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REVIEW

Advancements in Transcranial Magnetic Stimulation Research and the Path to Precision

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Abstract: Transcranial magnetic stimulation (TMS) has become increasingly popular in clinical practice in recent years, and there have been significant advances in the principles and stimulation modes of TMS. With the development of multi-mode and precise stimulation technology, it is crucial to have a comprehensive understanding of TMS. The neuroregulatory effects of TMS can vary depending on the specific mode of stimulation, highlighting the importance of exploring these effects through multimodal application. Additionally, the use of precise TMS therapy can help enhance our understanding of the neural mechanisms underlying these effects, providing us with a more comprehensive perspective. This article aims to review the mechanism of action, stimulation mode, multimodal application, and precision of TMS.

Keywords: transcranial magnetic stimulation, mechanism, stimulation mode, multimodal application, precision

Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive and painless neurophysiological technique that allows for stimulation of the human brain by applying a magnetic field to the intact scalp. The basic principle of TMS involves the use of an electrically conducting coil, which produces a magnetic field that is oriented at a right angle to the direction of the coil. This pulse of magnetic field permeates the brain, producing a corresponding induced current that causes the release of neuron action potentials, activation of brain networks, and ultimately achieving neural regulation.[1] TMS pulses have the ability to selectively modulate neural activity by depolarizing neurons in a precise spatial and temporal manner. This results in changes to the excitability of the cortex, as well as the activation of distant cortical-subcortical and spinal structures via specific neural pathways.[2] Since its invention by Barker in 1985, interest in TMS has been increasing, and research on this topic has expanded, enhancing our understanding of the human brain. TMS has become an effective means of basic medical and clinical research and has been widely used in clinical treatment. This paper will discuss the mechanism of action, stimulation mode, multimodal application, and precision of TMS.

The Mechanism Underlying the Effects of TMS

The mechanisms of action of transcranial magnetic stimulation (TMS) are related to the plasticity of spike timing-dependent plasticity (STDP)[3] and Hebb's theory.[4] TMS has both direct and after-effects on cortical excitability and can affect both nearby and distant areas of the brain.

The direct-effects of TMS are caused by action potentials in stimulated neurons and neural networks, while the after-effects result from changes in synaptic plasticity, leading to long-term potentiation (LTP) and long-term depression (LTD) of synaptic transmission.[5] The local effect is generated by action potentials evoked in the target area, while the distal effect is generated by the propagation of action potentials from the target area to distant areas through multisynaptic connections.

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The mechanism underlying the effects of TMS can be described at several levels, including the cellular, synaptic, and network levels.

At the cellular level, TMS-induced electrical currents can depolarize neurons, leading to the firing of action potentials. Neurons communicate via electrical impulses known as action potentials. These impulses can trigger specific intracellular signaling pathways that mediate the strength and plasticity of inter-neuronal connections. Such modifications may lead to alterations in information processing and storage within the brain, referred to as long-term potentiation (LTP) or long-term depression (LTD) depending on whether the inter-neuronal connections are strengthened or weakened, respectively.

At the synaptic level, TMS has the ability to alter the release of neurotransmitters, specifically glutamate and GABA, which can affect synaptic strength and plasticity.[6] TMS can cause depolarization or hyperpolarization of cell membranes by inducing an electric field in neurons under a transcranial magnetic stimulation coil, resulting in changes in ion channel activity.[7] For example, TMS can lead to an increase in voltage-gated calcium channel activity, resulting in an increase in intracellular calcium levels.[8] By regulating calcium channel activity, TMS can influence cellular processes and brain function.

By inducing synaptic plasticity, TMS can induce long-lasting changes in the connectivity between brain regions, which underlies its ability to induce lasting changes in brain function and may be important for its therapeutic effects in certain conditions.

In addition, TMS can also modulate the activity of other ion channels, such as potassium channels and chlorine channels, which can further promote TMS-induced changes in neural activity.[9] TMS can induce changes in membrane protein channels by inducing an electric current in neurons under the TMS coils, leading to the activation or inhibition of voltage-gated ion channels and other membrane-binding proteins, including neurotransmitter receptors.[10]

TMS has been demonstrated to elicit the generation of neurotrophins, a class of proteins that aid in neuronal growth, survival, and function in the brain. More specifically, TMS has been shown to enhance the secretion of Brain-Derived Neurotrophic Factor (BDNF), a critical mediator of neuronal plasticity that contributes to the brain's capacity to adapt and modify. BDNF has been implicated in the pathogenesis of various neurological and psychiatric illnesses.[11] Animal studies have shown that TMS can increase BDNF levels in the hippocampus.[12] In humans, studies have found that TMS can increase BDNF levels in the prefrontal cortex and other brain regions, and this effect may be more pronounced in individuals with depression or other psychiatric disorders.[13]

At the network level, TMS has the ability to alter the functioning and interconnections of extensive neural networks by altering the excitability of neurons and altering the synaptic connectivity between them. TMS has the potential to selectively modify the excitability of specific brain regions, resulting in changes in the functioning of interconnected regions and ultimately affecting the activity of the entire network.[14]

TMS Model

Transcranial Magnetic Stimulation (TMS) modalities can be classified into three types: single-pulse, paired-pulse, and repetitive. Single-pulse and paired-pulse transcranial magnetic stimulation (TMS) are typically utilized to explore brain functioning, whereas repetitive TMS is commonly used to induce alterations in brain activity.

Single-Pulse Transcranial Magnetic Stimulation (spTMS)

Single-pulse transcranial magnetic stimulation (spTMS) generates a short-lived electrical impulse in the cortex, which triggers rapid depolarization of neurons. spTMS has been found to be an effective tool for diagnosing and treating neurological disorders because it permits accurate localization of particular brain regions. Historically, the motor cortex has been the most frequently selected region in TMS investigations owing to its measurable and conveniently accessible neurophysiological results. spTMS is a standard choice of stimulation protocol for assisting in diagnosis with suprathreshold stimulation intensity and stimulation areas focused on cortical motor area M1[15] or visual cortex.[16] Motor-evoked potential (MEP) analysis can be used to evaluate the functionality of the corticospinal tract by comparing the amplitude and latency of the MEP to the spTMS event.[17]

TMS is an effective and potent method for investigating the workings of the brain and can be used to measure a variety of electrophysiological indicators. In addition to MEP, spTMS can be used to measure motor threshold (MT),

stimulus-response curves, cortical silent period (CSP), central motor conduction time (CMCT), and motor evoked potential recruitment curves.[18] It is also useful in localizing functional brain areas and detecting changes in motor cortical excitability and corticospinal tract conduction integrity.

However, MEP recordings can be more variable than peripheral compound muscle action potential (CMAP) due to spinal cord repetitive discharge and phase offset, even when the external stimuli remain consistent in terms of their intensity and location.[19] To improve the reliability of MEP recordings, the triple stimulation technique (TST) is often used as a hedging technique. This technique involves applying three consecutive stimuli to the same location, with the second and third stimuli being sub-threshold and suprathreshold, respectively. This helps to reduce variability in MEP recordings and improve their reliability.[20]

Paired Pulse Transcranial Magnetic Stimulation (ppTMS)

Paired-pulse transcranial magnetic stimulation (ppTMS) is an effective instrument for assessing cortical excitability and intracortical processing. Through the administration of two TMS pulses with varying interstimulus intervals and stimulus intensities, ppTMS can induce changes in MEP amplitude, which reflect intracortical facilitation (ICF) or intracortical inhibition (ICI).[19] This technique can be used to investigate various forms of facilitation and inhibition, such as long-interval intracortical facilitation (LICF), long-interval intracortical inhibition (LICI), Short-interval intracortical facilitation (SICF), short-interval intracortical inhibition (SICI), interhemispheric inhibition (IHI), short-latency afferent inhibition (SAI), and long-latency afferent inhibition (LAI), paired associative stimulation (PAS).

LICF refers to the phenomenon where MEP amplitude is facilitated with an interstimulus interval of 50–200ms, whereas LICI induces inhibition with an interstimulus interval of 100–200ms.[21,22] SICF and SICI share a similar interstimulus interval of 1–5ms, but differ in their effects on excitatory circuits, with SICF reflecting facilitation mediated by facilitatory interneurons and SICI reflecting inhibition mediated by inhibitory interneurons.[23,24] IHI refers to the reduction of corticomotor excitability in the contralateral hemisphere following transcranial magnetic stimulation of the ipsilateral hemisphere.[25,26] SAI and LAI involve the inhibition of MEP amplitude by peripheral nerve stimulation at short (20–25ms) and long (200–300ms) latencies, respectively.[27–29]

PAS is a technique that involves stimulating the peripheral nerves along with TMS of the motor cortex in order to induce cortical plasticity. It is possible to induce either LTP or LTD effects, depending on the timing of the stimulation.[30] The timing of the PAS protocol is crucial to induce either LTP or LTD effects.[31] To induce greater excitability, the time between the afferent stimulus and TMS should be either the same as or slightly longer than the latency of the cortex of the individual. The N20 latency is a commonly used reference point for this timing, as it represents the latency of the somatosensory evoked potential that corresponds to the arrival of afferent input to the primary somatosensory cortex.[32] The PAS protocol will induce LTD if the interval is shorter than the N20 latency.[33]

Furthermore, the technique has been expanded with cortico-cortical paired associative stimulation (ccPAS)[34] and cortico-subcortical paired associative stimulation (Cortico-Subcortical PAS).[35] ccPAS combines cortical elements by applying a conditioned stimulus to the contralateral motor cortex and a test stimulus to the ipsilateral motor cortex. Cortico-Subcortical PAS, on the other hand, combines cortical and subcortical elements by targeting both the cortex and subcortical structures such as the basal ganglia. These techniques have facilitated an enhanced comprehension of the processes that govern the brain's ability to change and adapt, and their possible usefulness in treating various neurological and psychiatric conditions.

By utilizing ppTMS, researchers can refine their understanding of the mechanisms of cortical excitability and plasticity, and how this knowledge can potentially be applied in the diagnosis and treatment of various neuropsychiatric disorders.

Repetitive Transcranial Magnetic Stimulation (rTMS)

Repetitive transcranial magnetic stimulation (rTMS) is a technique for non-invasive brain stimulation that uses repetitive magnetic pulses applied to the scalp to modify the excitability of cortical neurons. Low-frequency rTMS (1 Hz or less) is employed to reduce cortical excitability, whereas high-frequency rTMS (5–20 Hz) is utilized to boost cortical

excitability.[36] However, the impact of rTMS varies considerably among individuals and is contingent upon the state of the brain during stimulation.[37]

To improve the reliability of rTMS, patterned rTMS protocols have been developed, such as theta burst stimulation (TBS).[38] TBS is a type of rTMS that combines both high and low frequency stimulation to produce either cortical inhibition or excitation, depending on the pattern of stimulation. Continuous TBS (cTBS) is a protocol that uses low frequency stimulation to produce cortical inhibition, while intermittent TBS (iTBS) uses high frequency stimulation to promote cortical excitation.

Studies investigating the impacts of iTBS and cTBS on the primary motor cortex has shown that these protocols can produce longer-lasting changes in cortical plasticity compared to traditional rTMS protocols.[38,39] Moreover, they are often more effective at inducing changes in cortical excitability than conventional rTMS protocols.[38] These findings suggest that patterned rTMS protocols like TBS may have important clinical applications in the treatment of various neuropsychiatric disorders.

Quadripulse stimulation (QPS) is an advanced form of rTMS that involves delivering four monophasic TMS pulses at an interval of 5 seconds for 30 minutes to modulate cortical excitability.[40,41] QPS has been shown to be more effective than conventional rTMS using biphasic pulses, as it induces longer-lasting after-effects. The intensity of the QPS stimulus is usually set to 90% of the active motor threshold (AMT), and the inter-pulse interval (IPI) determines the level of LTP or LTD induced. Short interval QPS (QPS1.5, QPS5, and QPS10) increases cortical excitability, while long interval QPS (QPS30, QPS50, and QPS100) suppresses cortical excitability.[42] QPS50 has been found to be the most effective at inducing LTD. QPS is considered the most powerful and reliable non-invasive brain stimulation (NIBS) method for inducing neuroplasticity in humans.[40]

Multimodal Application of TMS Combined with Other Technologies

Multimodal approaches to assessing cortical excitability can supply a more thorough grasp of the brain's response to TMS stimulation. While MEP amplitude is a useful tool for assessing cortical excitability, it has limited ability to quantify the level of cortical excitability in particular brain regions where MEPs cannot be elicited. To address this, techniques such as electroencephalogram (EEG), positron emission tomography (PET), functional magnetic resonance imaging (fMRI), functional near-infrared spectroscopy (fNIRS), and other neurophysiological and neuroimaging techniques can be used to evaluate the direct and after-effects of transcranial magnetic stimulation (TMS).[43] This allows for the identification of the best brain regions to target and the tailoring of treatments to individual patients, ensuring the provision of the most efficient treatment.

Combination of TMS and EEG

Combining TMS with high-density EEG allows for a more comprehensive assessment of human brain networks. By applying magnetic fields to these regions, TMS causes the neurons in that area to become excited and activate interconnected networks. This increased neuronal activity can be measured using EEG (electroencephalography), which records the electrical activity of the brain. The peak effect of TMS on brain activity occurs within 15 to 300 milliseconds after the TMS pulse. The TMS-evoked potential (TEP) is a characteristic sequence of positive and negative deflections obtained when multiple EEG recordings of pulses (ie brain waves) occurring in the same region of the brain are combined and averaged together. TEPs can provide information about the timing and magnitude of cortical activation in response to TMS, and can be used to study the functional connectivity between different brain regions.[44] TEP (transcranial electrical stimulation) can effectively communicate information about the timing of activation of different regions of the brain's connectivity, which makes it possible to determine the cause-and-effect relationship between two regions within a functional network.[45] Furthermore, certain TEP peaks or elements have been linked to the facilitation or inhibition of neurotransmitter activity in the brain.

TEPs are produced only when certain areas of the brain are stimulated and functioning correctly. This strongly indicates that TEPs are a direct reflection of cortical activity, rather than being mere random electrical or physiological signals.[46] Additionally, when considering certain areas of the brain, TEPs show a high level of consistency when measured repeatedly in the same individual, suggesting that they reflect stable patterns of cortical activity.[47]

TEPs in the primary motor cortex (M1) exhibit various peaks, including N15, P30, N45, P55, N100, P180, and N280, which reflect the sequential activation of different groups of neurons in M1. In contrast, TEPs in the dorsolateral prefrontal cortex (DLPFC) are generally smaller in amplitude than those in M1, and they consist of P25, N40, P60, N100, and P185 peaks.[48]

The amplitude of the N45 peak in TEPs appears to be modulated by the interplay between GABA-mediated inhibitory processes and the excitatory effects of glutamatergic signaling through NMDA receptors.[49,50] Similarly, the N100 peak has been associated with GABABergic inhibition and the activity of the cortico-striato-thalamo-cortical loops and long-distance corticocortical connections.[49] This peak is thought to reflect inhibitory processes and the regulation of cortical excitability, which are vital for normal brain function.

The exact neuropharmacological mechanisms underlying the late TEP components are not fully understood, but some research suggests a potential connection to GABAB-related activity. Additionally, there is evidence to suggest that the later TEP components may be linked to cholinergic neurotransmission.[49]

In addition to TEP, TMS-EEG can yield a variety of measurements, such as TMS pulse-evoked cortical oscillations. These oscillations can reveal thalamocortical activity as well as local and global markers of cortical reactivity.[51] Such measurements can offer a more comprehensive comprehension of the neural mechanisms responsible for alterations in brain activity due to TMS application, and aid in customizing TMS protocols for individual patients.

Combination of TMS and fMRI

As previously mentioned, TMS-EEG has a high temporal resolution, which is beneficial for inferring valid connections. However, EEG has very low spatial resolution in both localizing target regions and estimating the origin of TMS-induced responses. To address this limitation, TMS is frequently used in combination with MRI to precisely locate and target specific brain areas. This approach allows for greater accuracy and consistency in TMS studies across different individuals.[52] This approach enables precise definition of regions of interest, allowing for more accurate navigation during TMS.[52]

Offline TMS-fMRI is often preferred due to the separation of TMS and fMRI in time and space, but it has limitations in sensitivity for capturing post-stimulation effects and studying connectivity in the brain as a result of TMS. To understand the direct effects of TMS on brain connectivity and mechanisms of TMS-induced neuroplasticity, combining TMS with fMRI can provide valuable insights, but the strong magnetic fields used in both techniques can result in reduced signal-to-noise ratio in online TMS-fMRI experiments. Additionally, MRI scans can induce reverse currents in the TMS coil, making control difficult. However, a TMS system that is compatible with MRI has been developed, allowing researchers to conduct a series of online TMS experiments. TMS researchers use concurrent or simultaneous TMS-fMRI with off-/online block or interleaved designs when exploring TMS.[53]

Combination of TMS and fNIRS

Functional near-infrared spectroscopy (fNIRS) is a non-invasive neuroimaging technique that measures changes in the concentration of oxygenated and deoxygenated hemoglobin in the brain.[54] TMS-fNIRS offers a comprehensive approach to studying the effects of TMS both online and offline due to its immunity to electromagnetic interference. This method allows for the stimulation of specific brain regions using TMS while simultaneously monitoring cerebral blood flow with fNIRS. By combining TMS and fNIRS, researchers can non-invasively measure TMS-induced changes in cortical activation and connectivity. fNIRS also provides valuable information about the metabolic changes that occur in response to TMS, which can complement the information obtained from other neuroimaging techniques.[55] For instance, fNIRS can be used to investigate the effects of TMS on brain metabolism and oxygen consumption, offering insight into the underlying mechanisms of TMS-induced neural plasticity. Moreover, fNIRS can objectively measure the effects of rTMS on specific brain regions even when there are no observable behavioral changes. Current studies have shown that excitatory rTMS can increase HbO and that hemodynamic activity after TMS stimulation is associated with the efficacy of TMS.[56,57]

Combination of TMS and PET

Positron Emission Tomography (PET) is a neuroimaging technique that can be used in conjunction with TMS to study the effects of TMS on brain function. This method allows for the detection of changes in subcortical and cortical structures and the identification of neural circuits involved in TMS-induced neural plasticity and network connectivity. With TMS-PET, researchers can stimulate a specific brain region while measuring changes in cerebral blood flow or glucose metabolism. This methodology allows for the detection of the direct impacts of TMS on brain activity and the neural processes underlying TMS-induced neural plasticity. Additionally, conducting a study using TMS-PET can offer valuable insights into the long-term effects of TMS on brain function and connectivity. Such research has the potential to shed light on the therapeutic benefits of TMS for various neurological and psychiatric disorders.

Most studies using rTMS-PET have concentrated on examining alterations in regional cerebral blood flow (rCBF), glucose metabolism, and the dopaminergic system. One study demonstrated the efficacy of rTMS-PET in investigating the human brain.[58] Cortical activation was positively correlated with rTMS frequency, according to Strafella. rTMS stimulates the ipsilateral subgenual anterior cingulate (ACC), medial orbitofrontal cortex, primary motor cortex (M1), and left dorsolateral prefrontal cortex(DLPFC), leading to the discharge of dopamine.[59,60] rTMS applied over M1 or left DLPFC increased rCBF in both low and high frequency applications. Additionally, the modulations of rTMS had different effects on remote brain regions. Recent PET studies have indicated that enhancements in metabolism in the bilateral precuneus and right temporal lobe are associated with the effectiveness of rTMS in treating treatment-resistant depression (TRD).[61]

Combination of TMS and DTI

Diffusion tensor imaging (DTI), a non-invasive neuroimaging technique, utilizes the diffusion of water molecules in brain tissue to map the structural connections between different brain regions. In TMS-DTI studies, researchers can use TMS to stimulate a specific brain region while simultaneously measuring changes in white matter connectivity using DTI. This approach can offer insights into how TMS-induced changes in cortical activity are transmitted through the white matter tracts that connect different brain regions.

Moreover, TMS-DTI can also be used to investigate the effects of TMS on the microstructure of white matter tracts, such as changes in axonal density, myelination, and fiber orientation. DTI measures such as fractional anisotropy (FA) and mean diffusivity (MD) can be used to quantify these changes.[62,63]

Exploration of TMS Precision

Administering TMS to a larger area of the brain, such as a whole hemisphere or cortical region, is called global stimulation. This approach can affect multiple neural circuits and functions simultaneously, which can have more widespread effects on brain function. Global stimulation may be useful for enhancing or suppressing brain activity in cases like treating psychiatric disorders or investigating general brain function. However, it can also cause unintended changes or side effects in non-targeted brain regions. To improve TMS technology, identifying stimulation targets, locating coils reproducibly, and exploring network connectivity and mechanisms of TMS effects can help to identify more precise modulation targets.

Precision of TMS with Neuroimaging

One way to improve the precision of TMS is by using neuroimaging techniques, such as MRI, to accurately identify the location of brain stimulation targets. This can help to ensure that the TMS coil is placed over the intended target area, resulting in more precise and consistent stimulation. Additionally, the use of neuronavigation systems, which combine MRI with real-time tracking of the TMS coil position, can further improve the accuracy and reproducibility of TMS.[64]

The effects of TMS on cortical and subcortical activity rely on the integrity of white matter fiber tracts.[65] Leveraging the high spatial precision of diffusion fiber tractography, we can use targets identified through diffusion imaging to accurately locate the stimulation site. By employing DTI, we can identify a superficial cortical site closely connected to the predetermined deep brain region and subsequently stimulate this superficial cortex with TMS to indirectly activate the deep brain area. TMS-fMRI enables us to interfere with and measure the activity of the entire brain network, providing compelling evidence of the direct involvement of both superficial and deep brain targets. Notably, fMRI recordings reveal

that single-pulse TMS stimulation at frontal targets significantly activates deep targets. This activation amplifies with increasing TMS intensity, illustrating that TMS directly activates the deep targets via synaptic transmission, and the level of activation correlates with the intensity of TMS stimulation.[66]

Precision of TMS with Brain Network

The TMS-fMRI technique can be used to measure the activity of the entire brain network and provide evidence for the impact of TMS on both superficial and deep brain nodes. Brain regions exhibiting statistically dependent fluctuations in BOLD signals are referred to as resting-state networks. Nodes within these resting-state networks may be part of larger networks, such as the dorsal attention network (DAN), salience network (SN), central executive network (CEN), and default mode network (DMN). Numerous studies have investigated the role of brain network connections in accurately identifying stimulation sites and explored the local and distal effects of rTMS.[67] A functional and anatomical brain network connection is crucial for rTMS to produce changes in remote brain regions.[68] Therefore, understanding the network connections can enhance our comprehension of the regions activated during rTMS and help identify potential targets for stimulation. Recent research has shown that the location of lesions in brain regions related to depression can be pinpointed to a particular brain network.[69] Identifying such a more specific brain network can help us to set it up as a modulatory target, avoiding homogenization of the modulatory region.

Precision of TMS with Neural Oscillations

The precision of neuromodulation through the use of rhythmic TMS patterns is enhanced by coupling with neural oscillations of specific frequencies in the target region of the brain. This approach allows for a more focused stimulation of specific subpopulations of neurons and neural networks, enhancing the precision of the modulation process. Adopting this methodology makes it feasible to customize the stimulation target based on the cortical activity linked with a particular task. We need to concurrently record the patients' brain electrical signals to ensure the correlation between the brain's electrical rhythms and the frequency of TMS stimulation. For instance, suppose a particular cognitive task requires a specific frequency of neural oscillations in a specific brain region. In that case, TMS can be utilized at the same frequency and location to alter the neural network activity involved in that particular task.[70] By using this approach, the precision of individualizing the cortical areas involved in a particular cognitive task is improved. The coupling of TMS with neural oscillations can also be used to enhance the efficacy of TMS therapy.[71,72]

Precision of TMS with Open-Loop or Closed-Loop

Open-loop TMS finds current application in both research and clinical contexts, including the treatment of depression, chronic pain, and movement disorders.[73,74] In open-loop TMS, pre-determined stimulus parameters are used to standardize TMS therapy, but this approach has limitations as it may not take into account individual differences in neural activity or response to TMS. Closed-loop TMS allows for more precise and personalized TMS applications. Closed-loop based TMS refers to the use of real-time monitoring of neural activity to guide the timing and location of TMS stimulation. In a closed-loop TMS system, neural activity is monitored by techniques such as EEG, MEG or fMRI.[75,76] Neural activity is then analyzed in real time to determine the appropriate timing and location of TMS stimulation. By targeting stimulation to specific patterns of neural activity associated with these disorders, it is possible to improve the efficacy of treatment and reduce side effects. Thus, closed-loop TMS promises to be a more precise and personalized approach to TMS treatment.[77]

Precision of TMS with Genetics

Genetic variations in ion channels and neurotransmitter receptors have been linked to individual variability in response to TMS. Ion channels regulate the flow of ions across the neuronal cell membrane and are crucial for neuronal excitability. Genetic variations can affect the function of ion channels, which in turn may influence TMS response.

One relevant genetic factor is the BDNF Val66Met gene polymorphism, which has been demonstrated to explain inter-individual differences in TMS response in studies of the motor system. Individuals with the ValVal genotype appear

to have consistently better responses to TMS for major depressive disorder (MDD). Differences in the modulation of motor cortex excitability and the susceptibility of synapses to undergo LTP and LTD may account for this.[78]

Other genetic variations that may be implicated in cortical excitability and TMS response include polymorphisms in the transient receptor potential vanilloid (TRPV1) channels. Some polymorphisms may facilitate greater cortical reaction to TMS than others.[79] Genetic variations in neurotransmitter receptors such as the serotonin transporter (5-HTT) and the dopamine receptor (DRD2) have also been associated with individual differences in TMS response.[80,81]

Recent studies involving whole-genome sequencing have discovered differentially expressed genes in rTMS responders as opposed to non-responders with major depressive disorder. Some of these genes consist of APP, GRID2, and SPPL2A.[82]

Conclusion

TMS has arisen as a valuable instrument for modulating brain activity non-invasively and exploring the underlying neural mechanisms. However, studies have shown that only 50% of participants exhibit the expected plasticity effects following a specific stimulation protocol, highlighting the large interindividual variability in the neuroplasticity effects produced by TMS.[83]

This variability arises from a complex interplay between the stimulation parameters and individual differences in brain structure and function. A crucial challenge for the discipline is to refine the combination of TMS parameters to prompt plasticity in a controlled fashion both within and between individuals. To achieve this, it is necessary to have an in-depth comprehension of the neurobiological mechanisms involved in TMS-induced neuroplasticity, along with the capability of monitoring and controlling brain activity in real-time.

Fortunately, advancements in brain science, including the development of novel imaging techniques and computational models, are providing new insights into the mechanisms underlying TMS-induced neuroplasticity and the factors that contribute to interindividual variability. By integrating these findings, it may be possible to develop more targeted and personalized TMS protocols that optimize treatment outcomes.

Further enhancement of TMS techniques and the associated neurobiological understanding presents immense potential for the management of neurological and psychiatric disorders. With further research, it is hoped that TMS will become an even more powerful tool for studying the brain and treating a range of disorders, leading to significant advancements in brain science and improved patient outcomes.

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