

Research Status and Prospect Analysis of Autism Spectrum Disorders on the Basis of TMS and tDCS

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Abstract. Autism spectrum disorder (ASD) has become one of research hotspots in recent years. With the increasing number of patients, dominated by children, finding effective therapies has been under study, ranging from medication to stimulation treatments. Additionally, due to the heterogeneity of ASD symptoms, simple and universal biomarkers are also needed to be found to improve accuracy of diagnosis. This article reviews Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tDCS) with the key recording technique, Electroencephalogram (EEG), in the treatment of individuals with ASD. The author selects 10 representative research papers published on PubMed in the past 5 years for discussion. The author separately analyzes their major methods, results and new discoveries, followed by potential problems and future development directions of these two kinds of therapy methods. The Related Works in this review is organized in the order of different stimulation sites for each stimulation, including most common sites dorsolateral prefrontal cortex (DLPC) and right temporoparietal junction (rTPJ). In the end of this review, the expectations for future research and treatments of ASD are proposed from the perspective of the author. Based on recent studies and reasonable speculation by the author, homogenous subgroup analysis and more broadly available therapy research will be scientific trends for ASD therapy in the future.

Keywords: Autism Spectrum Disorder (ASD); Transcranial Magnetic Stimulation (TMS); Transcranial Direct Current Stimulation (tDCS); Electroencephalogram (EEG).

1. Introduction

Autism spectrum disorder (ASD) is one of increasing neuropathological diseases among children and young adults around the world. ASD patients suffer many kinds of deficits representing by atypical core symptoms, commonly ranging from altered executive functions [1], abnormal perceptual and cognitive functions [2-4], to adaptive functioning deficits (such as reduced auditory cortical adaptation in [5]), to other impaired functions (such as reduced visual cortical plasticity in [6]). There are also social behavioral deficits in ASD, leading to social communication and social interaction problems in young patients, who cannot meet the basic needs of life corresponding to the growth stages [7]. Now, even though autism can be diagnosed from many different physical and mental performance mentioned above, it remains really difficult to find universal standards or measures to judge with one hundred percent certainty, due to the heterogeneous nature of ASD, an important aspect that still needs to be better explained by neuroscientists in the future.

In terms of heterogeneity, ASD patients among populations show inconsistent indices even measured by the same method. Compared to neurotypical (NT) controls, some ASD patients are over-reactive while others are under-reactive to stimuli, which poses a challenge in the search for appropriate diagnostic biomarkers [5].

For the treatments of ASD, no effective treatment has been approved by regulators up to now, even though numerous different trials are in the process. Even for the treatments already passing through their endpoints, uncertain counter results may appear in the clinical stage [8]. What's more, many other co-occurring associated diseases, like irritability and attention deficit hyperactivity disorder (ADHD) make ASD more difficult to solve completely [8]. Recently, scientists attempt to solve ASD from many different approaches. For instance, there are several new agents or therapeutic ways in development that target at altering transcriptional pathway, epigenetic regulation, neurotransmission

pathway, or more specifically targeting at DNAs or RNAs [8]. Besides, the treatments based on brain stimulations are also promising, since the impaired dysplastic foci are located in regions of brain, especially prefrontal cortices. Transcranial direct current stimulation (tDCS) or repetitive transcranial magnetic stimulation (rTMS) are popular and effective ways among pilot trials in recent years.

From the perspective of mechanism, pyramidal cells and interneurons play important roles in normal development of brain. However, without above cells migrating to proper location, neurodevelopmental abnormalities (such as the focal cortical dysplasia) can occur and result in altered functions of ASD. For TMS studies, some recent studies focus on parvalbumin-positive GABAergic interneurons because previous animal models have demonstrated that lower than normal parvalbumin expression levels are associated with ASD [2].

Technically, transcranial magnetic stimulation (TMS), as one kind of non-invasive brain stimulation, is one of common treatments of modulating abnormal oscillations in brains, even though exact biological effects of TMS are still under study. The effects of stimulations vary with stimulation spots and forms and specific effects depend on individuals. However, usually, low frequency TMS (less than 1 Hz) has inhibitory effect, while high frequency TMS (more than 5 Hz) has excitatory effect [2].

Transcranial direct current stimulation (tDCS) is another common way of stimulation for ASD and other neurodevelopmental disorders, which is also a non-invasive, safe and stable method with ease of clinical application [9]. It induces changes in brains by using weak electrical direct current, and the effects of stimulation depends on stimulation polarity-the anodal end has excitatory effect while the cathodal end has inhibitory effect [10]. Besides, tDCS's modulatory effects are not limited in local cortex, and instead it can be used to study the connectivity in the whole brain [11].

For both TMS and tDCS, dorsolateral prefrontal cortex (DLPC) is targeted mostly for a series of stimulation session in trials, because it is assumed to take charge of the integration work over the whole brain networks, and can be seen as the center of high-level cognitive ability [1-3]. The neuromodulation of DLPC, such as normalization of gamma oscillations, has the potential to improve the performance of ASD patients. Additionally, for depression, a sound high-frequency-rTMS treatment has been approved [12], which implies the possibility to find the same or similar enhancement of cognitive functions in ASD in future studies. Besides, most studies of tDCS applied stimulation over unilateral dorsolateral prefrontal cortex (DLPC), while some recent pilot studies attempted to stimulate bilateral cortical areas like in [7]. Other targets for TMS and tDCS include the right temporoparietal junction (rTPJ) (which is also engaging in integration work in human brains, especially multisensory processing [4]) or other areas in temporal parietal lobes [8].

In most published studies of ASD, both repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are safe and acceptable for ASD patients with no serious adverse effects reported, while some argue that young patients may suffer slight discomfort and headaches during the process of TMS [6] and tDCS [13].

One of convenient non-invasive ways to identify the performance of patients before and after stimulation is through electroencephalogram EEG. For example, it can detect the illusory figure from gamma activity on EEG results [14]. Gamma oscillations (typically around 30 to 80 Hz) are of the greatest recent interest in studies, because they have a close relationship with the cortical connectivity in brains and the cognitive ability of patients [2]. For instance, the reduction of gamma synchronization may cause visual and auditory processing deficits in ASD patients [12]. For interpretation of EEG graph, two classifications are very important, evoked gamma-band activity (about 100 milliseconds after stimulation) and induced gamma-band activity (about 250 milliseconds after stimulation) [2], of which the former is much easier to be investigated due to its phase-locked property [3]. EEG-based gamma neurofeedback has been combined with TMS to improve clinical approaches [2]. Apart from evoked EEG, resting state EEG is another common character in EEG recordings that can, for example, reflect the dynamic configuration and reconfiguration process of brain network [11]. The advantage of EEG over fMRI is that EEG is much easier to detect, especially in children with ASD, where the EEG recording process is very short.

In this review, the author mainly focuses on the effects of TMS and tDCS treatments assisted with EEG and other outcome measures in autism spectrum disorder (ASD). In the part of Discussion, the author will summarize the difficulty of ASD research and treatments, important aspects of TMS and tDCS in existing and future research of ASD. Finally, the author will conclude the possible future directions based on recent studies and the author's own understanding of this field.

2. Related Works

In this part the author reviews some related works about TMS and tDCS on ASD patients in recent years. The author selects five highly representative and valuable articles for each stimulation technique and demonstrate the contribution of each article to current research and future treatment of ASD.

2.1 Transcranial Magnetic Stimulation

The scientific research about Transcranial Magnetic Stimulation (TMS) in ASD patients is quite limited, so the author mainly focuses on some valuable studies on the effects of TMS on DLPC and rTPJ.

In recent years, Manuel F. Casanova, et al. have been studying the therapeutic effects of low frequency (<1Hz) TMS on dorsolateral prefrontal cortex (DLPC or DLPFC) in ASD patients [2,3,15]. From a series of published research, they focused mainly on the gamma-band activity (30-80 Hz), and the significance behind the change of gamma response before and after the above treatment of TMS. They had considered gamma related abnormality as one of potential biomarkers for ASD, due to the prevalence of this phenomenon in ASD patients. Hence, they have been studying on the road of modulation of gamma oscillations for ASD. Additionally, DLPC plays an important role in supervising and organizing the functions of brain networks especially in higher cognitive functions in order to adapt to a changing environment, while ASD patients who are in absence of normal gamma activity show typical ASD symptoms such as excessive or repetitive activities, irritability and social withdrawal [2], so they mainly focus on studying gamma activity with TMS over DLPC region.

In many different experiments, they mainly used a Kanizsa visual attention task, which can help them to distinguish the gamma responses of subjects between target and non-target stimuli. In ASD, they found increased power of gamma oscillations, and decreased difference between gamma responses to target and non-target stimuli, both of which can be cured by low frequency TMS [2,3]. And from the EEG recordings of event-related potential, ASD patients are also more likely to be distracted by irrelevant distraction than controls [2]. More importantly, the lack of topographical difference in evoked gamma power between frontal and parietal regions in ASD patients suggests that studies of ASD abnormalities should not examine the effects of only one region in isolation, and based on this they proposed the idea of exploiting downstream effects of DLPC to treat ASD, even if not yet successfully [3].

From their studies, they are firmly convinced that the ringing at gamma frequencies stands for an inhibitory deficit in ASD with four sound reasons listed in [2]. And then, based on physical principles and models, they invented a new measure-envelope analysis-to investigate the gamma-band activity in EEG recordings, which can indicate excitatory/inhibitory balance of the cortex as well as the impedance of human brains non-invasively [3, 15]. In short, with several attempts to cure the deficits in ASD such as impaired abilities of self-monitoring and self-correcting, in their studies, they confirmed the safety and efficacy of low-frequency TMS over DLPC in ASD symptoms, even though more large-sample, follow-up studies and other auxiliary tests are still needed [2]. One of limitations of their studies is that they only focused on the gamma band, while the theta band also has a great influence on the treatment effects, which needs to be investigated in future studies of the theta-gamma coupling effect [3].

When it comes to studies related to high frequency rTMS targeting DLPC, very limited number of recent studies can be found, one of which Stephanie H. Ameis, et al. published in 2020 [1]. In this

study, since executive function (EF) deficits are quite common in ASD, they implemented a pilot randomized controlled trial (RCT) on these with analysis of moderating effects of baseline adaptive functioning and gender. Unfortunately, they didn't get some significant results among all ASD patients. However, they found that, compared with other ASD patients, the improvement of EF was more obvious in the ASD subgroup of severe baseline adaptive functioning deficits, which could be predicted by the connectivity of frontoparietal control network [16]. Besides, despite of the ceiling effect of their specific measure outcomes across gender subsets, they proposed that further studies should consider the influence of gender on the validation of rTMS performance, or separate males and females to study due to the intrinsic neurobiological differences.

Other than many protocols of TMS over DLPC, J. Fujino et al. attempted another site, right temporoparietal junction (rTPJ), in TMS therapy for ASD in their published paper in 2021. As has mentioned before, rTPJ takes an important part in processing multiple pieces of sensory information, and the effects of intermittent theta burst stimulation (iTBS) and continuous theta burst stimulation (cTBS) over the motor cortex have been proven excitatory and inhibitory respectively in a previous study [17]. Hence, they chose to stimulate the anterior part of rTPJ with iTBS and cTBS for ASD patients. As a result, they found that cTBS had a similar result (inhibition) on the anterior side of the rTPJ as over the motor cortex, whereas iTBS had no effect. One of their limitations was the bias of sample selection, which was made up of only high-functioning ASD patients.

2.2 Transcranial Direct Current Stimulation

Compared with TMS, in recent published tDCS trials the author finds more diversified stimulation sites, including conventional ones, such as dorsolateral prefrontal cortex (DLPC) and right temporoparietal junction (rTPJ), as well as innovative ones, such as cerebellar hemispheres [18]. Some representative studies will be reviewed in details as follows.

For the DLPC site, earlier studies are most focused on unilateral stimulus (left or right DLPC). Among them, some of the outcomes are disputed with others, which still needs to be explained by more supportive studies in the future. However, some researchers proposed that the dysfunctions of two hemispheres might be different significantly (left one is close to communication and social behaviors, while right one is close to motor impairments) [19], so Hikmat Hadoush et al. [7] piloted bilateral anodal tDCS (with anodal electrodes placed on the FC1 and FC2) on premotor area, and the motor cortical areas in ASD. Their major outcome measure is ATEC which covers 4 subscales resulting in comprehensive results and they gave some possible reasons of these results. Specifically, bilateral stimulation enhanced a subscale II of sociability, possibly because the prefrontal cortex, a key area that controls social and imitation functions, may have been stimulated. Also, the enhanced subscale IV of health, physical condition, and behavior shows that bilateral stimulation over sensorimotor cortices might influence GABA levels to enhance the performance of ASD, even though more follow-up studies are necessary to prove it. On the other hand, the results that no significant improvement of other two subscales (I: speech, language, and communication; III: sensory and cognitive awareness) were observed, were explained by a possible reason that not all related regions in these functions were being excited by bilateral stimulation in this study. One limitation of this study is that they didn't change the magnitude of their stimulus based on the head sizes of their subjects (children aged between 4 and 14), which means that more patient-oriented research is needed rather than purely experimental oriented research.

New perspectives of studying tDCS over DLPC are as follows. Tianyi Zhou et al. [11] utilized network-based methods to discover how tDCS changes brain functional network structures in ASD patients. Based on the rightward lateralization hypothesis [20] and the fact that anodal tDCS is more efficient than cathodal tDCS [21], they used anodal tDCS over right-sided DLPC as their stimulation method. Previous studies had shown that: Low-frequency bands of EEG (i.e., delta, theta and alpha) reflect more information of global connectivity [22], while high-frequency ones (i.e., beta and gamma) reflect more information of local changes [23]; ASD patients have long-range under-connectivity and short-range over-connectivity [24]. In the new study [11], they focused on two important points: First,

tDCS increased the speed of reconstruction as analyzed by temporal network dynamics, which may indicate future potential for executive functioning and mood improvement in clinical ASD. Second, tDCS could promote interhemispheric over-synchronization and local under-synchronization in alpha, beta and gamma bands, which suggests that tDCS can influence functional connectivity structure in human brains. Finally, they also encouraged the further comparative studies of TMS and tDCS based on their ability to alter network dynamics [25].

Other EEG features were also be used in research projects related to tDCS effects on ASD. For instance, Changcheng Sun et al. [9] worked on mismatch negativity (MMN) features of EEG recordings including MMN latency and MMN amplitude. Compared with fMRI, evoked EEG signals are more acceptable and accessible for young patients in ASD.

MMN acts as an auditory component of evoked EEG recordings that is highly correlated (even linearly) with behavioral ability. Besides, ASD children without the ability to concentrate for a long time don't need to actively engage in the process of EEG and are measured unconsciously. Therefore, MMN is a promising method to evaluate the behavioral abilities of children with ASD from both qualitative and quantitative perspectives. To be more specific, in the study [9], they compared three different types of stimuli (i.e., Frequency-Deviation Stimulation (FDS), Time Deviation Stimulation (TDS) and Frequency Deviation Stimulation (TFDS)) with the two dimensions of their MMN features (i.e., amplitude and latency). They observed an decrease in MMN latency and increased activation area on brain topographic map after tDCS treatment over DLPC in children with ASD, reflecting the effectiveness of this treatment. They concluded that MMN could be used to evaluate behavior ability due to the fact that MMN features, especially MMN amplitude, are highly consistent with the aberrant behavior checklist (ABC) scale (which is a comprehensive test of ASD severity). Their study shows that the synergism of conventional rehabilitation treatment and the use of anode tDCS was more effective than only conventional rehabilitation treatment alone.

For the rTPJ site, only one case report can be found by the author, indicating this area remain basically untouched. Joan Esse Wilson et al. [13] conducted a case study of an 18-year-old high-functioning ASD patient for over a year. During and after tDCS treatment at the rTPJ with ipsilateral electrode placement, the patient's social deficits associated with ASD (such as ignoring other people's feelings, irritability, etc.) was significantly improved, and researchers explained this phenomenon by the close relationship between deficits in social functioning of ASD patients and rTPJ showed by functional neuroimaging [26]. The advantage of this study is their long-time (over 1 year) follow-up indicating possible positive persistent effects of this tDCS protocol. However, the study of only one participant is unconvincing because there are many interfering factors that have not been ruled out. More importantly, they suggested that the future study should consider the optimal timing of tDCS treatment due to the great influence of age.

The most innovative study the author finds was conducted by Hikmat Hadoush and Ashraf Hadoush, as their anodal tDCS RCT study was over bilateral cerebellar hemispheres, there not previously studied. Based on the study of the human cerebellum, the cerebellum plays a role in fronto-parietal and other networks, affecting social ability [27]. Hikmat Hadoush et al. paid attention to cerebellum dysfunction associated with ASD to further the research of tDCS treatment. In their study, bilateral anodal tDCS over cerebellum increased the complexity of the resting-state brain, indicating the potential to alleviate deficits of great brain complexity in ASD. Their indices were approximate entropy (ApxEnt) values of resting-state EEG, even though the data point length of approximate entropy (ApxEnt) remains unproven theoretically. Their results show a therapeutic bias in favor of the right hemisphere (that is more increase in right frontal cortical region), and they found two explanations in previous studies (right-side dominance in ASD [27] and rightward asymmetric brain systems in ASD [28]) to support it. Although more clinical support is necessary to validate therapeutic value of their innovative protocol, they did push forward with the development of tDCS treatment of ASD.

3. Discussion

Autism spectrum disorder (ASD) has been studied for many different aspects. For the two kinds of stimulation, namely Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS), up to now, no effective general treatment has been found, let alone approved for clinical use. From the symptoms of ASD, in recent years, during many experiments, the wide range of possible observed behavior changes and index changes due to the heterogeneous nature of ASD is still the trickiest problem based on recent articles, and thus homogenous subgroups will be the main focus in the future research. Another difficulty lies in the characteristics of patients with ASD. Patients are young children most of whom also suffer social or communicative deficits, making it difficult to accurately report the symptoms and exclude the effects of normal growth. As a result, ASD is still unsolved and lacks effective universal approaches.

There are several noteworthy aspects of TMS and tDCS research in ASD: First, more theoretical supports are needed to improve the whole experimental research, especially for the elaborate processes of regulatory effects of TMS and tDCS are still not clear enough. Actually, it is very important to understand the underlying biological and psychological mechanisms because theories can largely accelerate the research process and avoid useless work. For instance, due to the previous studies that dysfunctions in left hemisphere cause communication and social behavior problems [29] while dysfunctions in right hemisphere cause physical activity problems [19], the following studies adopted bilateral anodal tDCS stimulation over the DLPFCs in both hemispheres with the expected successful results [7]. As another example, the speculation that brain regions are closed related to each other and function together suggests that studying anatomical brain structure in isolation is not very promising [2]. So, the author thinks that in the future more basic knowledge about the regulatory mechanisms of different stimulations, and even neuroscience and technology, can largely improve the research process.

Second, among a dazzling array of protocols, which one is the best? Does the best protocol exist? How to define the best? These leads to an inevitable issue – how to find reliable outcome measures or biomarkers in measured EEG signals, neurobehavioral manifestation or both? Before thinking this, how to compare different experiments? Every study has their own subtle but influential differences among their method setting, including but not limited to stimulating spots (F3, F4, P7, P8, etc.), unilateral or bilateral stimuli, physical and mental states of patients etc. Worse still, limited numbers of subjects and studies make it hard to evaluate the advantages or disadvantages of different specific protocols among different articles. More importantly, most research articles are stuck in simply analyzing EEG recordings after a particular stimulus and discussing whether the results are significant or not. This means that their results and conclusions can only provide some direct evidence, and cannot be combined or compared with other existing studies due to differences in the subjects and the outcome evaluation systems. In a nutshell, a set of comprehensive evaluation and judgement criteria is needed, and many correlational series of studies are also needed to enhance comparability between trials.

Third, almost all the existing researches face some common limitations: (1) Only a small number of subjects are available for each experiment. Of course, as is mentioned above, the heterogeneity of ASD poses a challenge to current and further study. Before official approvals for treatments, more large ASD population studies are necessary. (2) Long-term follow-ups need to confirm the safety and efficacy of protocols, even though many articles have shown good results in small groups of patients with ASD, showing therapeutic potential of TMS or tDCS within their own innovative protocols, including different methods, such as targeting rTPJ, DLPC or other new sites, low-frequency or high-frequency TMS and so on. In fact, it is very difficult to exclude all the interference factors for a long period of time especially when the relationship between ASD and many environmental factors is not explored completely. Experiments over several years may aggravate the psychological burden in patients or their families of sham-stimulation groups, single blinding or double blinding, because in order to avoid interference during the experiments these patients (mainly children), may miss the chance of taking other non-stimulation treatments, leading to worse or unexpected results. Therefore,

the author believes that new protocols for long-term experiments should also allow all the young patients to receive necessary auxiliary treatments (such as, some previous drugs or therapies that have been proved partially or temporarily effective), putting them and their families at ease.

Actually, when it comes to clinical feasibility, there is still a long way to go: Based on the current research, it is not very promising to find a universal treatment among the population of ASD, and many treatments specific to one or limited kinds of deficits in ASD cannot be very efficient since they do not eradicate the relapse of severe ASD, but instead rely temporarily on seemingly effective stimulus. On the other hand, some well-supported findings are more promising to specific homogenous subgroups of patients, such as these with high-functioning ability [4,13] or a high level of intelligence. Even in this case, more comprehensive evaluation for the safety and efficacy of therapeutic methods passed the preliminary tests are in great need to deal with clinical diagnosis and treatment with ASD.

The author puts forward some promising pathways of TMS and tDCS methods in future ASD research based on the published articles in recent years. (1) Subdivide the ASD symptoms into homogenous subgroups, and then propose the protocols targeting each homogenous character. And then treat each patient simultaneously or sequentially with several different approved protocols depending on the severity and symptoms of ASD. (2) Focus more on general ASD patients or subgroups than on specific individuals. (3) Study the possible interference in experiments under non-ideal conditions to prepare for clinical application. (4) Consider implementing treatment options that have already shown a certain level of efficacy in long-term trial designs. (5) Combine advantages of different therapies to achieve optimal synergy effects [2,7,11].

4. Conclusion

In this review, the author selects and sorts out ten recent studies about TMS and tDCS for ASD research and treatment, and then analyzes each of their methods, results and conclusions that are helpful to improve the overall understanding of ASD. As a whole, the amount of available knowledge about ASD and corresponding stimulation treatments has been quite limited up to now, and the existing researches all face limitations, such as small sample size and no long-term follow-up study. Therefore, the author points out the difficulty of finding promising and long-term ASD therapies generally effective among ASD patients, and discusses several important aspects of future studies - homogenous subgroup studies are expected to find more effective protocols, interference factors and complementary treatments are worth considering in long-term experiments, and the combination of different treatments is a new direction for future ASD research attempts.

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