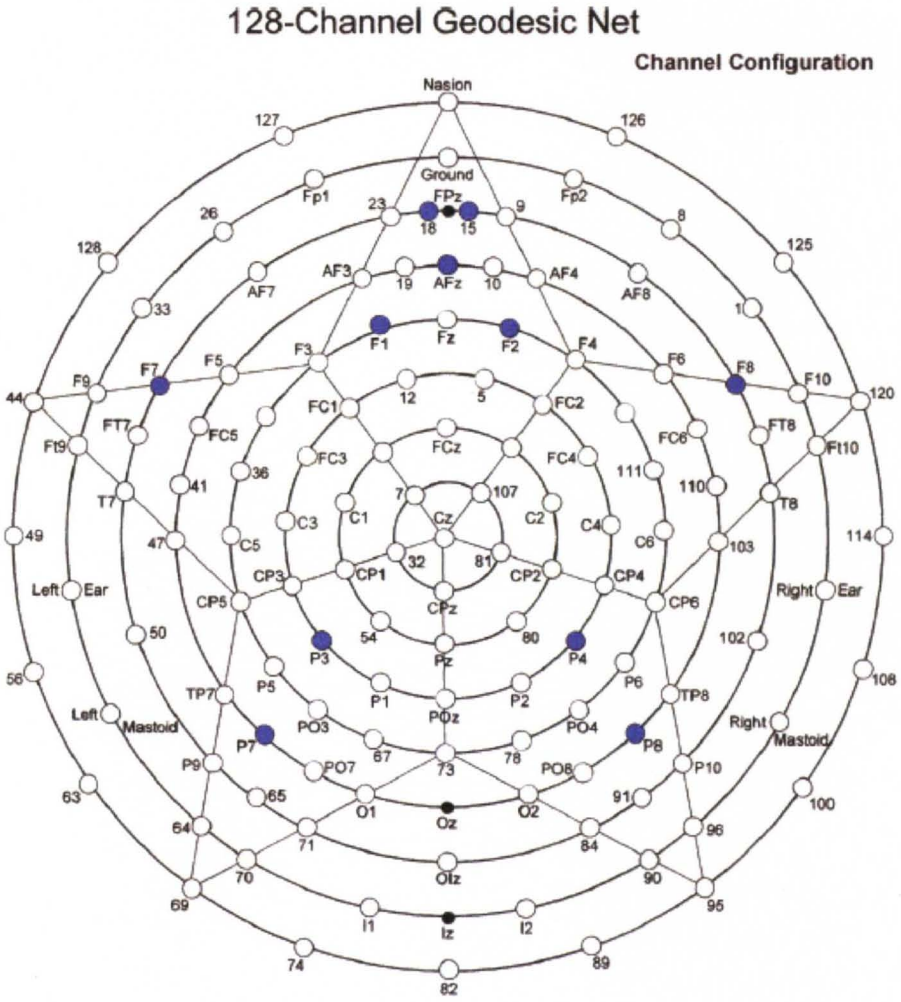

Figure 29: Sensor layout of the 128-channel Geodesic net (EGI, Eugene, Oregon) with selected channels labeled (Baruth et al., 2010a)

Participants were instructed to press the first button on a five-button keypad with their right index finger when a target appears and ignore when the non-target Kanizsa or standard stimuli appear. All stimulus presentation and behavioral response (reaction time [RT], accuracy) collection was controlled by a PC computer running E-prime software (Psychology Software Tools, Sharpsburg, PA). Participants were instructed to remain as still as possible with their eyes on the fixation mark and to refrain from blinking. Autistic patients had at least one session for EEG net conditioning and getting familiar with the experimental room.

The stimulus types used in the experiment were Kanizsa square (target), Kanizsa triangle (nontarget), non-Kanizsa square, and non- Kanizsa triangle (standards). The non-target Kanizsa triangle is introduced to differentiate the processing of Kanizsa figures and targets. The stimuli consist of either three or four inducer disks, which are considered the shape feature, and they either constitute an illusory figure (square, triangle) or not (collinearity feature; Figure 30). One block of 240 trials was presented. Participants with Autism were administered the Kanizsa, illusory figure test before (pre-TMS) and after (post-TMS) treatment. There was also a randomly assigned waiting-list group where individuals with ASD were administered the same Kanizsa illusory figure test twice (with an 8-week interval) to control for the TMS treatment. Control participants were administered the Kanizsa illusory figure test once.

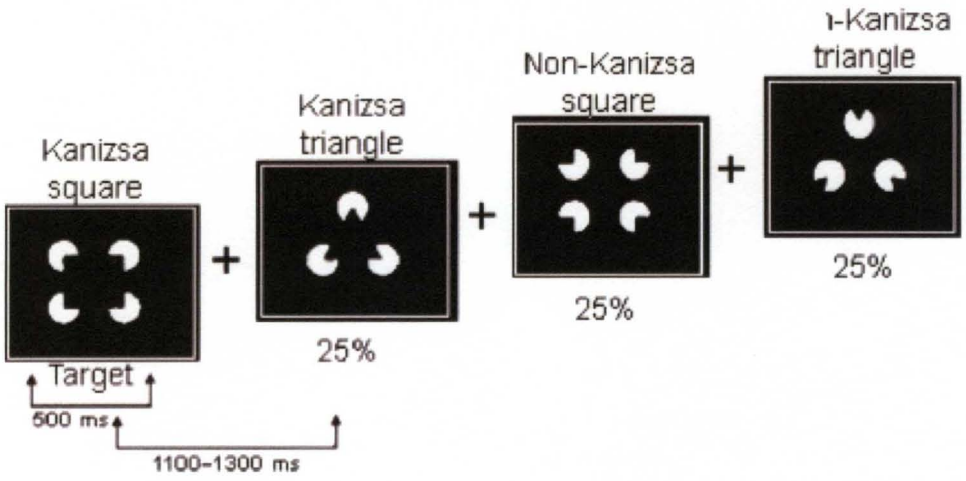

Figure 30: Kanizsa and non-Kanizsa figures were used as stimulus material in this experiment. In particular, the stimulus types are Kanizsa square (target), Kanizsa triangle, non-Kanizsa square, and non-Kanizsa triangle. The non-target Kanizsa triangle is introduced to differentiate processing of Kanizsa figures and targets. The stimuli consist of either three or four inducer disks which are considered the shape feature, and they either constitute an illusory figure (square, triangle) or not (collinearity feature).

TMS Procedure

A trained electrophysiologist delivered rTMS using a Magstim Rapid (Model 220) instrument (Magstim Corporation, Sheffield, England) with a 70-mm wing span figure eight coil. Motor threshold (MT) was determined for each hemisphere in all individuals by gradually increasing the output of the machine by 5% until a 50 μV deflection or a visible twitch in the First Dorsal Interosseous (FDI) muscle was identified in two out of three trials of stimulation over the cortical area controlling the contralateral FDI. Electromyographic responses were monitored on a continuous base with a C-2 J&J Engineering physiological monitor (Poulsbo, WA). Motor-evoked potentials were

recorded from the hand contralateral to stimulation using the C2 J&J system with USE-2 Physiodata software applications. Heart rate, heart rate variability, skin conductance, and skin temperature were also recorded. EMG and other physiological recordings were stored for later analysis. Autistic patients were encouraged to visit the laboratory at least once beforehand to get familiar with the TMS procedure.

The TMS treatment course was administered once per week for 12 weeks (a total of twelve 1Hz rTMS treatments); the first 6 treatments were over the left DLPFC, and the remaining 6 were over the right DLPFC. The site for stimulation was found by placing the coil 5 cm anterior, and in the parasagittal plane, to the site of maximal FDI stimulation. The figure-eight coil, with a 70-mm wing diameter was kept flat over the scalp. Participants were wearing a swimming cap on their head. Stimulation was done at 1Hz and 90% MT, with a total of 150 pulses / day (fifteen 10-s trains with a 20- to 30-s interval between the trains). 1Hz was chosen as the stimulation frequency as studies have shown that low-frequency rTMS ($\leq$1 Hz) increases inhibition of stimulated cortex (e.g., Boroojerdi et al., 2000); there is also a lower risk for seizures the lower the rTMS frequency. Selection of 90% of the MT was based on the experience of numerous publications where rTMS was used for the stimulation of DLPFC in different psychiatric and neurological conditions (for reviews, see Daskalakis et al., 2002; Gershon et al., 2003; Greenberg, 2007; Holtzheimer et al., 2001; Loo & Mitchell, 2005; Rosenberg et al., 2002; Wassermann & Lisanby, 2001). The stimulation power was kept below MT as an extra safety precaution due to the increased risk of seizure within this study population. The minimal number of TMS pulses during a TMS session has varied from 30 to 2,000 pulses per session on a once-per-week over 8 weeks to twice-a-day basis over

10 days (Daskalakis et al., 2002). It has been concluded that less than 100 pulses per session is not very promising in terms of therapeutic efficacy (see Helmich et al., 2006 for review).

Statistical Analysis

Statistical analyses were performed on participant-averaged EEG data with the participant averages being the observations. The primary analysis model was the repeated measures analysis of variance (ANOVA), with dependent variables being relative gamma power at the 11 selected EEG channels just described. Relative gamma power at the selected EEG channels was analyzed using ANOVA with stimulus (target, non-target, standard) and hemisphere (left, right) as factors (all within participants); differences in anterior and posterior relative gamma power were also analyzed. For hemispheric differences the following channel combinations were compared: left and right lateral frontal (F7, F8); left and right medial frontal (F1, F2); left and right lateral parietal (P7, P8); left and right medial parietal (P3, P4). For anterior and posterior differences the following channel combinations were compared: lateral left anterior and posterior (F7, P7); medial left anterior and posterior (F1, P3); lateral right anterior and posterior (F8, P8); medial right anterior and posterior (F2, P4). The between-subject factors included the following group comparisons: baseline (ASD vs. controls), treatment (ASD pre-TMS vs. ASD post-TMS), and wait-list (ASD Pre-WTL vs. ASD Post-WTL; i.e., no TMS). For all ANOVAs, Greenhouse-Geisser corrected p values were employed where appropriate. SPSS v.14 and Sigma Stat 3.1 packages were used for statistical analysis.

Results

Participant Characteristics

Twenty-five autistic patients (ASD group) were enrolled, 21 male and 4 female, with a mean age of 13.8 ± 4.3 years. Sixteen of them were randomly assigned to active 1.0 Hz TMS treatment (TMS group), whereas 9 were randomly assigned to the waiting-list group (WTL group) (see Figure 31). Mean age of participants in the TMS group was 13.9 ± 5.3 years and 13.5 ± 2.0 years in the waiting-list group. Mean Full-Scale IQ score for children with ASD was 86.0 ± 24.7. The mean Full-Scale IQ of the active TMS group was not significantly different from the randomly assigned waiting-list group. Twenty control participants were recruited (CNT group), 12 male and 8 female (*M* age = 15.3 ± 5.1 years). There were no statistically significant age or IQ differences between the groups.

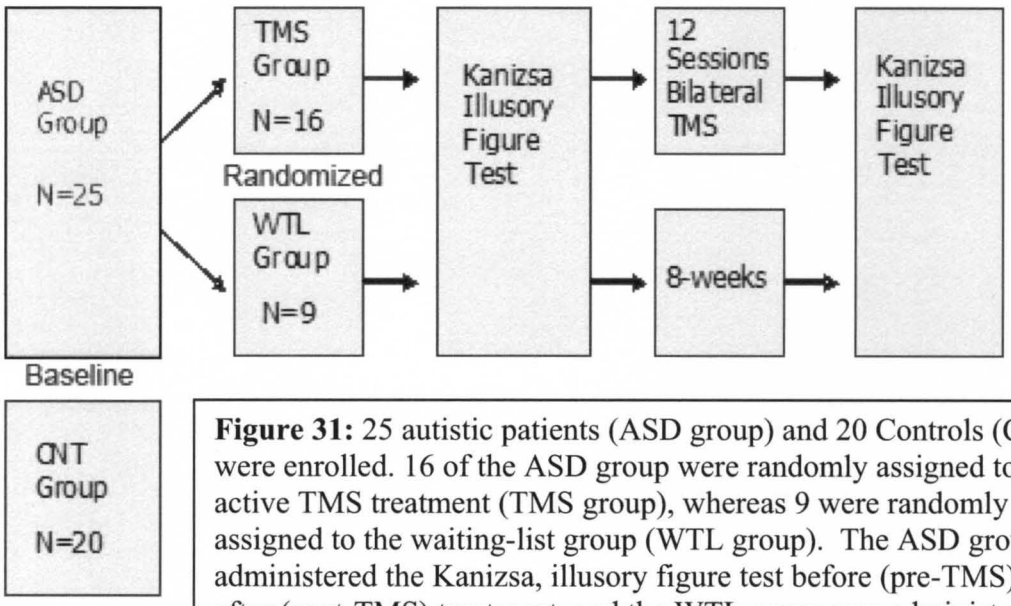

Figure 31: 25 autistic patients (ASD group) and 20 Controls (CNT) were enrolled. 16 of the ASD group were randomly assigned to active TMS treatment (TMS group), whereas 9 were randomly assigned to the waiting-list group (WTL group). The ASD group was administered the Kanizsa, illusory figure test before (pre-TMS) and after (post-TMS) treatment, and the WTL group was administered the test before and after an 8-week interval to control for the TMS. Control participants were administered the Kanizsa illusory figure test once for a baseline comparison.

Baseline (Pre-TMS) Group Differences

Evoked and Induced EEG activity

One-way ANOVA analysis revealed that evoked gamma power was significantly higher to target Kanizsa stimuli at all channels in the control group compared to the ASD group ($p<.001$). A Stimulus (target, non-target) X Group (ASD, control) interaction was significant at all channels ($p<.001$) indicating significantly higher evoked gamma power to target Kanizsa stimuli compared to non-target Kanizsa stimuli in controls, whereas the ASD group had a minimal difference in evoked gamma power between target and non-target Kanizsa stimuli actually demonstrating more gamma power to non-targets (Figure 32). An analysis of differences in evoked gamma power between anterior and posterior regions revealed a Topography (anterior, posterior) X Group (ASD, control) interaction over the left hemisphere to all stimuli where controls had higher evoked gamma power over frontal (F7) compared to posterior (P7) regions ($F=5.4891$, $p=.024$), whereas the ASD group showed a negligible difference with slightly higher evoked gamma power over posterior (P7) regions. There were no significant hemispheric differences elucidated between ASD and control groups in evoked gamma power during baseline analysis. Additionally, analysis revealed no significant baseline group differences in induced gamma power between the ASD and control groups (Figures 33 & 34).

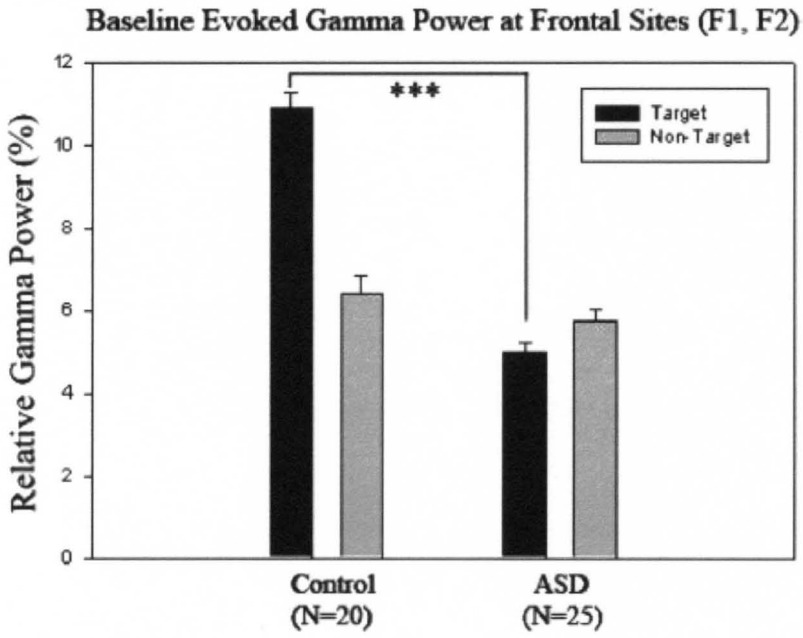

Figure 32: Relative evoked gamma power at frontal sites (F1, F2) in control (N=20) and Autism Spectrum Disorder (ASD) groups (N=25) to target and non-target stimuli. Note. Controls have significantly higher evoked gamma power to target Kanizsa stimuli compared to the ASD group ($p<.001$) with more of a pronounced difference between target and non-target stimuli (Baruth et al., 2010a).

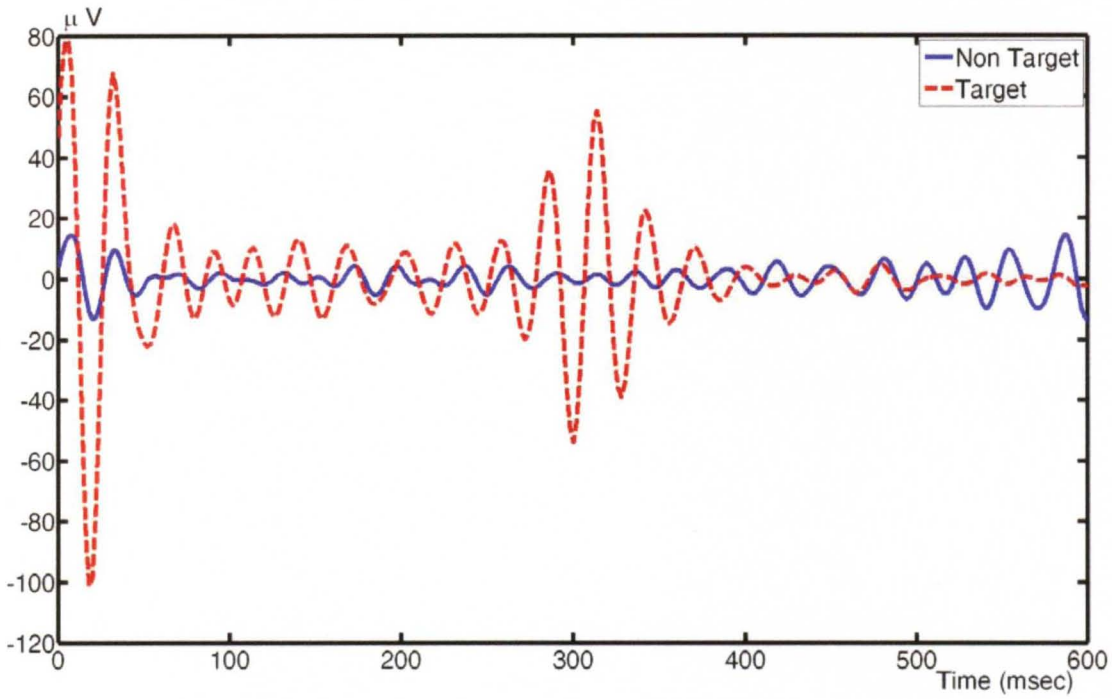

Figure 33: Average amplitude of evoked and induced gamma oscillations in response to non-target and target Kanizsa stimuli in control participants (N=20) over left lateral frontal EEG recording sites (F7, F1, AFZ). Single-trial EEG was averaged across 30 trials in each condition (non-target, target).

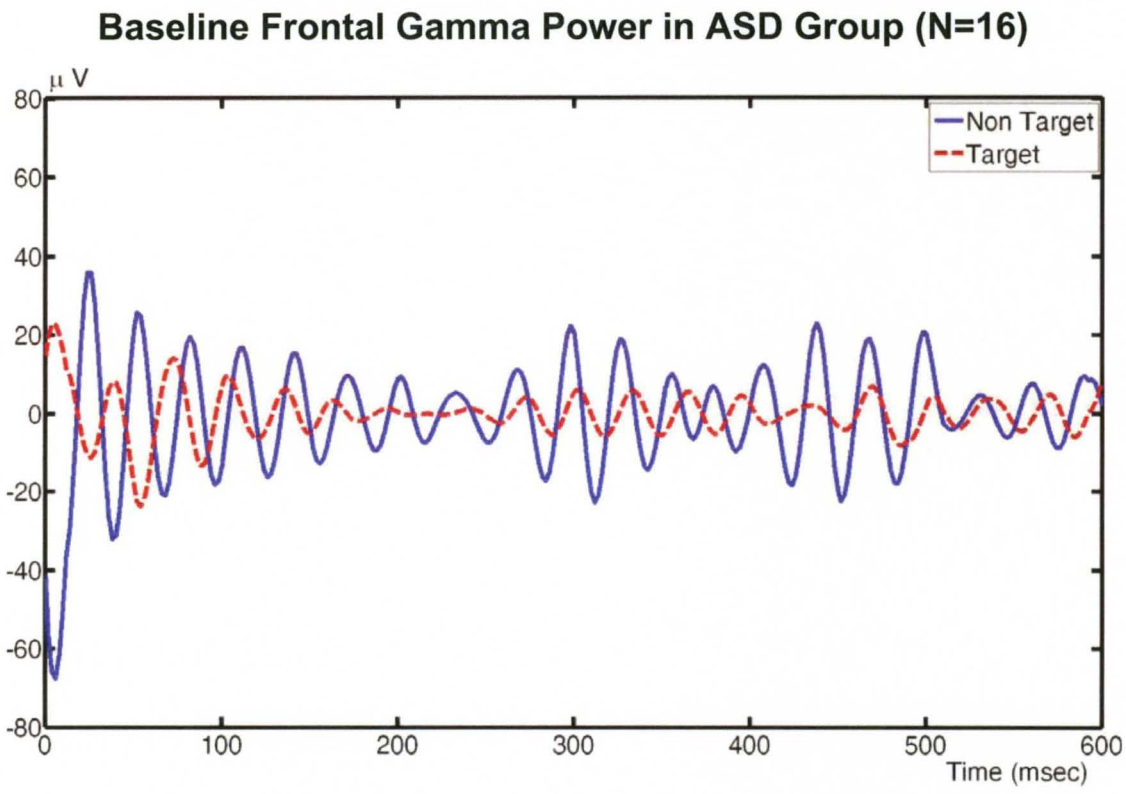

Figure 34: Baseline average amplitude of evoked and induced gamma oscillations in response to non-target and target Kanizsa stimuli in ASD participants (N=16) over left lateral frontal EEG recording sites (F7, F1, AFZ). Single-trial EEG was averaged across 30 trials in each condition (non-target, target).

Post-TMS Group Differences

Evoked and Induced EEG activity

One-way ANOVA analysis revealed that evoked gamma power significantly increased to target Kanizsa stimuli at all channels as a result of rTMS treatment ($p<.001$). A Stimulus (target, non-target) X Group (pre-rTMS, post-rTMS) interaction was significant at all channels ($p<.001$) indicating increases in evoked gamma power to target stimuli with a decrease to non-targets following treatment (Figures 35 & 36). There were no significant, topographic (hemisphere, anterior vs. posterior) differences revealed following rTMS treatment. Also, there were no significant differences in induced gamma power revealed as a result of rTMS. The waiting-list group (i.e., ASD patients with an 8-week interval between Kanizsa, illusory figure tests with no rTMS treatment) did not show significant evoked gamma power increases to target Kanizsa stimuli at any channels following the waiting period. In fact, they showed the opposite effect at two posterior EEG channels: Evoked-gamma power decreased to targets following the waiting period at P4 ($F=9.455$, $p=.008$) and P7 ($F=5.862$, $p=.029$). In addition, repeated measures analysis revealed significant Stimulus (target, nontarget) X Group (prewait, postwait) interactions at F1, F2, P3, P4 (all $ps<.05$) indicating a significant increase in evoked gamma power to non-targets with a slight decrease to targets following the waiting period (Figure 37). There were significant differences in induced gamma power revealed following the waiting period.

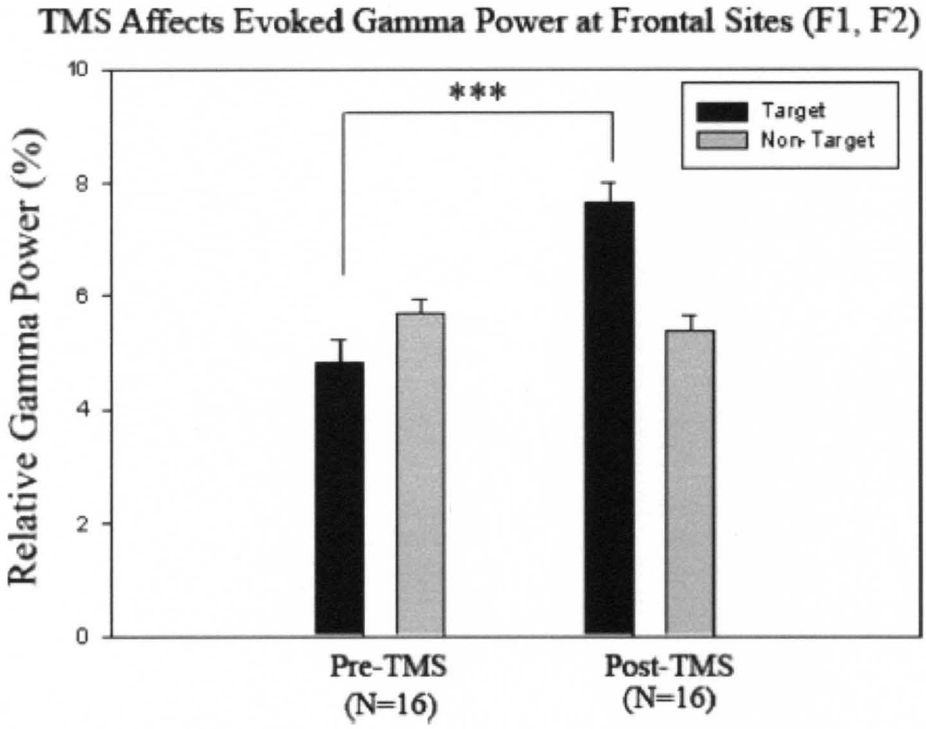

Figure 35: Relative evoked gamma power at frontal sites (F1, F2) in pretranscranial magnetic stimulation (TMS; N=16) and post-TMS groups (N=16) to target and non-target stimuli. Note. Relative evoked gamma power significantly increases to target stimuli ($p<.001$) with more of a pronounced difference between target and non-target stimuli as a result of repetitive TMS (Baruth et al., 2010a).

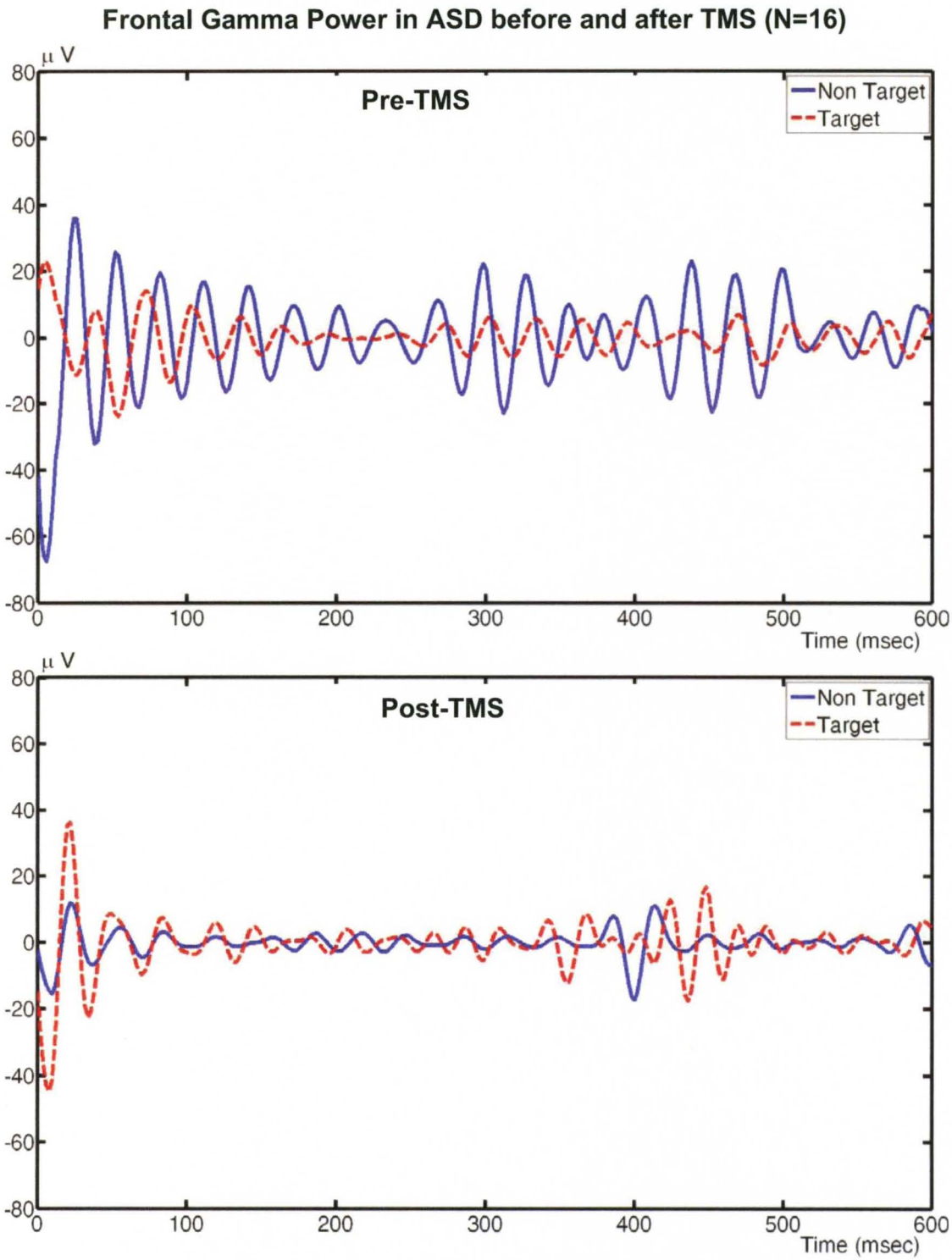

Figure 36: Average amplitude of evoked and induced gamma oscillations in response to non-target and target Kanizsa stimuli in participants with Autism Spectrum Disorder before (N=16) and after repetitive transcranial magnetic stimulation (rTMS; N=16) over left lateral frontal EEG recording sites (F7, F1, AFZ). Single-trial EEG was averaged across 30 trials in each condition (non-target, target).

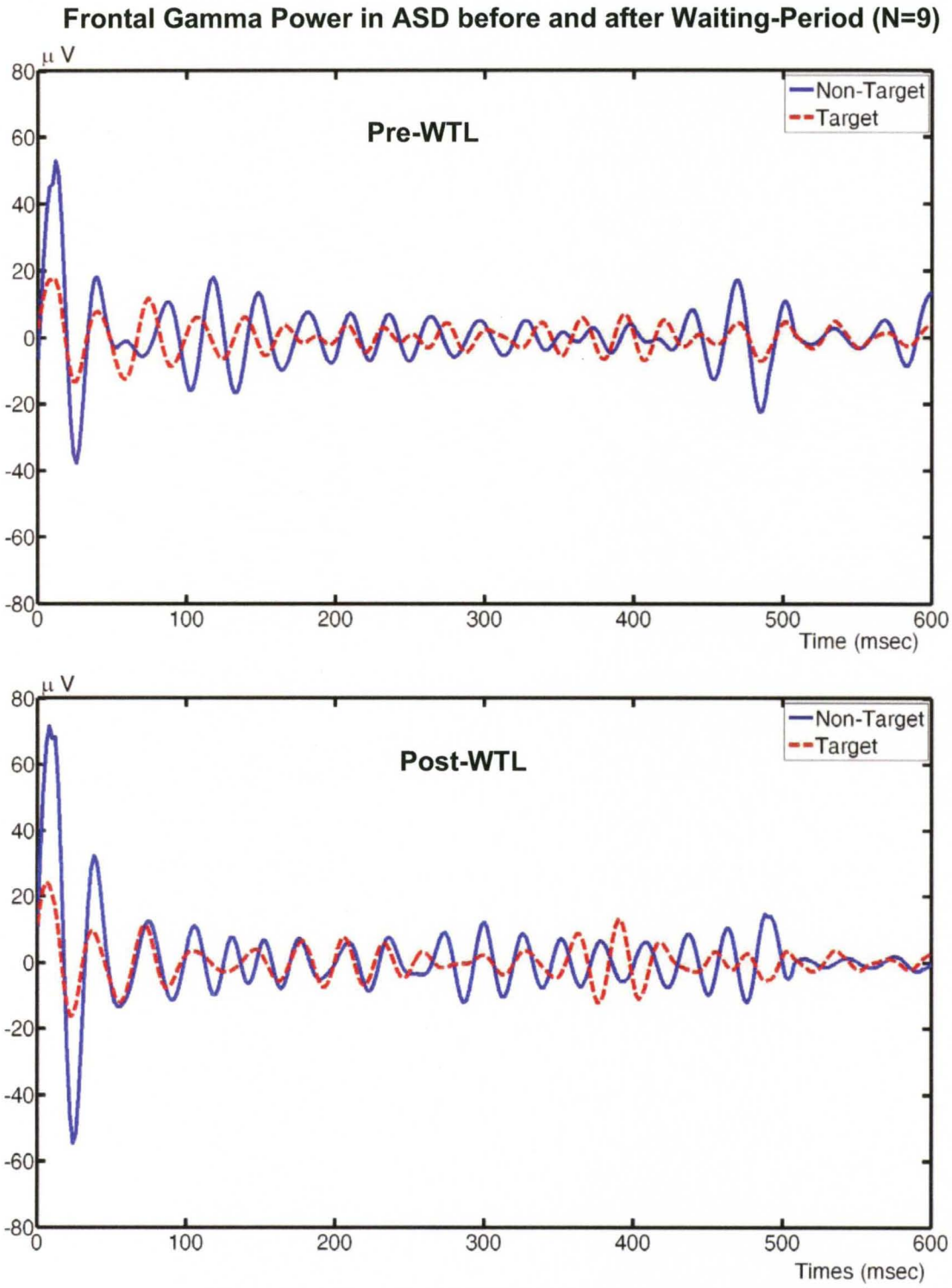

Figure 37: Average amplitude of evoked and induced gamma oscillations in response to non-target and target Kanizsa stimuli over left lateral frontal EEG recording sites (F7, F1, AFZ) in participants with Autism Spectrum Disorder before and after (N=9) an 8-week waiting period. Single-trial EEG was averaged across 30 trials in each condition (non-target, target).

Reported Side Effects of TMS

Before each session participants and their primary caregivers were asked if any side effects were experienced as a result of their previous TMS session. The most commonly (i.e., 5 of 16 in active TMS group) reported side effect was an 'itching' sensation around the nose during stimulation. One participant reported a mild, transient tension-type headache on the day of stimulation. There was no discomfort reported due to the sound of the pulses. Overall, no participants reported any lasting side effects.

Discussion

Our hypothesis was that individuals with ASD would show amplified and indiscriminative gamma power in response to illusory figures at early (i.e., evoked) and later (i.e., induced) stages of visual processing and that 12 sessions of bilateral, slow rTMS would attenuate amplified, gamma activity and improve discriminatory gamma activity between relevant and irrelevant visual stimuli. Our results indicate that prior to rTMS individuals with ASD had a minimal difference in evoked gamma power between target and non-target Kanizsa stimuli at all channels. In fact, evoked gamma power responses were slightly larger in response to non-target Kanizsa stimuli relative to targets. In contrast the control group had a significantly higher evoked gamma power to target Kanizsa stimuli compared to non-target Kanizsa stimuli showing clear differences in visual stimulus discrimination. In addition, the control group showed a greater difference in evoked gamma power between frontal and parietal regions to all stimuli over the left hemisphere: Controls had more frontal as compared to parietal gamma

activity, whereas the ASD group showed negligible topographic differences. These baseline findings are similar to the findings of Grice et al. (2001) where individuals with Autism did not show significant differences in frontal gamma activity during the processing of upright and inverted faces, whereas control participants showed clear discriminative increases in frontal gamma activity when the faces where presented upright compared to inverted. These findings also correspond to our previous investigation (Sokhadze, El-Baz, Baruth, et al., 2009b) where we found positive differences in gamma oscillation power (i.e., 30–80 Hz, 0–800 msec) between target and non-target Kanizsa stimuli where decreased, especially over the lateral frontal (F7, F8) and parietal (P7, P8) EEG sites, in adolescents and young adults with ASD; this was mainly due to significant increases in gamma power at all recording sites, especially evoked gamma (i.e., ~100 ms) over frontal channels, to non-target Kanizsa stimuli compared to controls.

It has been argued that evoked gamma band activity reflects the effect of attention on early visual processing (Herrmann & Mecklinger, 2000) and sensory-memory matching processes (Herrmann, Munck, & Engel, 2004). In addition, evoked gamma activity has been associated with the binding of perceptual information within the same cortical area, as compared to the feed-forward and feed-back processing (i.e., over a whole network of cortical areas) associated with induced gamma oscillations. Our baseline results indicate that in ASD evoked gamma activity is not discriminative of stimulus type, whereas in controls early gamma power differences between target and non-target stimuli are highly significant.

There are a few plausible explanations as to why the gamma response does not allow for discrimination between stimuli in ASD. It is well known that ASD is associated with amplified responses to incoming sensory information. Studies suggest that the neural systems of individuals with ASD are overactivated (Belmonte & Yurgelun-Todd, 2003), and there is a lack of cortical inhibitory tone (e.g., Casanova et al., 2002a; Casanova et al., 2002b; Casanova et al., 2006a; Rubenstein & Merzenich, 2003). Deficits in cortical inhibitory processes and poor signal-to-noise ratios may result in increased simultaneous activity of competing local networks where no pattern can emerge to dominate and constrain perceptual processing. In a network that is overactivated and 'noisy,' local cortical connectivity may be enhanced at the expense of long-range cortical connections and individuals with ASD may have difficulty directing attention: It may not be possible for them to selectively activate specific perceptual systems based on the relevance of a stimulus (i.e., target vs. nontarget).

Our previous findings investigating event-related potentials (ERPs) during a novelty processing task further supports the idea of difficulty discriminating task-relevant from irrelevant stimuli in ASD (see Baruth, Casanova, Sears, & Sokhadze, 2010b; Sokhadze, Baruth, et al., 2009a). Briefly, we found that participants with ASD showed a lack of stimulus discrimination between target and non-target stimuli compared to controls, and this was mainly due to significantly augmented ERP components to irrelevant distracter stimuli over frontal and parietal recording sites. Early ERP components (e.g., P50, N100) were especially increased to irrelevant distracter stimuli in the ASD group indicating augmented responses at early stages of visual processing (i.e., ~100 ms). Early gamma components (i.e., evoked) are measured at the same time over

the same cortical regions as these early ERP components. The very early burst of gamma activity between 80 and 120 ms found by Brown et al. (2005) and our findings of augmented evoked gamma activity and early ERP responses (Baruth et al., 2010b; Sokhadze, Baruth, et al., 2009a) to task irrelevant stimuli support the idea of disturbances in the activation task-relevant neuronal assemblies and the perceptual control of attention in ASD. Although we found significant group differences in relative evoked gamma power in processing relevant and irrelevant visual stimuli in this study, it is important to mention why we did not find significantly amplified relative evoked gamma power in the ASD group compared to controls. We attribute this to the fact that relative gamma band power is calculated in reference to the entire EEG spectrum, and in ASD it has previously been shown that other frequency ranges are augmented as well (e.g., Dawson, Klinger-Grofer, Panagiotides, Lewy, & Castelloe, 1995; Stroganova et al., 2007).

Additionally we did not find significant baseline differences in induced gamma power between the ASD and control groups. This may be related to the fact that induced gamma band activity occurs later (i.e., ~250 ms) (Brown et al., 2005) and is less reflective of sensory processing as ASD has been associated with overactivated sensory systems (Belmonte & Yurgelun-Todd, 2003). Consequently when gamma activity is calculated relative to the entire spectrum in ASD the difference between gamma power and the power of other frequency ranges may be better elucidated at early stages of processing (i.e. evoked).

Our findings after 12 sessions of bilateral rTMS to the DLPFC showed that evoked gamma power significantly increased to target Kanizsa stimuli in the ASD group at all channels. Furthermore, repeated measures analysis revealed highly significant

increases in evoked gamma power to target stimuli with a slight decrease to non-targets following treatment. Individuals with ASD showed significant improvement in discriminatory gamma activity between relevant and irrelevant visual stimuli following rTMS treatment. These findings corroborate with our previous study (Sokhadze, El-Baz, Baruth, et al., 2009b) where we found that six sessions of slow (i.e., 0.5 Hz) rTMS significantly reduced gamma power (i.e., 30–80 Hz, 0–800 ms) to non-target stimuli, thereby improving discriminatory gamma activity. As mentioned earlier in nonimpaired individuals, gamma activity has been shown to increase during 'target-present' compared to 'target-absent' trials (Brown et al., 2005; Müller et al., 1996; Tallon-Baundry et al., 1996). Our findings show that before rTMS individuals with ASD are unable to selectively activate evoked gamma activity based on the relevance of a stimulus, which may reflect 'noisy' perceptual processing and a reduction in cortical inhibitory tone; this may be related to the strong aversive reactions to sensory stimuli commonly recorded in autistic individuals. Twelve sessions of bilateral, slow rTMS applied to the DLPFC significantly improved differences in discriminatory gamma activity at early stages of visual perception. We hypothesize that slow rTMS increased inhibitory tone by selectively activating double-bouquet cells at the periphery of cortical minicolumns, and over a course of treatment attenuated noisy and amplified cortical activity improving discriminatory gamma activity.

The randomly assigned waiting-list group (i.e., ASD patients with an 8-week interval between Kanizsa, illusory figure tests and no rTMS treatment) did not show significant improvement in discriminatory gamma activity. In fact, at two posterior EEG

channels (i.e., P4, P7) evoked gamma power significantly decreased to target stimuli following the waiting period and repeated measures analysis revealed significant increases in evoked gamma power to non-targets with a slight decrease to targets at frontal and parietal channels (i.e., F1, F2, P3, P4). Moreover, the waiting-list group showed the opposite effect as compared to the active rTMS group validating the effect of rTMS and discrediting any effect of practice.

Methodologically speaking, the 30–45 Hz portion of the gamma band has been especially associated with visual information processing and attentional perceptual mechanisms (e.g., Müller et al., 2000). Refining our method of analysis to isolate this portion of the gamma band relative to the entire EEG spectrum (i.e., percentage of relative gamma power) proved to be a useful approach in isolating this activity and avoided any complications due to power line interference. This methodological approach is in contrast to our previous study (Sokhadze, El-Baz, Baruth, et al., 2009b) where we calculated gamma band power between 30–80 Hz. Overall our updated method of analyzing gamma band activity is better defined and adjusted to effectively assess group differences in discriminatory gamma activity.

Our study had some limitations that should be addressed. We included 3 participants older than 17, which increased the standard deviation of age for our ASD participants. For future studies we are limiting our enrollment to include only children and young adults between the ages of 8 and 17. In addition, we enrolled 2 participants who were previously diagnosed as mentally retarded, and this increased the standard deviation of IQ for the ASD group. Despite these limitations, all participants were able to perform the required tasks.

In conclusion, there is surmounting evidence of augmented and indiscriminative cortical activity at early-stages of visual processing in individuals with ASD. In this study we showed that in ASD evoked gamma activity is not discriminative of stimulus type, whereas in controls early gamma power differences between target and nontarget stimuli were highly significant. In a network that is overactivated and 'noisy,' it may not be possible for individuals with ASD to selectively activate specific perceptual systems based on the relevance of a stimulus (i.e., target vs. non-target). Following 12 sessions of bilateral slow rTMS treatment individuals with ASD showed significant improvement in discriminatory gamma activity between relevant and irrelevant visual stimuli; slow rTMS may have increased cortical inhibitory tone and improved differences in evoked gamma activity between stimuli by attenuating amplified cortical activity. Our preliminary findings suggest rTMS has the potential to become a unique therapeutic tool capable of addressing some of the core symptoms of ASD. Considering the few therapeutic options currently available for ASD, TMS is a welcome option capable of playing an important role in improving the quality of life for many with the disorder.

CHAPTER 4: BEHAVIORAL FINDINGS

Introduction

As stated earlier Autism is considered to be an etiologically heterogeneous and biologically determined developmental disorder characterized by severe disturbances in reciprocal social relations, impaired development of language and communication skills and by a limited repertoire of behavioral patterns with a restricted ability of abstraction (American Psychiatric Association, 2000; [DSM–IV–TR] 4th ed., text rev.). The term autism spectrum disorder (ASD) is used to encompass three conditions sharing a similar core symptomatology: Autism, Asperger syndrome, and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). Individuals with ASD share common behavioral characteristics (see Charman, 2008). First, they have qualitative impairments in social interaction. These impairments are manifested by the use of nonverbal behaviors to regulate social interaction, a failure to develop peer relationships, a deficiency in the spontaneous sharing of interests and a lack of emotional reciprocity. Secondly, ASD patients show qualitative impairments in social communication. These deficits are generally indicated by delayed language development without nonverbal compensation, problems starting and sustaining conversations, stereotyped language, and a lack of imagination in their play.

Thirdly, individuals with ASD also show a limited compilation of interests, behaviors, and activities. Impairments of this nature manifest themselves by an abnormal overfocus on certain topics, adhering to nonfunctional routines, the display of stereotyped motor mannerisms and a preoccupation with object parts rather than the complete whole. According to Cannon et al. (2010) repetitive and stereotyped behavior in ASD includes both repetitive sensory-motor actions and insistence on sameness. Repetitive sensory-motor actions include 'hand and finger mannerisms', 'unusual sensory interests', 'repetitive use of objects', 'complex mannerisms' and 'rocking'. Insistence on sameness includes 'difficulties with minor changes in personal routine or environment', 'resistance to trivial changes in environment' and 'compulsions/rituals'. Finally, it has been reported that individuals with ASD have abnormal reactions to the sensory environment (Charman, 2008) and perceptual abnormalities (Happe´, 1999) including aversive reactions to visual, auditory, and/or tactile stimuli (Casanova et al., 2003).

Stigler, Erikson, Mullett, Posey, and McDougle (2010) add that individuals with ASD often exhibit severe irritability such as aggression, self injurious behavior, and tantrums which can impact quality of life and participation in formal education. Also, according to Murray (2010) ASD is frequently marked by symptoms consistent with attention-deficit/hyperactivity disorder (ADHD), namely inattention, hyperactivity, and impulsivity. Recent work has established that about half of the ASD population also meets diagnostic criteria for ADHD, although the comorbid diagnoses are precluded by the DSM-IV-TR. Individuals with co-occurring ASD and ADHD symptoms are more severely impaired, with significant deficits seen in social processing, adaptive functioning, and executive control (Murray, 2010).

It may be hypothesized that 12 sessions of bilateral, slow rTMS stimulation applied to the dorsolateral prefrontal cortices (DLPFC) will improve cortical inhibitory tone and decrease the ratio of cortical excitation to inhibition in ASD which may not only modulate regions proximal to stimulation but induce transsynaptic effects. Behaviors associated with ASD and prefrontal cortical function may be improved as interneurons play a prominent role in finely tuning cortical information processing and disturbances in prefrontal cortical function include disturbances in social interaction, executive function, and cognitive control (Levitt et al., 2004; Casanova, 2006a; Ward, 2006); this includes planning, cognitive flexibility, abstract thinking, rule acquisition, initiating appropriate actions and inhibiting inappropriate actions, and selecting relevant sensory information (Stuss & Knight, 2004).

Material and Methods

Participants

Participants with ASD were recruited through the University of Louisville Weisskopf Child Evaluation Center. Diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000; [DSM–IV–TR] 4th ed., text rev.) and further ascertained with the Autism Diagnostic Interview–Revised (LeCouteur et al., 2003). They also had a medical evaluation by a developmental pediatrician. All participants had normal hearing based on past hearing screens. Participants either had normal vision or wore corrective lenses. Participants with a history of seizure disorder, significant hearing or visual impairment, a brain abnormality

conclusive from imaging studies, or an identified genetic disorder were excluded. All participants were assessed for IQ using the Wechsler Intelligence Scale for Children, Fourth Edition (Wechsler, 2003) or the Wechsler Abbreviated Scale of Intelligence (Wechsler, 2004).

Pre- and Post- TMS Behavioral Measures

Social and behavioral functioning for participants was evaluated utilizing caregiver reports and clinician ratings of improvement. Participants were evaluated prior to receiving TMS and 2 weeks following treatment. There was also a waiting-list group with an eight week interval (i.e., no TMS) between behavioral assessments to control for TMS. The following were the included measures:

Aberrant behavior checklist (ABC). The ABC (Aman & Singh, 1994) is a clinician administered rating scale assessing five problem areas: Irritability, Lethargy/Social Withdrawal, Stereotypy, Hyperactivity, and Inappropriate Speech based on caregiver report. Each area contains multiple items receiving a rating from 0 to 3. Items are summed and high scores for each area reflect severity of the problem area. The ABC has been shown to be effective in assessing behavior changes in Autism (Aman, 2004). Specifically, for this study the Irritability and Hyperactivity subscales of the ABC were used as outcome measures.

Social responsiveness scale (SRS). The SRS (Constantino & Gruber, 2005) is a caregiver-completed rating scale assessing social interest and interaction. The scale provides a dimensional measure of social interaction allowing the rating of social skills in Autism as well as non-autistic individuals. For this study the Social Awareness subscale of the SRS was used as an outcome measure. A higher score indicates more impairment.

Repetitive behavior scale–revised (RBS). The RBS (Bodfish, Symons, & Lewis, 1999) is a caregiver-completed rating scale assessing repetitive and restricted behavior patterns. The RBS is a measure of different behaviors: stereotyped, self-injurious, compulsive, ritualistic, sameness, and restricted range (Bodfish, Symons, Parker, & Lewis, 2000). Items from scales are summed to obtain a measure of severity of repetitive behavior. A higher score indicates more impairment.

TMS Procedure

A trained electrophysiologist delivered rTMS using a Magstim Rapid (Model 220) instrument (Magstim Corporation, Sheffield, England) with a 70-mm wing span figure eight coil. Motor threshold (MT) was determined for each hemisphere in all individuals by gradually increasing the output of the machine by 5% until a 50 μV deflection or a visible twitch in the First Dorsal Interosseous (FDI) muscle was identified in two out of three trials of stimulation over the cortical area controlling the contralateral FDI. Electromyographic responses were monitored on a continuous base with a C-2 J&J Engineering physiological monitor (Poulsbo, WA). Motor-evoked potentials were

recorded from the hand contralateral to stimulation using the C2 J&J system with USE-2 Physiodata software applications. Heart rate, heart rate variability, skin conductance, and skin temperature were also recorded. EMG and other physiological recordings were stored for later analysis. Autistic patients were encouraged to visit the laboratory at least once beforehand to get familiar with the TMS procedure.

The TMS treatment course was administered once per week for 12 weeks (a total of twelve 1Hz rTMS treatments); the first 6 treatments were over the left DLPFC, and the remaining 6 were over the right DLPFC. The site for stimulation was found by placing the coil 5 cm anterior, and in the parasagittal plane, to the site of maximal FDI stimulation. The figure-eight coil, with a 70-mm wing diameter was kept flat over the scalp. Participants were wearing a swimming cap on their head. Stimulation was done at 1Hz and 90% MT, with a total of 150 pulses / day (fifteen 10-s trains with a 20- to 30-s interval between the trains). 1Hz was chosen as the stimulation frequency as studies have shown that low-frequency rTMS ($\leq$1 Hz) increases inhibition of stimulated cortex (e.g., Boroojerdi et al., 2000); there is also a lower risk for seizures the lower the rTMS frequency. Selection of 90% of the MT was based on the experience of numerous publications where rTMS was used for the stimulation of DLPFC in different psychiatric and neurological conditions (for reviews, see Daskalakis et al., 2002; Gershon et al., 2003; Greenberg, 2007; Holtzheimer et al., 2001; Loo & Mitchell, 2005; Rosenberg et al., 2002; Wassermann & Lisanby, 2001). The stimulation power was kept below MT as an extra safety precaution due to the increased risk of seizure within this study population. The minimal number of TMS pulses during a TMS session has varied from 30 to 2,000 pulses per session on a once-per-week over 8 weeks to twice-a-day basis over

10 days (Daskalakis et al., 2002). It has been concluded that less than 100 pulses per session is not very promising in terms of therapeutic efficacy (see Helmich et al., 2006, for review).

Statistical Analysis

Statistical analyses were performed on the subject-averaged behavioral questionnaire data with the subject averages being the observations. For each behavioral measure a *Group* (waiting-list vs. treatment) X *Time* (pre- vs. post-TMS) ANOVA was completed to determine changes associated with TMS. A-priori hypotheses were tested with independent samples two-tailed t-tests for 2 groups with unequal variance. For all ANOVAs, Greenhouse-Geisser corrected p-values were employed where appropriate. SPSS v.14 and Sigma Stat 3.1 packages were used for statistical analysis.

Results

Participant Characteristics

Twenty-five autistic patients (ASD group) were enrolled, 21 male and 4 female, with a mean age of 13.8 ± 4.3 years. Sixteen of them were randomly assigned to active 1.0 Hz TMS treatment (TMS group), whereas 9 were randomly assigned to the waiting-list group (WTL group) (Figure 38). Mean age of participants in the TMS group was 13.9 ± 5.3 years and 13.5 ± 2.0 years in the waiting-list group. Mean Full-Scale IQ score for

children with ASD was 86.0 ± 24.7. The mean Full-Scale IQ of the active TMS group was not significantly different from the randomly assigned waiting-list group.

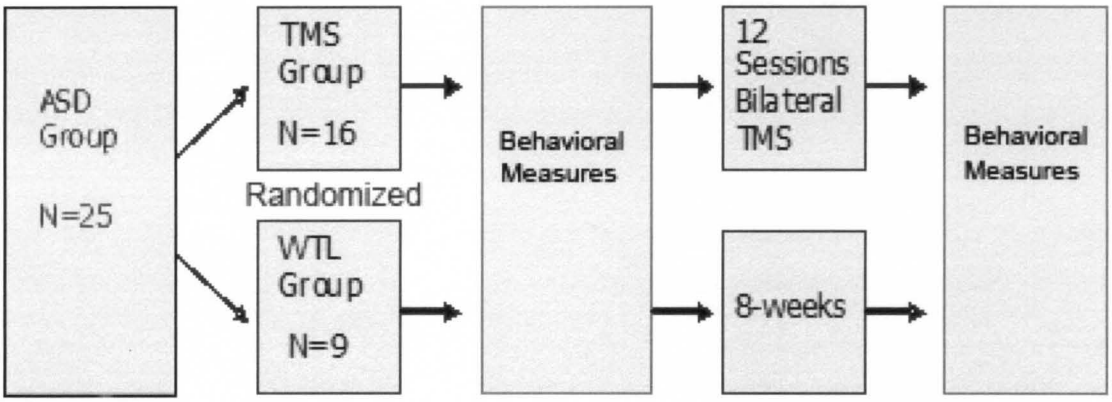

Figure 38: 25 autistic patients (ASD group) were enrolled. 16 of the ASD group were randomly assigned to active TMS treatment (TMS group), whereas 9 were randomly assigned to the waiting-list group (WTL group). Participants were evaluated prior to receiving TMS and 2 weeks following treatment. There was also a waiting-list group with an eight week interval (i.e., no TMS) between behavioral assessments to control for TMS.

Results

Following 12 sessions of bilateral rTMS there was a significant reduction in repetitive and restricted behavior patterns as measured by the RBS (p=0.02) (Figure 39).

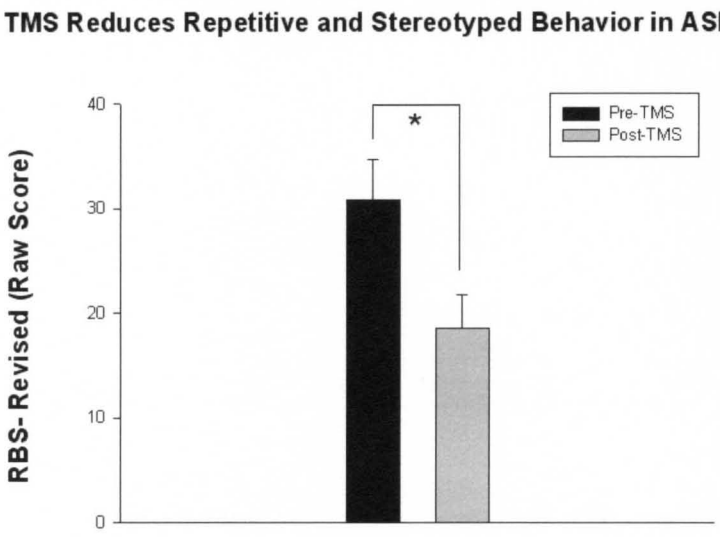

Figure 39: Independent sample t-test results indicated a significant reduction in repetitive behavior raw scores in ASD as a result of 12 sessions of bilateral rTMS (p=0.02).

Also, participants showed a statistically significant reduction in irritability as measured by the irritability subscale of the ABC (p=0.002) (Figure 40).

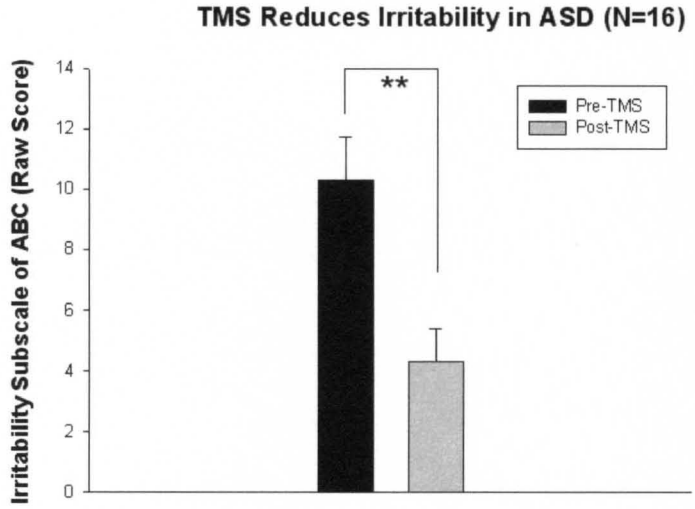

Figure 40: Independent sample t-test results indicated a significant reduction in irritability raw scores in ASD as a result of 12 sessions of bilateral rTMS (p=0.002).

No changes in social awareness or hyperactivity reached significance as a result of rTMS. Additionally, there were no significant differences in behavioral assessments after the eight-week interval (i.e., no TMS) in the waiting-list group. For group statistics of behavioral assessments as well as results of independent samples t-tests see figures 41 and 42.

Group Statistics

	trial	N	Mean	Std. Deviation	Std. Error Mean
RBS	PRE-TMS	16	30.875	15.4008	3.8502
	POST-TMS	16	18.500	12.8841	3.2210
SRS	PRE-TMS	16	82.000	10.0731	2.5183
	POST-TMS	16	78.563	9.3236	2.3309
IRRIT	PRE-TMS	16	10.313	5.7818	1.4454
	POST-TMS	16	4.313	4.2539	1.0635
HYPER	PRE-TMS	16	14.875	7.3383	1.8346
	POST-TMS	16	10.813	7.1946	1.7987

Figure 41: Pre- and Post-TMS group (N=16) means, standard deviations, and standard errors for the *Repetitive Behavior Scale* (RBS), the social awareness subscale of *Social Responsiveness Scale* (SRS), and the irritability and hyperactivity subscales of the *Aberrant Behavior Checklist* (ABC).

Independent Samples Test

		t-test for Equality of Means			
		t	df	Sig. (2-tailed)	Mean Difference
RBS	Equal variances assumed	2.465	30	.020	12.3750
	Equal variances not assumed	2.465	29.093	.020	12.3750
SRS	Equal variances assumed	1.002	30	.324	3.4375
	Equal variances not assumed	1.002	29.822	.325	3.4375
IRRIT	Equal variances assumed	3.344	30	.002	6.0000
	Equal variances not assumed	3.344	27.559	.002	6.0000
HYPER	Equal variances assumed	1.581	30	.124	4.0625
	Equal variances not assumed	1.581	29.988	.124	4.0625

Figure 42: There was a significant difference in the *Repetitive Behavior Scale* (RBS) indicating less impairment as a result of rTMS ($p < 0.05$). There was also a significant difference in the irritability subscale of the *Aberrant Behavior Checklist* (ABC) indicating less impairment as a result of rTMS ($p<0.01$)

Discussion

The main hypothesis was that 12 sessions of bilateral, slow rTMS stimulation applied to the dorsolateral prefrontal cortices (DLPFC) would improve behaviors associated with ASD by not only modulating regions proximal to stimulation but also inducing transsynaptic effects. Cortical inhibitory tone and the ratio of cortical excitation to inhibition would be improved as a result of rTMS, and this may improve prefrontal cortical function including disturbances in social interaction, executive function, and cognitive control.

Analysis of behavioral questionnaires showed statistically significant reductions in repetitive behavior as a result of rTMS. As stated earlier the DLPFC circuit originates in the DLPFC and projects to a part of the striatum called the dorsolateral head of caudate

nucleus. From this region neurons project to the lateral mediodorsal part of the globus pallidus interna and to the rostrolateral part of the substantia nigra. The neurons then move on to the parvocellular portions of the ventral anterior and mediodorsal thalamus and finally project back to the DLPFC (for a summary, see Tekin & Cummings, 2002). The DLPFC circuit is also interconnected with the lateral orbitofrontal circuit, the anterior cingulate circuit, the motor circuit, and the oculomotor circuit (Tekin & Cummings, 2002).

According to Amaral et al. (2008) experimental animal studies as well as lesion studies and functional imaging studies in human patients have implicated the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), the basal ganglia (BG), and the thalamus (Th) with the repetitive and stereotyped behaviors of autism. Considering TMS has been shown to modulate functionally interconnected regions (e.g., Gerschlager, et al., 2001; Bohning et al., 1999) and may operate by selectively depotentiating enhanced synaptic weights associated with pathological conditions (Hoffmann and Cavus, 2002), it may be putatively assumed that increasing the inhibitory tone of the DLPFC may in fact also be transynaptically modulating other regions. It has been shown that the effects of low- frequency rTMS can contribute to naturally occurring neuroplasticity and induce long-term depression or a reduction in cortical activation for several days or even weeks (e.g., Speer et al., 2000). It may plausibly be concluded that low-frequency rTMS may have significantly reduced the repetitive and stereotyped behaviors in ASD by modulating not only the DLPFC but also the OFC or ACC transynaptically.

Additionally, analysis of behavioral questionnaires showed statistically significant reductions in irritability as a result of rTMS. According to Cerqueira et al. (2010) irritability is associated with functional changes in a limited set of brain regions implicated in the mediation of emotional states, mainly the subgenual cingulate and dorsal anterolateral prefrontal cortices; they argue changes in prefrontal and cingulate areas may be related to effortful cognitive control aspects that gain salience during the emergence of irritability. As stated earlier the prefrontal cortex is associated with executive function and cognitive control (Casanova et al., 2006a; Ward, 2006; Stuss & Knight, 2004) including planning, cognitive flexibility, abstract thinking, rule acquisition, initiating appropriate actions and inhibiting inappropriate actions, and selecting relevant sensory information. Low-frequency rTMS may have putatively modulated the ratio of cortical excitation to inhibition in the DLPFC which may have transynaptically modulated prefrontal and cingulate areas related to the cognitive control of irritability; this may also be related to the promising findings in recent years showing that TMS affects mood in healthy subjects and improves depressive symptoms in patients with major depression (e.g., Holtzheimer et al., 2010; Kito, Hasegawa, Okayasu, Fujita, & Koga, 2010). Consequently TMS has been approved for the treatment of major depressive disorder by the FDA.

Furthermore, no changes in social awareness or hyperactivity reached significance as a result of rTMS. Amaral et al. (2008) suggest through animal studies, lesion studies in human patients or functional imaging studies the putative neural systems impacted in autism responsible for regulating social behavior include the temporal cortex, the parietal cortex, and the amygdala (i.e., fusiform gyrus, superior temporal sulcus, amygdala mirror

neuron regions, and posterior parietal cortex). Additionally, Kobel et al. (2010) postulate that the loci involved in the inattentive and hyperactive symptoms of ADHD mainly include structural and functional abnormalities in the temporal lobe. Therefore, it may presumably be concluded that no changes in social awareness or hyperactivity reached significance as a result of rTMS in this study due to limited interconnectivity of the DLPFC circuit to the amygdala as well as temporal and parietal cortices. Considering caregivers of individuals with ASD often find repetitive behaviors (i.e., stereotyped, ritualistic, restricted range) and irritability to be particularly challenging, rTMS may prove to be a valuable treatment option in addressing this subset of core behaviors in ASD.

SUMMARY AND DISCUSSION

During the early postnatal period it has been reported that the brain of individuals with ASD undergoes an accelerated period of growth (Courchesne et al., 2003); this increase in volume is primarily due to an augmentation of the prefrontal white matter containing short corticocortical connections (Herbert et al., 2004). It has been suggested that additional white matter in autism is the result of an increased amount of short range association fibers which are required by an increased number of cortical minicolumns (Casanova, 2007). Minicolumns have been described as the basic anatomical and physiological unit of the cerebral cortex essentially correlating to small processing units (Mountcastle, 2003); they contribute to a circumferential zone of inhibitory and disinhibitory activity gating communication of the central minicolumnar core with surrounding cortical areas and contain pyramidal cells that extend throughout laminae II-VI; they are surrounded by a neuropil space consisting of, among other elements, several species of GABAergic, inhibitory interneurons (i.e., double-bouquet, basket, and chandelier cells; Casanova, 2007). Double-bouquet cells provide a 'vertical stream of negative inhibition' (Mountcastle, 1997, 2003) surrounding the minicolumnar core and maintain a constant geometric orientation perpendicular to the pial surface (Douglas & Martin, 2004).

A number of studies have indicated that minicolumns are reduced in size and increased in number in the autistic brain, especially in the dorolateral prefrontal cortex (DLPFC) (Casanova et al., 2002ab, 2006ab). More specifically minicolumns in the brains of autistic patients are narrower and contain less peripheral, neuropil space (Casanova, 2006ab). A lack of appropriate neuropil space and associated lateral inhibition may adversely affect the functional distinctiveness of minicolumnar activation and could result in enhanced localized activation in the context of a lack of associated inhibition (Rippon, Brock, Brown, & Boucher, 2007). The orchestration of an appropriate signal-to-noise ratio is imperative for the output of any network to be sufficiently robust and distinct enough to successfully achieve necessary processing (Rippon et al., 2007; Shadlen & Movshon, 1999; Treisman, 1999). Behaviorally speaking signal/sensory amplification may impair functioning, raise physiological stress, and adversely affect social interaction in patients with ASD (Ratey, 1998).

The DLPFC forms a circuit interconnected with parts of the straitum, globus pallidus, substantia nigra, and thalamus as well as other circuits including the lateral orbitofrontal circuit, the anterior cingulate circuit, the motor circuit, and the oculomotor circuit. The DLPFC is involved in selecting a possible range of responses while suppressing inappropriate ones, manipulating the contents of working memory (Ward, 2006), and directing attention in a controlled manner (Gray et al., 2003). Although interneurons are at the periphery of the minicolumn, they play a prominent role in finely tuning cortical information processing. Functionally speaking, 'disturbances in prefrontal cortical function provide for a brain which is less equipped to use learning as an adaptive

strategy and has diminished resources (plasticity) to handle social interaction/behaviors' (Casanova et al., 2006, p. 4).

TMS Transcranial magnetic stimulation (TMS) allows scientists to stimulate the brain in a safe, noninvasive manner. It is based on the principle of electromagnetic induction which proposes that a changing magnetic field induces the flow of electric current in a nearby conductor--in this case the neurons below the stimulation site. In body tissue the magnetic field induces a perpendicularly orientated electric field, or voltage difference, and charge is moved across an excitable cellular membrane creating a transmembrane potential (see George & Belmaker, 2007). It may be theorized that contrary to other inhibitory cells (i.e., basket and chandelier), whose projections keep no constant relation to the surface of the cortex, the geometrically exact orientation of double-bouquet cells and their location at the periphery of the minicolumn (inhibitory surround) makes them an appropriate candidate for induction by a magnetic field applied parallel to cortex.

Studies have shown that low-frequency or 'slow' rTMS ($\leq$1Hz) increases inhibition of stimulated cortex (e.g., Boroojerdi et al., 2000). The most relevant model for understanding the inhibitory effect of low-frequency rTMS is a phenomenon referred to as 'depotentiation,' whereby potentiated synaptic weights are 'reset' to baseline levels (Hoffmann and Cavus, 2002). It has been shown that rTMS can contribute to naturally occurring neuroplasticity that can last for many weeks (e.g., Weiss, et al. 1995). Additionally a number of studies have indicated that low-frequency rTMS is capable of not only modulating regions proximal to stimulation but can induce transsynaptic effects

presumably by functional connections (e.g., Gerschlager, et al. 2001; Bohning et al. 1999).

Event-related potentials (ERPs) represent scalp-recorded, transient changes in the electrical activity of the brain in relation to the onset of a stimulus, and provide a neurobiological measure of perceptual and cognitive processing. In the visual task of selective attention within this study individuals with ASD showed augmented and indiscriminative baseline cortical responses at early stages of visual processing compared to controls. These findings may be related to sensory over reactivity in individuals with ASD in early stages of visual processing and may reflect deficits in cortical inhibitory processes. Later-stage ERP indices of selective attention (e.g., P2a, N2a, P3a) in ASD also showed abnormal patterns of amplitude and latency indicative of ineffective later-stage stimulus discriminatory processes and impaired response inhibition. It may be proposed that early stage sensory over reactivity could be inundating higher level integrative centers with task-irrelevant information, and this may result in ineffective later-stage stimulus discrimination. There were no statistically significant baseline amplitude or latency differences in very late (i.e., N2b orP3b) indices of selective attention detected between the ASD and control groups however which may imply minimal group differences at the stage of processing closure; however, this finding confounds with the significantly higher percentage of motor response errors in the ASD group.

After six sessions of low-frequency rTMS individuals with ASD showed significant reductions in augmented cortical responses at very early stages of visual processing (i.e., P50) and improved stimulus discrimination and evaluative attentional

processes at later stages (e.g., P2b, P3a). There was a reduction in motor response errors following TMS, but this reduction didn't reach statistical significance. As the DLPFC is involved in selecting a possible range of responses while suppressing inappropriate ones, manipulating the contents of working memory (Ward, 2006), and directing attention in a controlled manner (Gray et al., 2003), low-frequency rTMS may have subsequently depotentiated enhanced synaptic weights in this area of cortex thereby improving selective attention and executive function within in this population.

It has been proposed that the generation of normal gamma oscillations directly depends on the integrity of the connections of GABAergic interneurons within cortical minicolumns (Whittington et al., 2000) and a higher occurrence of gamma EEG oscillations in children with autism suggests an imbalance in the ratio between cortical excitation and inhibition (Rubenstein and Merzenich, 2003). Electrophysiological research has provided evidence that gamma activity is a physiological indicator of the coactivation of cortical cells engaged in processing visual stimuli (e.g., Keil et al., 2001) and integrating different features of a stimulus (Müller, et al., 2000). Gamma band activity can be divided into either evoked or induced: Evoked gamma band activity has been identified at a latency of around 100 ms after stimulus onset (Bertrand & Tallon-Baundry, 2000; Herrmann & Mecklinger, 2000) and is highly phase locked to the onset of the stimulus; induced gamma band activity occurs later with a variable onset, although it has been reported to start at around 250 ms (Brown et al., 2005). It has been proposed that evoked gamma band activity reflects the effect of attention on early visual processing and the binding of perceptual information within the same cortical area (i.e., intra-areal), whereas induced gamma band activity reflects the later binding of feed-forward and feed-

back processing in a whole network of cortical areas (corticocortical; Brown et al., 2005; Müller et al., 2000; Shibata et al., 1999).

The baseline results of this study indicate that prior to rTMS individuals with ASD had a minimal difference in evoked gamma power between target and non-target Kanizsa stimuli at all channels. In fact, evoked gamma power responses were slightly larger in response to non-target Kanizsa stimuli relative to targets. In contrast the control group had a significantly higher evoked gamma power to target Kanizsa stimuli compared to non-target Kanizsa stimuli showing clear differences in visual stimulus discrimination. In addition, the control group showed a greater difference in evoked gamma power between frontal and parietal regions to all stimuli over the left hemisphere: Controls had more frontal as compared to parietal gamma activity, whereas the ASD group showed negligible topographic differences. These baseline results indicate that in ASD evoked gamma activity is not discriminative of stimulus type, whereas in controls early gamma power differences between target and non-target stimuli are highly significant.

After 12 sessions of bilateral rTMS to the DLPFC evoked gamma power significantly increased to target Kanizsa stimuli in the ASD group at all channels. Furthermore, repeated measures analysis revealed highly significant increases in evoked gamma power to target stimuli with a slight decrease to non-targets following treatment. Individuals with ASD showed significant improvement in discriminatory gamma activity between relevant and irrelevant visual stimuli as a result of rTMS treatment.

Early gamma components (i.e., evoked) are measured at the same time over the same cortical regions as early ERP components (e.g., P50), and the results indicate that

both early ERP components and evoked gamma activity are amplified and indiscriminative in ASD. Furthermore, induced gamma activity and later stage ERP components (e.g., P3b) were relatively intact in ASD pointing to mainly disturbances in early stages of sensory processing in ASD. It has been proposed that neural systems in the brains of individuals with ASD are often inappropriately activated (e.g., Belmonte & Yurgelin-Todd, 2003), and there is a disruption in the ratio between cortical excitation and inhibition (Casanova et al., 2002ab; Casanova, 2006ab; Rubenstein and Merzenich, 2003). In a network that is overactivated and 'noisy,' it may not be possible for individuals with ASD to selectively activate specific perceptual systems based on the relevance of a stimulus (i.e., target vs. nontarget). Low-frequency rTMS may have putatively altered the disrupted ratio of cortical excitation and inhibition in ASD and subsequently minimized amplified early-stage cortical activity.

Individuals with ASD have qualitative impairments in social interaction and social communication, repetitive and stereotyped behavior patterns, and sensory abnormalities (Charman, 2008). Repetitive and stereotyped behavior in ASD includes both repetitive sensory-motor actions and insistence on sameness (Cannon et al., 2010). Individuals with ASD also often exhibit severe irritability such as aggression, self injurious behavior, and tantrums (Stigler et al., 2010), as well as symptoms consistent with attention-deficit/hyperactivity disorder (ADHD) (Murray, 2010).

Analysis of behavioral questionnaires showed statistically significant reductions in repetitive behavior as a result of rTMS. Studies suggest the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), the basal ganglia (BG), and the thalamus (Th) are implicated with the repetitive and stereotyped behaviors of ASD (Amaral et al., 2008).

TMS has been shown to modulate functionally interconnected regions (e.g., Gerschlager, et al., 2001; Bohning et al., 1999), and it may be putatively assumed that increasing the inhibitory tone of the DLPFC may in fact also be transynaptically modulating other regions interconnected with DLPFC circuit (e.g., OFC or ACC).

Additionally, analysis of behavioral questionnaires showed statistically significant reductions in irritability as a result of rTMS. Irritability has been associated with functional changes in a limited set of brain regions including prefrontal and cingulate areas (Cerqueira et al., 2010). Low-frequency rTMS may have putatively modulated the ratio of cortical excitation to inhibition in the DLPFC which may have transynaptically modulated prefrontal and cingulate areas related to the cognitive control of irritability.

Furthermore, no changes in social awareness or hyperactivity reached significance as a result of rTMS. It has been proposed that the neural systems responsible for regulating social behavior include the temporal cortex, the parietal cortex, and the amygdala (Amaral et al., 2008) while the brain regions responsible for the inattentive and hyperactive symptoms of ADHD include structural and functional abnormalities in the temporal lobe (Kobel et al., 2010). Therefore it may be concluded that no changes in social awareness or hyperactivity reached significance as a result of rTMS in this study due to limited interconnectivity of the DLPFC circuit to the amygdala as well as temporal and parietal cortices.

LIMITATIONS OF STUDY

ERP indices have been shown to vary throughout different stages of the developmental period (Jeste & Nelson, 2009). Although there was not a significant age difference between the groups in the ERP study the age range of participants may in part explain the ERP variability. Future studies should attempt to limit the age range further to control for the effect of age on neuronal functioning.

For the analysis of evoked and induced gamma power two participants enrolled were previously diagnosed as mentally retarded; this increased the standard deviation of IQ for the ASD group. However all participants were able to perform the required tasks.

The research design of this study included a wait-list group to control for the effects of TMS. This approach was practical within the context of this study; however using a sham TMS device to replicate the experience of receiving TMS (e.g., the sound of pulses) would be the ideal method of controlling for TMS and any effect of placebo.

Although all subjects were diagnosed with ASD, a small number of individuals were diagnosed with Asperger's Syndrome and one individual was diagnosed with pervasive developmental disorder-not otherwise specified (PDD-NOS). Future studies should attempt to control for subject variability within the autism spectrum by enrolling only a subset of individuals (e.g., autistic disorder).

FUTURE DIRECTIONS

Overall of neuroimaging tools used to elucidate brain circuitry, functional electrophysiology stands alone in the capacity to characterize early (i.e., in infancy) neural markers and endophenotypes (Jeste & Nelson, 2009), i.e. measures of abnormalities intermediate between genotypic vulnerability and the clinical expression of a disorder (Gottesman & Gould, 2003). Additional investigations characterizing early-stage visual processing deficits using similar 'oddball' paradigms maintain a large amount of significance for future ASD research and treatment. These visual tasks are capable of detecting difficulty in filtering irrelevant sensory stimuli in early stages of visual processing, and could potentially play an important role in identifying sensory endophenotypes characteristic of the disorder. Future research should improve the diagnostic capability of electroencephalography and event-related potentials, and may contribute to earlier diagnosis and intervention in ASD, a disorder where timely intervention is critical.

TMS has proven to be a safe, non-invasive method of neural modulation. It has the potential to become a unique therapeutic tool capable of addressing some of the core symptoms of ASD. Considering the few therapeutic options currently available for ASD, TMS is a welcome option capable of playing an important role in improving the quality of life for many with the disorder.

REFERENCES

Adamec, R.E. (1999). Evidence that limbic neural plasticity in the right hemisphere mediates partial kindling induced lasting increases in anxiety-like behavior: effects of low frequency stimulation (quenching?) on long-term potentiation of amygdale efferents and behavior following kindling. *Brain Research*, 839, 133–152.

Alexander, G.E., De Long, M.R., Strick, P.L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience*, 9, 357– 81.

Aman, M. G. (2004). Management of hyperactivity and other acting out problems in patients with autism spectrum disorder. *Seminars in Pediatric Neurology*, 11, 225–228.

Aman, M. G., & Singh, N. N. (1994). Aberrant behavior checklist—Community. Supplementary manual. East Aurora, NY: Slosson Educational Publications.

Amaral, D.G., Schumann, C.M., & Nordahl, C.W. (2008). Neuroanatomy of autism. *Trends in Neurosciences*, 31, 137-45.

Aylward, E.H., Minshew, N.J., Field, K., Sparks, B.F., & Singh, N. (2002). Effects of age on brain volume and head circumference in autism. Neurology, 59, 175–183.

American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders (DSM-IV TR) (4th ed.). Washington, DC: American Psychiatric Association. (text revised).

Baird, G., Robinson, R.O., Boyd, S., Charman, T. (2006). Sleep electroencephalograms in young children with autism with and without regression. *Developmental Medicine and Child Neurology*, 48, 604–608.

Barker, A.T., Jalinous, R., Freeston, I.L. (1985). Non-invasive magnetic stimulation of the human motor cortex. *Lancet*, 1,1106-1107.

Baruth, J.M., Casanova, M., El-Baz, A., Horrell, T., Mathai, G., Sears, L., Sokhadze, E. (2010a). Low-Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) Modulates Evoked-Gamma Oscillations in Autism Spectrum Disorder (ASD). *Journal of Neurotherapy*, 14, 179-194.

Baruth, J.M., Casanova, M., Sears, L., Sokhadze, E. (2010b). Early-Stage Visual Processing Abnormalities in Autism Spectrum Disorder (ASD). *Translational Neuroscience,* 1, 177-187.

Belmonte, M.K., Yurgelun-Todd, D.A. (2003). Functional anatomy of impaired selective attention and compensatory processing in autism. Cognitive Brain Research, 17, 651-664.

Bertrand, O., Tallon-Baudry, C. (2000). Oscillatory gamma activity in humans: A possible role for object representation. *International Journal of Psychophysiology*, 38, 211-223.

Blaxill, M.F. (2004). What's going on? The question of time trends in autism. Public Health Reports, 119, 536-51.

Bliss, T.V.P., Gardner-Medwin, A.R. (1973). Long-lasting potentiation of the synaptic transmission in the dentate area of the unanesthetized rabbit following stimulation of the perforant path. The Journal of Physiology, 232, 357–374.

Bodfish, J. W., Symons, F. J., & Lewis, M. H. (1999). Repetitive behavior scale. Morganton, NC: Western Carolina Center Research Reports.

Bodfish, J. W., Symons, F. S., Parker, D. E., & Lewis, M. H. (2000). Varieties of repetitive behavior in autism: Comparisons to mental retardation. *Journal of Autism and Developmental Disorders*, 30, 237–243.

Bohning, D.E., Shastri, A., McConnell, K.A., Nahas, Z., Lorberbaum, J.P., Roberts, D.R., Teneback, C., Vincent, D.J., George, M.S. (1999). A combined TMS/fMRI study of intensity-dependent TMS over motor cortex. *Biological Psychiatry*, 45, 385–394.

Bomba, M.D., Pang, E.W. (2004). Cortical auditory evoked potentials in autism: a review. *International Journal of Psychophysiology*, 53, 161-9

Boroojerdi, B., Prager, A., Muellbacher, W., et al. (2000). Reduction of human visual cortex excitability using 1-Hz transcranial magnetic stimulation. *Neurology*, 54, 1529-1531.

Boyle, C., & Alexander, M. (2005). Public health research at the CDC: implications for communication sciences and disorders, *Journal of Communication Disorders*, 38, 263-70.

Brambilla, P., Perez, J., Barale, F., Schettini, G., Soares, J.C. (2003). GABAergic dysfunction in mood disorders. *Molecular Psychiatry*, 8, 721-37.

Brown, C., Gruber, T., Boucher, J., Rippon, G., & Brock, J. (2005). Gamma abnormalities during perception of illusory figures in autism. *Cortex*, 41, 364–376.

Bruneau, N., Garreau, B., Roux, S., Lelord, G. (1987). Modulation of auditory evoked potentials with increasing stimulus intensity in autistic children. *Electroencephalography and Clinical Neurophysiology*, Supplement, 40, 584-589.

Bruneau, N., Roux, S., Adrien, J., & Barthelemy, C. (1999). Auditory associative cortex dysfunction in children with autism: Evidence from late auditory evoked potentials (N1 wave-T complex). *Clinical Neurophysiology*, 110, 1927–1934.

Butler, P.D., Javitt, D.C. (2005). Early-stage visual processing deficits in schizophrenia. *Current Opinion in Psychiatry*, 18, 151–157.

Buxhoeveden, D.P., Switala, A.E., Roy, E., Casanova, M.F. (2000). Quantitative analysis of cell columns in the cerebral cortex. *Journal of Neuroscience Methods*, 97, 7-17.

Cannon, D.S., Miller, J.S., Robison, R.J., Villalobos, M.E., Wahmhoff, N.K., Allen-Brady, K., McMahon, W.M., Coon, H. (2010). Genome-wide linkage analyses of two repetitive behavior phenotypes in Utah pedigrees with autism spectrum disorders. *Molecular Autism*, 1, 3.

Carper, R.A., Moses, P., Tigue, Z.D., & Courchesne E. (2002). Cerebral lobes in autism: early hyperplasia and abnormal age effects. *Neuroimage*, 16, 1038–1051.

Carper, R., Courchesne, E. (2005). Localized enlargement of the frontal lobe in autism. Biological Psychiatry, 57, 126–133.

Casanova, M. F., Buxhoeveden, D. P., & Brown, C. (2002a). Clinical and macroscopic correlates of minicolumnar pathology in autism. *Journal of Child Neurology*, 17, 692–695.

Casanova, M. F., Buxhoeveden, D. P., Switala, A. E., & Roy, E. (2002b). Minicolumnar pathology in autism. *Neurology*, 58, 428–432.

Casanova, M. F. (2004). White matter volume increase and minicolumns in autism. *Annals of Neurology*, 56, 453.

Casanova, M. F., van Kooten, I., Switala, A. E., van England, H., Heinsen, H., Steinbuch, H. W. M., et al. (2006a). Abnormalities of cortical minicolumnar organization in the prefrontal lobes of autistic patients. *Clinical Neuroscience Research*, 6, 127–133.

Casanova, M. F., van Kooten, I., van Engeland, H., Heinsen, H., Steinbursch, H. W. M., Hof, P. R., et al. (2006b). Minicolumnar abnormalities in autism II. Neuronal size and number. *Acta Neuropathologica*, 112, 287–303.

Casanova, M. F., Buxhoeveden, D., & Gomez, J. (2003). Disruption in the inhibitory architecture of the cell minicolumn: implications for autism. *The Neuroscientist*, 9, 496–507.

Casanova, M.F., (2007). The neuropathology of autism. *Brain Pathology*, 17, 422-433.

Casanova, M.F., Tillquist, C.R. (2008). Encephalization, emergent properties, and psychiatry: a minicolumnar perspective. *The Neuroscientist*, 1, 101-18.

Casanova, M.F., El-Baz, A., Mott, M., Mannheim, G., Hassan, H., Fahmi, R., Giedd, J., Rumsey, J.M., Switala, A.E., Farag, A. (2009). Reduced gyral window and corpus callosum size in autism: possible macroscopic correlates of a minicolumnopathy. Journal of Autism and Developmental Disorders, 39, 751-764.

Casanova, M.F., El-Baz, A., Vanbogaert, E., Narahari, P., Switala, A. (2010). A topographic study of minicolumnar core width by lamina comparison between autistic subjects and controls: possible minicolumnar disruption due to an anatomical element in-common to multiple laminae. *Brain Pathology*, 20, 451-8.

Center for Disease Control & Prevention. Prevalence of the autistic spectrum disorders (ASDs in multiple areas of the United States, 2000, 2002, 2006, 2007). MMWR 2007; 56:(SS 1-2).

Cerqueira, C.T., Almeida, J.R., Sato, J.R., Gorenstein, C., Gentil, V., Leite, C.C., Amaro, E. Jr., Busatto, G.F. (2010). Cognitive control associated with irritability induction: an autobiographical recall fMRI study. *Revista Brasileira de Psiquiatria*, 23,109-118.

Charman, T. (2008). Autism spectrum disorders. *Psychiatry*, 7, 331–334.

Chen, R., Classen, J., Gerloff, C., et al. (1997). Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology*, 48, 1398-1403.

Chen, W.R., Lee, S., Kato, K., Spencer, D.D., Shepherd, G.M., Williamson, A. (1996). Long-term modifications of synaptic efficacy in the human inferior and middle temporal cortex. *Proceedings of the National Academy of Sciences of the United States of America*, 93, 8011–8015.

Chez, M.G., Chang, M., Krasne, V., Coughlan, C., Kominsky, M., Schwartz, A. (2006). Frequency of epileptiform EEG abnormalities in a sequential screening of autistic patients with no known clinical epilepsy from 1996 to 2005. *Epilepsy and Behavior*, 8, 267–271.

Clark, V.P., Fan, S., & Hillyard, S.A. (1995). Identification of early visual evoked potential generators by retinotopic and topographic analyses. *Human Brain Mapping*, 2, 170–187.

Claus D, Weis M, Jahnke U, Plewe A, Brunhölzl C. (1992). Corticospinal conduction studied with magnetic double stimulation in the intact human. *Journal of Neurological Sciences*, 111, 180-8.

Coben, R., Clarke, A.R., Hudspeth, W., & Barry, R.J. (2008). EEG power and coherence in autistic spectrum disorder. Clinical Neurophysiology, 119, 1002-9.

Coles, M.G.H., Rugg, M.D. (1995). Event-related brain potentials: an introduction. In: Rugg, M.D., Coles, M.G.H., editors. *Electrophysiology of mind. Event-related brain potentials and cognition.* Oxford: Oxford University Press, pp 40–85.

Constantino, J. N., Gruber, C. P. (2005). The social responsiveness scale (SRS) manual. Los Angeles, CA: Western Psychological Services.

Courchesne, E., Courchesne, R. Y., Hicks, G., & Lincoln, A. J. (1985a). Functioning of the brain-stem auditory pathway in nonretarded autistic individuals. *Electroencephalography and Clinical Neurophysiology*, 61, 491–501.

Courchesne, E., Lincoln, A. J., Kilman, B. A., & Galambos, R. (1985b). Event-related brain potential correlates of the processing of novel visual and auditory information in autism. *Journal of Autism and Developmental Disorders*, 15, 55–76.

Courchesne, E., Lincoln, A. J., Yeung-Courchesne, R., Elmasian, R., & Grillon, C. (1989). Pathophysiologic findings in nonretarded autism and receptive developmental language disorder. *Journal of Autism and Developmental Disorders*, 19, 1–17.

Courchesne, E., & Pierce, K. (2005). Brain overgrowth in autism during a critical time in development: implications for frontal pyramidal neuron and interneuron development and connectivity. *International Journal of Developmental Neuroscience*, 23, 153-170.

Courchesne, E. (2004). Brain development in autism: early overgrowth followed by premature arrest of growth. *Mental Retardation and Developmental Disabilities Research Reviews*, 10, 106-111.

Courchesne, E., Karns, C.M. Davis, H.R., Ziccardi, R., Carper, R.A., Tigue, Z.D., Chisum, H.J., Moses, P., Pierce, K., Lord, C., Lincoln, A.J., Pizzo, S., Schreibman, L., Haas, R.H., Akshoomoff, N.A., & Courchesne, R.Y. (2001). Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. *Neurology*, 57, 245–254.

Courchesne, E., Carper, R., & Akshoomoff, N. (2003). Evidence of brain overgrowth in the first year of life in autism. *JAMA*, 290, 337–344.

Daskalakis, Z. J., Christensen, B. K., Fitzgerald, P. B., & Chen, R. (2002). Transcranial magnetic stimulation: A new investigational and treatment tool in psychiatry. *Journal of Neuropsychiatry and Clinical Neurosciences*, 14, 406–415.

Dawson, G., Klinger-Grofer, L., Panagiotides, H., Lewy, A., & Castelloe, P. (1995). Subgroups of autistic children based on social behavior display distinct patterns of brain activity. *Journal of Abnormal Child Psychology*, 23, 569–583.

Di Lazzaro, V., Oliviero, A., Megilo, M., et al. (2000). Direct demonstration of the effect of lorazepam on the excitability of the human motor cortex. *Clinical Neurophysiology*, 111, 794-799.

Doninger, G.M., Foxe, J.J., Murray, M.M., Higgins, B.A., Snodgrass, J.G., Schroeder, C.E., et al. (2000). Activation timecourse of ventral visual stream object-recognition areas: High density electrical mapping of perceptual closure processes. *Journal of Cognitive Neuroscience*, 12, 615–621.

Donkers, F. C. L., & van Boxtel, G. J. M. (2004). The N2 in go/no-go tasks reflects conflict monitoring not response inhibition. Brain and Cognition, 56, 165–176.

Douglas, R. J., & Martin, K. A. C. (2004). Neuronal circuits of the neocortex. *Annual Review of Neuroscience*, 27, 419–451.

Duffy, J.D., Campbell, J.J., 3rd. (1994). The regional prefrontal syndromes: a theoretical and clinical overview. *Journal of Neuropsychiatry and Clinical Neurosciences*, 6, 379-87.

Faraday, M: Effects on the production of electricity from magnetism (1831), in Michael Faraday. Edited by Williams LP. New York, Basic Books, 1965, p 531.

Ferree, T. C., Luu, P., Russell, G. S., & Tucker, D. M. (2001). Scalp electrode impedance, infection risk, and EEG data quality. *Clinical Neurophysiology*, 112, 444–536.

Ferri, R., Elia, M., Agarwal, N., Lanuzza, B., Musumeci, S. A., & Pennisi, G. (2003). The mismatch negativity and the P3a components of the auditory event-related potentials in autistic lowfunctioning subjects. *Clinical Neurophysiology*, 114, 1671–1680.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2001). *Structured clinical interview for DSM-IV-TR axis I disorders—non-patient edition (SCID-NP)*. New York: New York State Psychiatric Institute.

Fletcher, E. M., Kussmaul, C. L., & Mangun, G. R. (1996). Estimation of interpolation errors in scalp topographic mapping. *Electroctoencephalography and Clinical Neurophysiology*, 98, 422–434.

Foxe, J.J., Doninger, G.M., & Javitt, D.C. (2001). Early visual processing deficits in schizophrenia: Impaired P1 generation revealed by high density electrical mapping. *Neuroreport*, 12, 3815–3820.

Froc, D.J., Chapman, C.A., Trepel, C., Racine, R.J. (2000). Long-term depression and depotentiation in the sensorimotor cortex of the freely moving rat. *The Journal of Neuroscience*, 20, 438–445

Gehring, W.J., Knight, R.T. (2002). Lateral prefrontal damage affects processing selection but not attention switching. *Brain research. Cognitive brain research*, 13, 267-79.

George and Belmaker (2007) *Transcrainial Magenetic Stimulation in Clinical Psychiatry*. Arlington, VA: American Psychiatric Publishing, Inc.

Gerschlager, W., Siebner, H., Rothwell, J. (2001). Decreased corticospinal excitability after subthreshold 1 Hz rTMS over lateral premotor cortex. *Neurology*, 57, 449–455.

Gershon, A. A., Dannon, P. N., & Grunhaus, L. (2003). Transcranial magnetic stimulation in the treatment of depression. *American Journal of Psychiatry*, 160, 835–845.

Goldberg, J., Szatmari, P., & Nahmias, C. (1999). Imaging of autism: lessons from the past to guide studies in the future. *Canadian Journal of Psychiatry*, 44, 793-801.

Gomes, E., Pedroso, F. S., & Wagner, M. B. (2008). Auditory hypersensitivity in the autistic spectrum disorder. *Pro'-fono: Revista de atualizacao cientifica*, 20, 279–284.

Gomez-Gonzales, C. M., Clark, V. P., Fan, S., Luck, S., & Hillyard, S. A. (1994). Sources of attention-sensitive visual event-related potentials. *Brain Topography*, 7, 41–51.

Goto, Y., Brigell, M. G., & Parmeggiani, L. (1996). Dipole-modeling of the visual evoked P300. *Journal of Psychosomatic Research*, 41, 71–79.

Gottesman, I.I., Gould, T.D. (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *The American Journal of Psychiatry*, 160, 636-45.

Goupillaud, P., Grossman, A., & Morlet, J. (1984). Cycle-octave and related transforms in seismic signal analysis. *Geoexploration*, 23, 85–102.

Gray, J.R., Chabris, C.F., Braver, T.S. (2003). Neural mechanisms of general fluid intelligence. *Nature Neuroscience*, 6, 316–322.

Greenberg, B. D. (2007). Transcranial magnetic stimulation in anxiety disorders. In M. S. George & R. H. Belmaker (Eds.), Transcranial magnetic stimulation in clinical psychiatry (pp. 165–178). Washington, DC: American Psychiatric Publishing, Inc.

Grice, S.J., Spratling, M.W., Karmiloff-Smith, A., Halit, H., Csibra, G., De Haan, M., Johnson, M.H. (2001). Disordered visual processing and oscillatory brain activity in autism and Williams syndrome. *NeuroReport*, 12, 2697–2700.

Grothe, B., & Klump, G. M. (2000). Temporal processing in sensory systems. *Current Opinion in Neurobiology,* 10, 467–73.

Halgren, E., Marinkovic, K., & Chauvel, P. (1998). Generators of the late cognitive potentials in auditory and visual oddball tasks. Electroencephalography and Clinical Neurophysiology, 106, 156–164.

Handy, T. (2005). *Event-Related Potentials: A Mehtods Handbook.* Edited by Handy, T.C. Cambridge, MA: The MIT Press.

Hazlett, H.C., Poe, M., Gerig, G., Smith, R.G., Provenzale, J. Ross, A., Gillmore, J., & Piven J. (2005). Magnetic resonance imaging and head circumference study of brain size in autism: birth through age 2 years. Archives of General Psychiatry, 62, 1366–1376.

Hazlett, H.C., Poe, M.D., Gerig, G., Smith, R.G., & Piven, J. (2006). Cortical gray and white brain tissue volume in adolescents and adults with autism. Biological Psychiatry, 59, 1–6.

Happe′, F. G. E. (1999). Autism: Cognitive deficit or cognitive style? *Trends in Cognitive Sciences, 3,* 216-222.

Haxby, J.V., Hoffman, E.A., Gobbini, M.I. (2002). Human neural systems for face recognition and social communication. *Biological Psychiatry*, 51, 59-67.

Heinze, H.J., Mangun, G., Burchert, W., Hinrichs, H., Scholz, M., Münte, T.F., et al. (1994). Combined spatial and temporal imaging of brain activity during visual selective attention in humans. *Nature*, 372, 543–546.

Helmich, R. C., Siebner, H. R., Bakker, M., Munchau, A., & Bloem, B. R. (2006). Repetitive transcranial magnetic stimulation to improve mood and motor function in Parkinson's disease. *Journal of Neurological Sciences*, 248, 84–96.

Herbert, M.R., Ziegler D.A., Deutsch, C.K., O'Brien, L.M., Lange, N., Bakardjiev, A., Hodgson, J., Adrien, K.T., Steele, S., Makris, N., Kennedy, D.N., Harris, G.J., & Caviness, V.S., Jr. (2003). Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. *Brain*, 126, 1182–1192.

Herbert, M.R., Zieglar, D.A., Makris, N., Filipek, P.A., Kemper, T.L., Normandin, J.J., Sanders, H.A., Kennedy, D.N., & Caviness, V.S., Jr. (2004). Localization of white matter volume increase in autism and developmental language disorder. Annals of Neurology. 55, 530–540.

Herrman, C.S., Mecklinger, A., and Pfeirffer, E. (1999). Gamma responses and ERPs in a visual classification task. *Clinical Neurophysiology*, 110, 636-642.

Herrmann, C. S., & Mecklinger, A. (2000). Magnetoencephalographic responses to illusory figures: Early evoked gamma is affected by processing of stimulus features. *International Journal of Psychophysiology*, 38, 265–281.

Herrmann, C.S., Knight, R.T. (2001). Mechanisms of human attention: event related potentials and oscillations. *Neuroscience and Biobehavioural Reviews*, 25, 465-476.

Herrmann, C. S., Munck, M. H. J., & Engel, A. K. (2004). Cognitive functions of gamma-band activity: memory match and utilisation. *Trends in Cognitive Sciences*, 88, 347–355.

Herrmann, M.J., Ehlis, A.C., Ellgring, H., Fallgatter, A.J. (2005). Early stages (P100) of face perception in humans as measured with event-related potentials (ERPs). *Journal of Neural Transmission*, 112, 1073-81.

Heynen, A.J., Abraham, W.C., Bear, M.F. (1996). Bidirectional modification of CA1 synapses in the adult hippocampus in vivo. Nature, 381, 163–166

Hillyard, S.A., Hink, R.F., Schwent, V.L., Picton, T.W. (1973). Electrical signs of selective attention in the human brain. *Science*, 182, 177–180.

Hillyard, S.A., Mangun, G.R., Woldorff, M.G., & Luck, S.J. (1995). Neural mechanisms mediating selective attention. In M. S. Gazzaniga (Ed.), *The cognitive neurosciences.* Cambridge, MA: MIT Press.

Hoffman, R. E., & Cavus, I. (2002). Slow transcranial magnetic stimulation, long-term depotentiation, and brain hyperexcitability disorders. *American Journal of Psychiatry*, 159, 1093–1102.

Hoeksma, M. R., Kemner, C., Kenemans, J. L., & van Engeland, H. (2006). Abnormal selective attention normalizes P3 amplitudes in PDD. *Journal of Autism and Developmental Disorders*, 36, 643–654.

Holtzheimer, P. E., Russo, J., & Avery, D. H. (2001). A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. *Psychopharmacology Bulletin*, 35, 149–169.

Hopf, J.M., Vogel, E., Woodman, G., Heinze, H.J., & Luck, S.J. (2002). Localizingvisual discrimination processes in time and space. *Journal of Neurophysiology,* 88, 2088–2095.

Hruby T, Marsalek P. (2003). Event-related potentials--the P3 wave. Acta *Neurobiologiae Experimentalis*, 63, 55-63.

Isaacson, J.S., Solís, J.M., Nicoll, R.A. (1993). Local and diffuse synaptic actions of GABA in the hippocampus. *Neuron*, 10, 165-75.

Jäncke, L., Staiger, J.F., Schlaug, G., Huang, X., Steinmetz, H. (1997). The relationship between corpus callosum size and forebrain volume. Cerebral Cortex, 7, 48 –56.

Jansson-Verkasalo, E., Ceponiene, R., Valkama, M., Vainionpää, L., Laitakari, K., Alku, P., Suominen, K., Näätänen, R. (2003). Deficient speech-sound processing, as shown by the electrophysiologic brain mismatch negativity response, and naming ability in prematurely born children. *Neuroscience Letters*, 348, 5-8.

Jeste, S.S., Nelson, C.A. 3rd. (2009). Event related potentials in the understanding of autism spectrum disorders: an analytical review. *Journal of Autism and Developmental Disorders*, 39, 495-510.

Kanizsa, G. (1976). Subjective contours. *Scientific American*, 235, 48–52.

Kanner, L. (1943). Autistic disturbances of affective contact. *Nervous Child*, 2, 217-50.

Katayama, J., Polich, J. (1998). Stimulus context determines P3a and P3b. *Psychophysiology*, 35, 23-33.

Keil, A., Gruber, T., and Müller, M.M. (2001). Functional correlates of macroscopic high-frequency brain activity in the human visual system. *Neuroscience and Biobehavioral Reviews*, 25, 527-534.

Kemner, C., van der Gaag, R. J., Verbaten, M., & van Engeland, H. (1999). ERP differences among subtypes of pervasive developmental disorders. *Biological Psychiatry*, 46, 781–789.

Kenemans, J. L., Kok, A., & Smulders, F. T. (1993). Event-related potentials to conjunctions of spatial frequency and orientation as a function of stimulus parameters and response requirements. *Electroencephalography and Clinical Neurophysiology*, 88, 51–63.

Khalfa, S., Bruneau, N., Rogé, B., Georgieff, N., Veuillet, E., Adrien, J.L., et al. (2004). Increased perception of loudness in autism. *Hearing Research*, 198, 87-92.

Kito, S., Hasegawa, T., Okayasu, M., Fujita, K., Koga, Y. (2010). A 6-Month Follow-Up Case Report of Regional Cerebral Blood Flow Changes in Treatment-Resistant Depression After Successful Treatment With Bilateral Transcranial Magnetic Stimulation. *Journal of ECT*, Oct 1. [Epub ahead of print]

Klin, A. (1993). Auditory brainstem responses in autism. Brainstem dysfunction of peripheral hearing loss? *Journal of Autism and Developmental Disorders*, 23,15-34.

Knight, R. T. (1997). Distributed cortical network for visual attention. *Journal of Cognitive Neuroscience*, 9, 75–91.

Kobel, M., Bechtel, N., Specht, K., Klarhöfer, M., Weber, P., Scheffler, K., Opwis, K., Penner, I.K. (2010). Structural and functional imaging approaches in attention deficit/hyperactivity disorder: does the temporal lobe play a key role? *Psychiatry Research*, 183, 230-236.

Kogan, M.D., Blumberg, S.J., Schieve, L.A., Boyle, C.A., Perrin, J.M., Ghandour, R.M., Singh, G.K., Strickland, B.B., Trevathan, E., van Dyck, P.C. (2009). Prevalence of Parent-Reported Diagnosis of Autism Spectrum Disorder Among Children in the US, 2007. Pediatrics, 124, 1395-1403.

Kujirai, T., Caramia, M.D., Rothwell, J.C., Day, B.L., Thompson, P.D., Ferbert, A., Wroe, S., Asselman, P., Marsden, C.D. (1993). Corticocortical inhibition in human motor cortex. *The Journal of Physiology*, 471, 501-519.

Kulla, A., Reymann, K.G., Manahan-Vaughan, D. (1999). Time-dependent induction of depotentiation in the dentate gyrus of freely moving rats: involvement of group 2

metabotropic glutamate receptors. *The European Journal of Neuroscience*, 11, 3864–3872.

Le Couteur, A., Lord, C., & Rutter, M. (2003). *The autism diagnostic interview—Revised (ADI-R)*. Los Angeles, CA: Western Psychological Services.

Lepistö, T., Kujala, T., Vanhala, R., Alku, P., Huotilainen, M., Näätänen, R. (2005). The discrimination of and orienting to speech and non-speech sounds in children with autism. *Brain Research*, 1066, 147–57.

Levitt, P., Eagleson, K.L., Powell, E.M. (2004). Regulation of neocortical interneuron development and the implications for neurodevelopmental disorders. *Trends in Neurosciences*, 27, 400–6.

Lewine, J.D., Andrews, R., Chez, M., Patil, A.A., Devinsky, O., Smith, M., Kanner, A., Davis, J.T., Funke, M., Jones, G., Chong, B., Provencal, S., Weisend, M., Lee, R.R., Orrison, W.W. (1999). Magnetoencephalographic patterns of epileptiform activity in children with regressive autism spectrum disorders. *Pediatrics*, 104, 405–418.

Lincoln, A.J., Courchesne, E., Harms, L., Allen, M. (1995). Sensory modulation of auditory stimuli in children with autism and receptive developmental language disorder: event-related brain potential evidence. *Journal of Autism and Developmental Disorders*, 25, 521-39.

Loo, C., & Mitchell, P. (2005). A review of the efficacy of transcranial magnetic stimulation (TMS) treatment for depression, and current and future strategies to optimize efficacy. *Journal of Affective Disorders*, 88, 255–267.

Luck, S.J., Heinze, H.J., Mangun, G.R., and Hillyard, S.A. (1990). Visual event-related potentials index focused attention within bilateral stimulus arrays . II. Functional dissociation of P1 and N1 components. *Electroencephalography and Clinical Neurophysiology*, 75, 528-542.

Luu, P., Tucker, D. M. L., Englander, R., Lockfeld, A., Lutsep, H., & Oken, B. (2001). Localizing acute stroke-related EEC changes: Assessing the effects of spatial undersampling. *Journal of Clinical Neurophysiology*, 18, 302–317.

Maeda, F., Keenan, J.P., Tormos, J.M., et al. (2000). Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. *Clinical Neurophysiolgy*, 111, 800-805.

Mangun, G. R. (1995). Neural mechanisms of visual selective attention. *Psychophysiology*, 32, 4–18.

Manahan-Vaughan, D., Braunewell, K-H. (1999). Novelty acquisition is associated with induction of hippocampal long-term depression. Proceedings of the National Academy of Sciences of the United States of America, 96, 8739–8744.

Makeig, S., Debener, S., Onton, J., Delorme, A. (2004). Mining event related brain dynamics. *Trends in Cognitive Sciences*, 85, 204–210.

Matzel, L.D., Kolata, S. (2010). Selective attention, working memory, and animal intelligence. *Neuroscience and Biobehavioral Reviews*, 34, 23–30.

McCormick, D.A. (1992). Neurotransmitter actions in the thalamus and cerebral cortex. *Journal of Clinical Neurophysiology*, 9, 212-23.

McDonnell, M.N., Orekhov, Y., Ziemann, U. (2006). The role of GABA(B) receptors in intracortical inhibition in the human motor cortex. *Experimental Brain Research*, 173, 86-93.

Mountcastle, V.B. (2003). Introduction. Computation in cortical columns. *Cerebral Cortex*, 13, 2–4.

Mountcastle, V. B. (1997). The columnar organization of the neocortex. *Brain*, 120, 701–722.

Muellbacher, W., Ziemann, U., Boroojerdi, B., et al. (2000). Effects of low-frequency transcranial magnetic stimulation on motor excitability and basic motor behavior. Clinical Neurophysiology, 111, 1002-1007.

Müller, M.M., Bosch, J., Elbert, T., Kreiter, A., Sosa, M.V., Sosa, P.V., & Rockstroh, B. (1996). Visually induced gamma-based responses in human electroencephalographic activity – a link to animal studies. *Experimental Brain Research*, 112, 96-102.

Müller, M. M., Gruber, T., & Keil, A. (2000). Modulation of induced gamma band activity in the human EEG by attention and visual information processing. *International Journal of Psychophysiology*, 38, 283–299.

Müller, M.M., Gruber, T. (2001). Induced gamma-band responses in the human EEG are related to attentional information processing. *Visual Cognition*, 8, 579-592.

Murias, M., Webb, S.J., Greenson, J., Dawson, G. (2007). Resting state cortical connectivity reflected in EEG coherence in individuals with autism. Biological Psychiatry, 62, 270-3.

Murray, M.J. (2010). Attention-deficit/Hyperactivity Disorder in the context of Autism spectrum disorders. *Current Psychiatry Reports*, 12, 382-388.

Mecklinger, A., Maess, B., Opitz, B., Pfeifer, E., Cheyne, D., & Weinberg, D. (1998). An MEG analysis of the P300 in visual discrimination tasks. *Electroencephalography and Clinical Neurophysiology*, 108, 45–66

Mesulam, M.M. (2000). Behavioral neuroanatomy: large-scale networks, association cortex, frontal syndromes, the limbic system, and hemispheric specializations. In: Mesulam, M.M., editor.

Principles of behavioral and cognitive neurology. Oxford: Oxford University Press; p. 1-120, ch. 1.

Mesulam, M.M. (2002). The human frontal lobes: transcending the default mode through contingent encoding. In: Stuss, D.T., Knight, R.T., editors. Principles of frontal lobe function. Oxford: Oxford University Press; p. 8-30, ch. 2.

Näätänen, R., Gaillard, A. W. K., & Mäntysalo, S. (1978). Early selective attention effect on evoked potential reinterpreted. *Acta Psychologica*, 2, 313–329.

Näätänen, R., Schröger, E., Karakas, S., Tervaniemi, M., & Paavilainen, P. (1993). Development of a memory trace for a complex sound in the human brain. *Neuroreport*, 4, 503–506.

Nauta, W.J. (1972). Neural associations of the frontal cortex. *Acta Neurobiologiae Experimentalis*, 32, 125-40.

Nelson, C. A., Collins, P. F., & Torres, F. (1991). P300 brain activity in seizure patients preceding temporal lobectomy. *Archives of Neurology*, 48, 141–147.

Oades, R. D., Walker, M. K., Geffen, L. B., & Stern, L. M. (1988). Event-related potentials in autistic and healthy children on an auditory choice reaction time task. *International Journal of Psychophysiology*, 6, 25–37.

O'Donnel, B.F., Swearer, J.M., Smith, L.T., Hokama, H., and Mccarley, R.W. (1997). A topographic study of ERPs elicited by visual feature discrimination. *Brain Topography,* 10, 133-143.

Orekhova, E.V., Stroganova, T.A., Nygren, G., Tsetlin, M.M., Posikera, I.N., Gillberg, C., Elam, M. (2007). Excess of high frequency electroencephalogram oscillations in boys with autism. *Biological Psychiatry*, 62, 1022-9.

Palmen, S.J., Hulshoff Pol, H.E., Kemner, C., Schnack, H.G., Durston, S., Lahuis, B.E., Kahn, R.S., & Van Engeland, H. (2005). Increased gray-matter volume in medication naive high-functioning children with autism spectrum disorder. Psychological Medicine. 35, 561–570.

Pascual-Leone, A., Valls-Sole, J., Wasserman, E.M., et al. (1994). Responses to rapid-rate transcranial magnetic stimulation of the human cortex. *Brain*, 117, 847-858.

Pascual-Leone, A., Walsh, V., Rothwell, J. (2000). Transcranial magnetic stimulation in cognitive neuroscience--virtual lesion, chronometry, and functional connectivity. *Current Opinion in Neurobiology*, 10, 232-7.

Paavilainen, P., Tiitinen, H., Alho, K., Näätänen, R. (1993). Mismatch negativity to slight pitch changes outside strong attentional focus. *Biological Psychiatry*, 37, 23-41.

Perrin, E., Pernier, J., Bertrand, O., Giard, M., & Echallier, J. F. (1987). Mapping of scalp potentials by surface spline interpolation. *Electroencephalography and Clinical Neurophysiology*, 66, 75–81.

Peters, A., Walsh, T.M. (1972). A study of the organization of apical dendrites in the somatic sensory cortex of the rat. *Journal of Comparative Neurology*, 144, 253–268.

Peters, A., Sethares, C. (1996). Myelinated axons and the pyramidal cell modules in monkey primary visual cortex. *Journal of Comparative Neurology*, 365, 232–55.

Pfurtscheller, G., Aranibar, A. (1977). Event-related cortical desynchronisation detected by power measurements of scalp EEG. *Electroencephalography and Clinical Neurophysiology*, 42, 817–826.

Pfurtscheller, G., Lopes da Silva, F.H. (1999). Event-related EEG/MEG synchronisation and desynchronisation: basic principles. *Clinical Neurophysiology*, 110, 1842–1857.

Picton, T.W. (1992). The P300 wave of the human event-related potential. *Journal of Clinical Neurophysiology*, 9, 456–479.

Polich, J. (2003). Theoretical overview of P3a and P3b. In: Polich, J., editor. *Detection of Change: Event-related Potential and fMRI Findings*. Boston: Kluwer Academic Press, pp 83–98.

Posner, M.I., & Petersen, S.E. (1990). The attention system of the human brain. *Annual Revue in Neuroscience*, 13, 25–42.

Post, R.M., Kimbrell, T.A., Frye, M., George, M., McCann, U., Little, J., Dunn, R., Li, H., Weiss, S.R.B. (1997). Implications of kindling and quenching for the possible frequency dependence of rTMS. *CNS Spectrums*, 2, 54–60.

Post, R.M., Kimbrell, T.A., McCann, U.D., Runn, R.T., Osuch, E.A., Speer, A.M., Weiss, S.R. (1999). Repetitive transcranial magnetic stimulation as a neuropsychiatric tool: present status and future potential. The *journal of ECT*, 15, 39–56

Potts, G. F., Liotti, M., Tucker, D. M., & Posner, M. I. (1996). Frontal and inferior temporal cortical activity in visual target detection: Evidence from high spatially sampled event-related potentials. *Brain Topography*, 9, 3–14.

Potts, G. F., Dien, J., Harty-Speiser, A., McDougl, L. M., & Tucker, D. M. (1998). Dense sensor array topography of the event related potential to task-relevant auditory stimuli. *Electroencephalography and Clinical Neurophysiology*, 106, 444–456.

Potts, G. F., Patel, S. H., & Azzam, P. N. (2004). Impact of instructed relevance on the visual ERP. *International Journal of Psychophysiology*, 52, 197–209.

Pritchard, W. S. (1981). Psychophysiology of P300. *Psychological Bulletin*, 89, 506-540.

Quintana, H. (2005). Transcranial magnetic stimulation in persons younger than the age of 18. *The Journal of ECT*, 21:88-95.

Ratey, J.J., Johnson, C. (1997). *The shadow syndromes.* New York: Bantam Books.

Redcay, E., & Courchesne, E. (2005). When is the brain enlarged in autism? A meta-analysis of all brain size reports. Biological Psychiatry, 58, 1-9.

Rippon, G., Brock, J., Brown, C., & Boucher, J. (2007). Disordered connectivity in the autistic brain: Challenges for the 'new psychophysiology'. *International Journal of Psychophysiology*, 63, 164–172.

Rodriguez, E., George, N., Lachaux, J. P., Martinerie, J., Renault, B., & Varela, F. J. (1999). Perception's shadow: Long distance synchronization of human brain activity. *Nature*, 397, 430–433.

Rogers, R. L., Basile, L. F. H., Papanicolaou, A. C., & Eisenberg, H. M. (1993). Magnetoencephalography reveals two distinct sources associated with late positive evoked potentials during visual oddball task. *Cerebral Cortex*, 3, 163–169.

Rosenberg, P. B., Mehndiratta, R. B., Mehndiratta, Y. P., Wamer, A., Rosse, R. B., & Balish, M. (2002). Repetitive magnetic stimulation treatment of comorbid posttraumatic stress disorder and major depression. *Journal of Neuropsychiatry and Clinical Neurosciences*, 14, 270–276.

Rosenhall, U., Nordin, V., Brantberg, K., Gillberg, C. (2003). Autism and auditory brain stem responses. *Ear and Hearing.* 24, 206-14.

Rubenstein, J.L.R., Merzenich, M.M., (2003). Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes, Brain, and Behavior*, 2, 255–267.

Seeck, M., Michel, C.M., Mainwaring, N., Cosgrove, R., Blume, H., Ives, J., Landis, T., Schomer, D.L. (1997). Evidence for rapid face recognition from human scalp and intracranial electrodes. *Neuroreport*, 8, 2749-54.

Seldon, H.L. (1981). Structure of human auditory cortex. I: cytoarchitectonics and dendritic distributions. *Brain Research*, 229, 277–294.

Seri, S., Cerquiglini, A., Pisani, F., & Curatolo, P. (1999). Autism in tuberous sclerosis: Evoked potential evidence for a deficit in auditory sensory processing. *Clinical Neurophysiology*, 110, 1825–1830.

Shibata, T., Shimoyama, I., Ito, T., Abla, D., Iwasa, H., Koseki, K., Yamanouchi, N., Sato, T., and Nakajima, Y. (1999). Attention changes the peak latency of the visual gamma-band oscillation of the EEG. *Neuroreport*, 10, 1167-1170.

Singer, W., Gray, C. (1995). Visual feature integration and the temporal correlation hypothesis. *Annual Review of Neuroscience*, 18, 555-586.

Sokhadze, E., Baruth, J., Tasman, A., Sears, L., Mathai, G., El-Baz, A., et al. (2009a). Event-related potential study of novelty processing abnormalities in autism. *Applied Psychophysiology and Biofeedback,* 34, 37-51.

Sokhadze, E., El-Baz, A., Baruth, J., Mathai, G., Sears, L., Casanova, M. (2009b). Effects of low frequency repetitive transcranial magnetic stimulation (rTMS) on gamma frequency oscillations and event-related potentials during processing of illusory figures in autism. *Journal of Autism and Developmental Disorders*, 39, 619-34.

Sparks, B.F., Friedman, S.D., Shaw, D.W., Aylward, E.H., Echelard, D., Artru, A.A., Maravilla, K.R., Giedd, J.N., Munson, J., Dawson, G., & Dager, S.R. (2002). Brain structural abnormalities in young children with autism spectrum disorder. *Neurology*, 59, 184–192.

Speer, A.M., Kimbrell, T.A., Wassermann, E.M., Repella, J.D., Willis, M.W., Herscovitch, P., Post, R.M. (2000). Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. *Biological Psychiatry*, 48, 1133–1141.

Spencer, K.M., Dien, J., & Donchin, E. (2001). Spatiotemporal analysis of the late ERP responses to deviant stimuli. *Psychophysiology*, 38, 343–358.

Srinivasan, R., Tucker, D. M., & Murias, M. (1998). Estimating the spatial Nyquist of the human EEG. *Behavior Research Methods, Instruments, & Computers*, 30, 8–19.

Stäubli, U., Scafidi, J. (1999). Time-dependent reversal of long-term potentiation in area CA1 of the freely moving rat induced by theta pulse stimulation. *Journal of Neuroscience*, 19, 8712–8719.

Stigler, K.A., Erickson, C.A., Mullett, J.E., Posey, D.J., McDougle, C.J. (2010). Paliperidone for irritability in autistic disorder. *Journal of Child and Adolescent Psychopharmacology*, 20, 75-78.

Stroganova, T. A., Nygren, G., Tsetlin, M. M., Posikera, I. N., Gillberg, C., Elam, M., et al. (2007). Abnormal EEG lateralization in boys with autism. *Clinical Neurophysiology*, 118, 1842–1854.

Stuss, D. & Knight R.T. (Editors) (2002). *The Frontal Lobes*. New York: Oxford University Press

Tallon-Baudry, C., Bertrand, O., Delpuech, C., & Pernier, J. (1996). Stimulus specificity of phase-locked and non-phase-locked 40Hz visual responses in human. *Journal of Neuroscience,* 16, 4240-4249.

Tallon-Baudry, C., Bertrand, O. (1999). Oscillatory gamma activity in humans and its role in object representation. *Trends in Cognitive Sciences*, 3, 151–162.

Tekin, S., Cummings, J. (2002). Frontal-subcortical neuronal circuits and clinical neuropsychiatry: An update. *Journal of Psychosomatic Research*, 53, 647– 654.

Tendolkar, I., Ruhrmann, S., Brockhaus-Dumke, A., Pauli, M., Mueller, R., Pukrop, R.,Klosterkötter, J. (2005). Neural correlates of visuo-spatial attention during an antisaccade task in schizophrenia: an ERP study. *International Journal of Neuroscience*, 115, 681-98.

Townsend, J., Westerfield, M., Leaver, E., Makeig, S., Jung, T., Pierce, K., et al. (2001). Event-related brain response abnormalities in autism: Evidence for impaired cerebello-frontal spatial attention networks. *Cognitive Brain Research*, 11, 127–145.

Tuchman, R.F., Rapin, I. (1997). Regression in pervasive developmental disorders: Seizures and epileptiform electroencephalogram correlates. *Pediatrics*, 99, 560 –566.

Valls-Solé, J., Pascual-Leone, A., Wassermann, E.M., Hallett, M. (1992). Human motor evoked responses to paired transcranial magnetic stimuli. *Electroencephalography and Clinical Neurophysiology*, 85, 355-64.

Verbaten, M. N., Roelofs, J. W., van Engeland, H., Kenemans, J. K., & Slangen, J. L. (1991). Abnormal visual event-related potentials of autistic children. *Journal of Autism and Developmental Disorders*, 21, 449–470.

Vogel, E.K., Luck, S.J. (2000). The visual N1 component as an index of a discrimination process. Psychophysiology, 37, 190-203.

Vohs, J.L., Hetrick, W.P., Kieffaber, P.D., Bodkins, M., Bismark, A., Shekhar, A., O'Donnell B.F. (2008). Visual event-related potentials in schizotypal personality disorder and schizophrenia. *Journal of Abnormal Psychology*, 117, 119-31.

Ward, J. (2006). *The Student's Guide to Cognitive Neuroscience.* Hove and New York: Psychology Press.

Wassermann, E. M., & Lisanby, S. H. (2001). Therapeutic application of repetitive transcranial magnetic stimulation: A review. *Clinical Neurophysiology*, 112, 1367–1377.

Wassermann, E.M. (1996). Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of

Repetitive Transcranial Magnetic Stimulation, June 5-7. *Electroencephalography and Clinical Neurophysiology*, 108:1-16.

Wassermann, E.M., Wedegaertner, F.R., Ziemann, U.I., George, M.S., Chen, R. (1998). Crossed reduction of human motor cortex excitability by 1-Hz transcranial magnetic stimulation. *Neuroscience Letters*, 250, 141–144.

Wechsler, D. (2003). *Wechsler intelligence scale for children (4th ed.)*. San Antonio, TX: Harcourt Assessment, Inc.

Wechsler, D. (2004). *Wechsler abbreviated scale for intelligence*. San Antonio, TX: Harcourt Assessment, Inc.

Weiss, S.R.B., Xiu-Li, L., Rosen, J.B., Li, H., Heynen, T., Post, R.M. (1995). Quenching: inhibition of development and expression of amygdale kindled seizures with low frequency stimulation. Neuroreport, 6, 2171–2176.

West, R. (2003). Neural correlates of cognitive control and conflict detection in the Stroop and digit-location tasks. *Neuropsychologia*, 41, 1122–1135.

West, R., Bowry, R., & McConville, C. (2004). Sensitivity of medial frontal cortex to response and nonresponse conflict. *Psychophysiology*, 41, 739–748.

Whittington, M.A., Traub, R.D., Kopell, N., Ermentrout, B., Buhl, E.H. (2000). Inhibition-based rhythms: experimental and mathematical observations on network dynamics. *International Journal of Psychophysiology*, 38, 315–336.

Willoughby, J.O., Fitzgibbon, S.P., Pope, K.J., Mackenzie, L., Medvedev, A.V., Clark, C.R., *et al.* (2003). Persistent abnormality detected in the nonictal electroencephalogram in primary generalised epilepsy. *Journal of Neurology, Neurosurgery, and Psychiatry*, 74, 51–55.

Yamazaki, T., Kamijo, K., Kenmochi, A., Fukuzumi, S., Kiyuna, T., & Kuroiwa, Y. (2000). Multiple equivalent current dipole source localization of visual event-related potentials during oddball paradigm with motor response. *Brain Topography*, 12, 159–175.

Ziemann U (2004). TMS induced plasticity in human cortex. *Rev Neuroscience*, 15, 252-266.

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AWARDS & HONORS:

International Society for Neurofeedback and Research Student Presentation Award, 2010

Association for Applied Psychophysiology and Biofeedback Paper Citation Award, 2010

Association for Applied Psychophysiology and Biofeedback Travel Award, 2010

Research Louisville Poster Citation, 2009

International Society for Neurofeedback and Research Student Essay Award, 2010

Research Louisville First-Prize Poster Citation, 2008

Association for Psychological Science Student Travel Award, 2008

Phi Beta Kappa, 2005

Phi Kappa Phi, 2005

Mildred Lord Grief Essay Award, 2005

PROFESSIONAL SOCIETIES:

Society for Psychophysiological Research

International Society for Neurofeedback and Research

Association for Applied Psychophysiology and Biofeedback

COMMITTEES:

Graduate Student Council Representative, 2008-2010

Academic Grievance Council, 2008-2010

TEACHING:

Teaching Assistant, Medical Neuroanatomy, 2008

Teaching Assistant, Medical Neuroanatomy, 2010

PUBLICATIONS:

Baruth, J.M., Casanova, M., El-Baz, A., Horrell, T., Mathai, G., Sears, L., Sokhadze, E. (2010). Low-Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) Modulates Evoked-Gamma Oscillations in Autism Spectrum Disorder (ASD). *Journal of Neurotherapy*, 14, 179-194.

Baruth, J.M., Casanova, M., Sears, L., Sokhadze, E. (2010). Early-Stage Visual Processing Abnormalities in Autism Spectrum Disorder (ASD). *Translational Neuroscience,* 1, 177-187.

Sokhadze, E., Baruth, J.M., El-Baz, A., Horrell, T., Sokhadze, G., Carroll, T., Tasman, A., Sears, L.,Casanova, M.F. (2010). Impaired Error Monitoring and Correction in Autism. Journal of Neurotherapy, 14, 79-95.

Sokhadze, E., Baruth, J.M., Tasman, A., Mansoor, M., Ramaswamy, R., Sears, L., Mathai, G., El-Baz, A., Casanova, M.F. (2010). Low-Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) Affects Event-Related Potential Measures of Novelty Processing in Autism. *Applied Psychophysiology and Biofeedback*, 35, 147-161.

Sokhadze, E., Baruth, J.M., Tasman, A., Sears, L., Mathai, G., El-Baz, A., Casanova, M.F. (2009). Event-Related Potential Study of Novelty Processing Abnormalities in Autism. *Applied Psychophysiology and Biofeedback*, 34, 37-51.

Sokhadze, E., El-Baz, A., Baruth, J.M., Mathai, G., Sears, L., Casanova, M.F. (2009). Effects of Low Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) on Gamma Frequency Oscillations and Event-Related Potentials During Processing of Illusory Figures in Autism. *Journal of Autism and Developmental Disorders,* 39, 619-34.

CHAPTERS:

Baruth, J.M., Sokhadze, E., El-Baz, A., Mathai, G., Sears, L., Casanova, M.F. *Transcaranial Magentic Stimulation as a Treatment for Autism*. Siri K and Lyons T (Eds). Cutting Edge Therapies for Autism, Skyhorse Publishing: New York, ch. 63, pp. 388-397, 2010.

Casanova, M.F., Sokhadze, E., El-Baz, A., Baruth, J.M., Mathai, G., Sears, L. *Research at the University of Louisville Autism Center*. Siri K and Lyons T (Eds). Cutting Edge Therapies for Autism, Skyhorse Publishing: New York, ch. 68, pp 410-413, 2010.

INVITED PRESENTATIONS:

Baruth, J.M., Sears, L., Casanova, M., Sokhadze, E.M. Low-Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) Modulates Evoked-Gamma Frequency Oscillations in Autism Spectrum Disorder (ASD). International Society for Neurofeedback & Research, Annual Conference, Denver, Colorado, September 30, 2010.

Baruth, J.M., El-Baz, A., Ramaswamy, R., Sears, L., Casanova, M., Sokhadze, E.M. Transcranial Magnetic Stimulation Study of Gamma Frequency Induction in Response to Illusory Figures in Patients with Autism Spectrum Disorders. International Society for Neurofeedback & Research, Annual Conference, Indianapolis, Indiana, September 4, 2009.

POSTER PRESENTATIONS:

Baruth, J.M., Sokhadze, E.M., Sears, L., Casanova, M.F. Sensory Filtering Abnormalities in Autism Spectrum Disorder (ASD) International Society for Autism Research, Annual Meeting, Poster Presentation, Philadelphia, Pennsylvania, May 20-22, 2010.

Baruth, J.M., Sokhadze, E.M., Sears, L., Casanova, M.F. Early-Stage Visual Processing Abnormalities in Autism Spectrum Disorder (ASD) Applied Psychophysiology & Biofeedback, Annual Conference, Poster Presentation, San Diego, California, March 24-27, 2010.

Baruth, J.M., Sears, L., Casanova, M., Sokhadze, E.M. Low-Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) Modulates Evoked-Gamma Frequency Oscillations in Autism Spectrum Disorder (ASD). University of Louisville School of Medicine, Neursocience Day Poster, May 6, 2010.

Baruth, J.M., Sokhadze, E.M., Carroll, T., Horrell, T., Ramaswamy, R., Tasman, A., Casanova, M.Impaired Error Monitoring and Correction Function in Autism: an ERP Study. Association for Applied Psychophysiology & Biofeedback, Annual Conference, Poster Presentation, San Diego, California, March 24-27, 2010.

Baruth, J.M., Sokhadze, E.M., Sears, L., Casanova, M.F. Early-stage Visual ProcessingAbnormalities in Autism Spectrum Disorder (ASD) Research Louisville, Poster Presentation, University of Louisville School of Medicine, October 13, 2009.

Baruth, J.M., Casanova, M., Mansoor, M., Sears, L., Husk, M., and Sokhadze, E. Repetitive transcranial magnetic stimulation affects novelty processing in autism. Presented at the 21st annual convention of Association for Psychological Sciences, San Francisco, CA, May 22-25, 2009.

Baruth, J.M., Casanova MF, Sokhadze E , Sears L. The Effects of Transcranial Magnetic Stimulation on Novelty Processing in Autism. Research Louisville,

Poster Presentation, University of Louisville School of Medicine, October 21, 2008.

Baruth, J.M., Sokhadze, E., Tasman, A., Sears, L., Mathai, G., Casanova, M.F. Event-Related Potential Study of Novelty Processing Abnormalities in Autism. Association for Psychological Science Annual Convention, Poster Presentation, Chicago, May 23, 2008.

Baruth, J.M., Sears, L., Mathai, G., Casanova, M.F., Sokhadze, E. Abnormalities in Processing Distracters in a Novelty Attention Task in Autism. Neuroscience Day, Poster Presentation, University of Louisville School of Medicine, April 17, 2008.