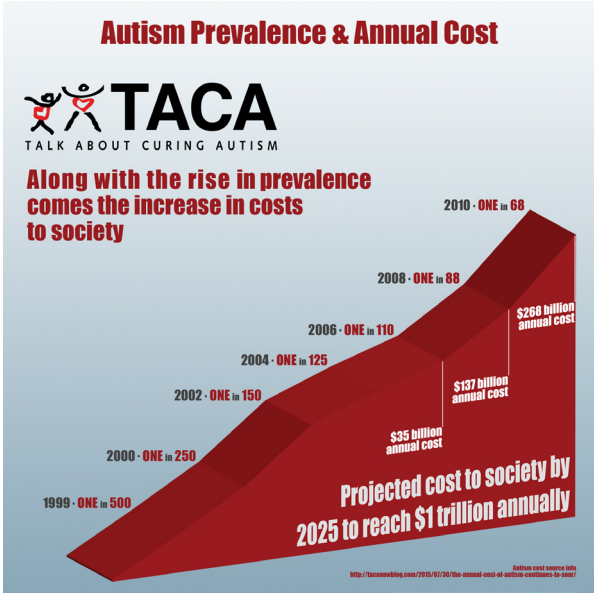
iSynchrony

Autism: The use of individualized Transcranial Magnetic Stimulation (iTMS) as a novel therapy

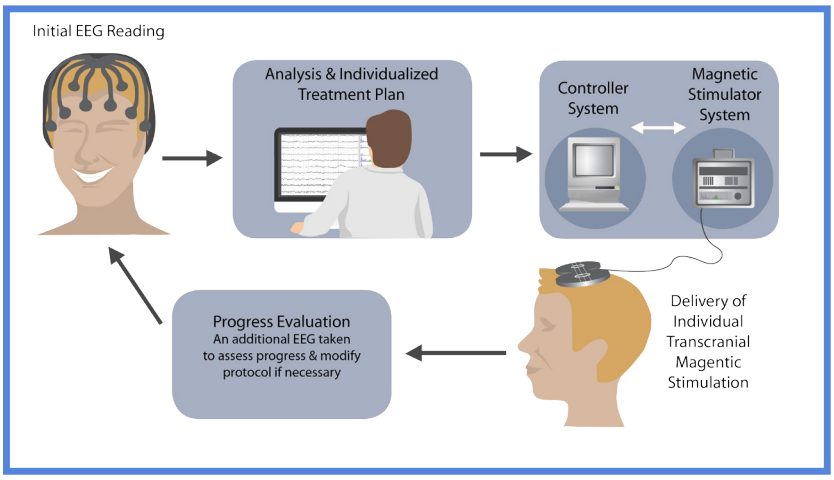
The latest U.S. Centers for Disease Control and Prevention (CDC) study identified 1 in 88 American children (1 in 54 boys) have autism spectrum disorders (ASD). The ratio of males to females is 4:1. This is a ten-fold increase in prevalence over the last 40 years. There are over 2 million cases in the US.

According to the Harvard School of Public Health, the cost to care for a child with autism is estimated at $3.2 million dollars over the child's lifetime. In 2012, the annual cost in the US was $250 billion. To a great extent, this was funded by tax dollars with approximately 90% of costs for adult services (i.e. assisted living, medical, etc). **Harvard School of Public Health; Ganz (2006)**



At the 2014 Autism One conference, the results of a 12-week randomized controlled trial of 24 autistic children, done by Dr. Jeff Bradstreet under the auspices of the Brain Treatment Center, were released showing that an individualized Transcranial Magnetic Stimulation (iTMS) protocol could dramatically improve autism with slightly less than half the children achieving a neuro-typical rating by Child Autism Rating Scale, and another quarter achieving a 30% improvement in their scores. ***These results open a new frontier for reversing autistic symptoms.***

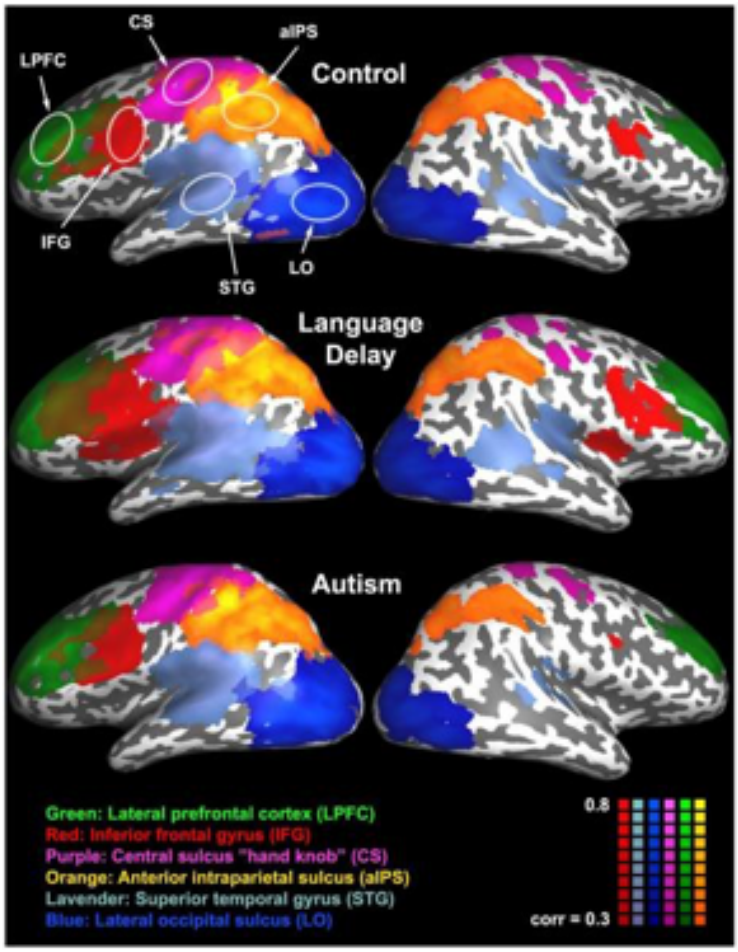
Transcranial Magnetic Stimulation (iTMS) is a novel treatment for ASD that uses noninvasive magnetic brain stimulation in an attempt to normalize neural activity and reverse autistic symptoms. iTMS has been in use for over 25 years and various devices are cleared by the FDA for other indications. While such devices have not been approved for the treatment of autism, it is common medical practice to use such devices for other indications when doctors feel patients may benefit. The FDA acknowledges this as lawful behavior as being under the practice of medicine and is referred to as "off-label use of a medical device or drug."



iTMS operates on the principles of electromagnetism. Current passed through a wire coil generates a strong magnetic field. This magnetic field is able to penetrate the scalp and skull to reach the surface of the brain. The magnetic field then induces an electric current that interacts with local neurons **(Opitz et al, 2011)** affecting behavior and function of the neurons (Hallet, 2000). This effect also extends to distant sites through different neural networks, affecting neuronal behavior accordingly **(Lisanby and Belmaker, 2000)**.

Children with autism have disrupted neural synchronization compared with controls **(Dinstein et al, 2011)**. The effect iTMS has on neural activity suggests a mechanism for its efficacy and a rationale for its use in treating a variety of neuropsychiatric disorders, including autism. In fact, stimulation at specific frequencies has been shown to not only influence brain waves, but to affect ASD symptoms.

Figure 1 Correlation maps averaged across toddlers from the typically-developing (top), language delay (middle), and autism (bottom) groups.



As a means of measuring brain wave activity, EEG has generally been used to monitor seizure activity or measure responsiveness to external stimuli. EEG oscillations are representative of synchronized neuronal activity, with variation of activity reflecting different states of the brain. EEG waveforms are complex but can be decomposed into a series of consecutive frequency bands through computer analysis. The presence of activity in each of these bands can be used to further understand the current brain state of a patient.

The EEG has been used to document many of the effects of iTMS. Of specific interest is the alpha wave, a brain oscillation falling between 8 and 13 Hz that is evident when the eyes are closed. In a normal control, alpha activity is uniform across the cortex and occurs at a single frequency, with more alpha activity in the occipital cortex and a slight gradient of activity forward toward the frontal lobe. However, patients with autism often show decreased alpha EEG activity compared with typical populations, particularly in the frontal cortex of the brain. Because this EEG deficit is associated with the severity of clinical symptoms, it may be an indicator of neural pathology in ASD.

Patient-specific treatment with iTMS tailored to each patient's unique alpha-EEG signal - serves as an effective therapy for autism by normalizing the alpha brain wave oscillation. The protocol for personalized iTMS includes a daily treatment with EEG guided alpha iTMS matched to each subject's unique alpha frequency. In each treatment session, we place a figure-8 ITMS coil above the middle of the forehead. Stimulation is administered at each subject's observed alpha EEG rhythm (8-13Hz) at 6 seconds per minute. (Source- EEG response to alpha stimulation: Therapeutic iTMS improves cortical synchrony and alpha power.)

Daily iTMS therapy is generally considered safe. No adverse effects (such as deterioration of cognitive performance, degradation of EEG, change in auditory threshold or structural change) have been reported **(Rossi et al. 2012)**. Immediate side effects of iTMS are generally limited to a minor headache or increased feelings of energy.

Table 1

Potential side effects of ITMS. Consensus has been reached for this table.

Side effect	Single-pulse iTMS	Paired-pulse iTMS	Low frequency iTMS	High frequency iTMS	Theta burst
Seizure induction	Rare	Not reported	Rare (usually protective effect)	Possible (1.4% crude risk estimate in epileptic patients; less than 1% in normals)	Possible (one seizure in a normal subject during cTBS) (see para 3.3.3)
Transient acute hypomania induction	No	No	Rare	Possible following left prefrontal stimulation	Not reported
Syncope	Possible as epiphenomenon (i.e., not related to direct brain effect)				Possible
Transient headache, local pain, neck pain, toothache, paresthesia	Possible	Likely possible, but not reported/ addressed	Frequent (see para. 3.3)	Frequent (see para. 3.3)	Possible
Transient hearing changes	Possible	Likely possible, but not reported	Possible	Possible	Not reported
Transient cognitive/ neuropsychological changes	Not reported	Not reported	Overall negligible (see Section 4.6)	Overall negligible (see Section 4.6)	Transient impairment of working memory
Burns from scalp electrodes	No	No	Not reported	Occasionally reported	Not reported, but likely possible
Induced currents in electrical circuits	Theoretically possible, but described malfunction only if iTMS is delivered in close proximity with the electric device (pace-makers, brain stimulators, pumps, intracardiac lines, cochlear implants)				
Structural brain changes	Not reported	Not reported	Inconsistent	Inconsistent	Not reported
Histotoxicity	No	No	Inconsistent	Inconsistent	Not reported

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