Natural Medicine

Clinical Significance of Functional MRI Guided Transcranial Magnetic Stimulation for Autism

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Introduction

Autism is a complicated neurodevelopment disorder of largely unknown cause. It is characterized by the difficulty to communicate and interact with others, often accompanied by significant behavioral challenges.

Autism is much more common than previously believed. Based on the 2007 CDC data,[1] validated by several other recent epidemiologic studies,[2-3] autism is diagnosed in 1 in 150 children in the United States and it affects four times as many boys than girls. The diagnosis of autism has increased ten-fold in the last decade. About 1.5 million Americans may have some form of autism when symptoms of milder variants are taken into consideration. This number continues to rise. Epidemiologists estimate that the number of autistic children in the US could reach up to 4 million in the next decade. The Centers for Disease Control and Prevention has called autism a national public health crisis with an estimated cost of over $90 billion a year. Despite the serious social impact of autism, study grants available for research is reported to be only 0.3% of the total NIH funding, much lower than what is available for other less common and less severe disorders.

Autism is a very important problem that needs to be addressed more urgently. Unraveling this complex disorder requires more research dedicated to change the way we understand and treat this very serious condition.

Autistic Brain and Scientific Challenges

The neurobiology and neuropathology of autism spectrum disorder (ASD) remains poorly defined. Brain imaging studies suggest that the major deficits of autistic brain in social cognition, language, communication and stereotypical pattern of behavior, are related to functional disturbance and "disconnectivity".[4-5] Both post-mortem and neuroimaging studies indicate the presence of increased brain volume,[6] cerebral hypo-perfusion,[7] inflammation,[8-10] oxidative stress,[11] immune dysregulation, relative mitochondrial dysfunction, neurotransmitter abnormalities, and impaired detoxification. These impairments are considered to be a consequence of abnormal pre- and post-natal development of a distributed neural network, affecting multiple brain regions. Most studies [12-16] support dysfunction in the amygdala, the frontal lobe, the temporal lobe and the cerebellum. In particular, many studies indicate abnormal amygdala with initial enlargement and subsequent shrinkage, cerebellar and related inferior olive atrophy and forebrain limbic system atrophy with abnormally small Hippocampus. Some of the areas do seem to be more related to core autistic symptoms, than do others. There has been growing evidence supporting the Limbic System Theory, which believes that damage to the amygdala and the frontal cortex contribute highly to social impairment, the primary symptom of autism. This theory has been considered to be one of the major theories of autism. There is good evidence for temporal lobe involvement in facial perception and social behavior of individuals with autism. In both cases, this may be the result of damage to other areas of the brain. The temporal lobe lesions contribute to impaired social behavior only when the amygdala is damaged. The other major theory is relatively new, so called the Cerebellum Theory, which is potentially promising. Proponents have hypothesized that the cerebellum is responsible for attention across a wide variety of systems. There is also research indicated that "microcolumns" in the brain, may be formed differently in autistic people,[17-18] in another word, autistic brain somewhat wired differently.

fMRI and Its Role in Brain Research

It is extremely difficult to point out one particular area of the brain and say that damage to that one structure causes autism. The effective treatment is clearly based on the better understanding of the autistic brain and their difference from neurotypical brain. Over the last decade, functional MRI has been an extremely promising technology in brain research. It has been used to map brain function, and detect connectivity providing insights on the physiological basis of dysfunction. It has a promising future use in neuro-oncology, neurosurgical planning, chronic pain management, diagnosis and treatment of schenzophrenia, depression, Azhneimer's disease, and seizure localization. fMRI has been extremely useful in localization of specific brain function such as visual, special, auditory, sport, emotion reaction to certain stimuli, the interaction and coordination among different brain regions. It has been also used in the studies of more complicated brain function such as learning process, memory, and specific behaviors. There has been some studies that use fMRI to measure certain brain function in autism.[19-22] There is also evidence that indicate functional disconnectivity of the medial temporal lobe in Asperger's Syndrome. Among those with autistic savant features, there is a common abnormality in the left arterial temporal lobe.

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TMS and Its Role in Brain Research

Transcranial magnetic stimulation (TMS) is a non-invasive method that excites neurons in the brain.[23-24] It could induce weak electric currents in the brain tissue via rapidly changing magnetic fields, which is known as electromagnetic induction. Using this technique, brain activity can be triggered with minimal discomfort, meanwhile the functionality of the circuitry and connectivity of the brain can be studied. Repetitive transcranial magnetic stimulation is known as rTMS which can produce prolonged changes.

Started in the 1980's, TMS was initially designed as a brain mapping tool, used with MRI and EEG. It works by stimulating the cortex and recoding the response. One reason TMS is important in neuroscience is that it can demonstrate causality. It is a non-invasive mapping technique, which allows one to see what regions of the brain are activated when a subject performs a certain task.[25-31] One may obtain maps of functional brain areas when a muscle is stimulated, or when the certain environmental changes are applied. One may measure the response of the cortex reaction to TMS and area-to-area connections.

Furthermore, TMS has not only been used as a diagnostic mapping tool, but also as a treatment device. TMS treatment alters the biochemistry and firing patterns of neurons in the brain nearest to the surface. Preliminary research indicates that TMS affects gene activity of the neurons and the levels of its dopamine and other neurotransmitters. The formation of proteins is important for cellular signaling and magnetic stimulation seems to affect several interconnected brain regions, starting in the cortex, where new cell growth may be important in regulating moods, and other brain activities.

TMS and Its Clinical Application

Numerous small-scale pilot studies have shown it could be a treatment tool for various neurologic conditions such as migraine, stroke, Parkinson's Disease, dystonia, tinnitus and psychiatric conditions like major depression.

It has been reported efficacy of TMS as a therapy for severe depression,[32-34] auditory hallucinations[36] and migraine headaches.[37] It is also under investigation for drug resistant epilepsy [36] and Parkinson's disease.[35]

It is noticeable that the FDA has approved transcranial magnetic stimulation system for treatment of major depressive disorder in adult patients with whom traditional therapies have failed. In a six week, randomized, placebo-controlled trial with 164 patients suffering from unipolar non-psychotic major depressive disorder, TMS was associated with a statistically significant improvement in symptoms ($p < 0.0006$) when compared with controls. TMS used to stimulate the cerebellum was associated with a significant increase in emotional response to happy facial expressions, implicating a direct relationship between the cerebellum and emotive information-processing. It will, on the other hand, provided further understanding the regulation of mood response, cerebellum involvement and the mechanism of depression.

TMS in Autism and its Significant Potential Impact in Science and Health

Although there is only limited research in this field, TMS has been widely recognized in the study and treatment of autism. Researchers from the University of Louisville applied pulsed low frequency magnetic field around the brain of 10 people with autism. The treatment was done for 20 minutes, twice a week for a total of 5 weeks. Patients showed fewer symptoms of hyperactivity, sensory overload and repetitive behaviors. The team assessed the symptom scores before and after treatment with standard neurological and psychological tests. The preliminary result showed a great deal of promise in reducing the severity of symptoms that help people with autism communicate and relate better. Thus their ability to function independently improved significantly. The team also found that the treatment did not seem to affect areas of giftness in the test group.[38]

Another study in Australia evaluating the use of rTMS to improve the Theory of Mind among adults with autism and Asperger's disorder, is currently recruiting patients. Imaging studies suggest that the bilateral medial pre-frontal cortex, the most important region in the Theory of Mind, is underactive in autism. This study uses repetitive TMS to bilateral medial pre-frontal cortex and preliminary data showed improvement in the Theory of Mind among adults with autism and Asperger's disorder.

There is an ongoing study at the Columbia University, currently recruiting volunteers with autism, Asperger's and PDD-NOS, that uses fMRI and TMS to check the neurocircuitry. This study is attempting to use low frequency TMS, fMRI to check the neurocircuitry of developmental differences in social and repetitive behaviors.

In summary, it is very promising to use functional MRI guilded non-invasive brain stimulation techniques such as TMS to study the basis of the different variants of autism, the connectivity of different brain regions and the correlation with its core symptoms by monitoring its change before and after the treatment. TMS could be evaluated in clinical trials to identify individualized treatment strategy, allowing comparison with other new experimental treatment options such as hyperbaric oxygen, stem cell therapy, vasodilator and anti-inflammatory therapy. It is extremely valuable to focus on the most important brain regions such as temporal lobe, pre-frontal and the cerebellum and the connectivity to target the core symptoms of autism. It is very likely that TMS will increase the disconnectivity and "atypical wiring", thus improving their communication, social behavior and independence. With fMRI guidance and monitoring, TMS will be able to target the specific dysfunctional or disordered brain area in each individual case. Thus the corresponding clinical problem will be expected to improve. For instance, for those with autistic savant (about 10% of autistic population), studies to design and address stimulation of a specific area to improve their performance and behaviors may allow better use of their talent. Also, by comparing different autistic sub-types, with their fMRI change and TMS response, we will obtain valuable information and new understanding about how the autistic brain functions, as well as the relationship of different brain regions, connectivity, neurocircuitry, hypo-perfusion distribution and status. If such study is applied in conjunction with laboratory tests to check inflammatory markers and cytokines, it will offer better understanding of the key mechanism of autism with hypo-perfusion and inflammation as proposed. It is hoped that this type research will eventually lead to novel therapeutic strategies which will help those affected individuals and their families. TMS has a potential to become an effective treatment for the major symptoms of autism and it is truly worthwhile exploring.

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