Transcranial Magnetic Stimulation of the Primary Motor Cortex

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Transcranial magnetic stimulation (TMS) has emerged as a novel technique to stimulate the human brain through the scalp. Over the years, identifying the optimal brain region and stimulation parameters has been a subject of debate in the literature on therapeutic uses of repetitive TMS (rTMS). Nevertheless, the primary motor cortex (M1) has been a conventional target for rTMS to treat motor symptoms, such as hemiplegia and spasticity, as it controls the voluntary movement of the body. However, with an expanding knowledge base of the M1 cortical and subcortical connections, M1-rTMS has shown a therapeutic efficacy that goes beyond the conventional motor rehabilitation to involve pain, headache, fatigue, dysphagia, speech and voice impairments, sleep disorders, cognitive dysfunction, disorders of consciousness, anxiety, depression, and bladder dysfunction.

transcranial magnetic stimulation | therapeutic use | primary motor cortex | non-motor symptoms

1. Introduction

The primary motor cortex (M1) consists of a population of neurons that play a crucial role in the voluntary regulation of movement [1]. Transcranial magnetic stimulation (TMS) was introduced to study the human M1 in 1985 as a novel, painless technique that can be delivered non-invasively [2]. Application of TMS in a repetitive manner can induce neuroplastic effects in the targeted region and its functionally connected networks and thus alter neuronal excitability beyond the period of stimulation [3]. Conventional repetitive TMS (rTMS) protocols in research and clinical practice include high-frequency (HF)-rTMS (5–20 Hz) and low-frequency (LF)-rTMS (≤1 Hz), which can increase or decrease M1 excitability, respectively, for several minutes after stimulation [4][5]. Another rTMS protocol, known as theta-burst stimulation (TBS), was developed later with reduced administration duration. The TBS protocol consists of extremely high-frequency (50 Hz) stimulation in the pattern of three bursts at the theta range (5 Hz) [6]. This protocol can be applied as intermittent TBS (iTBS) or continuous TBS (cTBS), which have comparable efficacy to HF-rTMS and LF-rTMS, respectively [6]. The impact of HF-rTMS/iTBS on enhancing M1 excitability and LF-rTMS/cTBS on reducing M1 excitability is thought to rely on principles of long-term potentiation (LTP) and long-term depression (LTD) plasticity, respectively [7]. At the cellular level, LTP/LTD plasticity results from a prolonged strengthening/inhibition of synaptic transmission following synchronous/asynchronous presynaptic and postsynaptic activity [8].

To localize the primary motor cortex (M1), a single-pulse TMS is applied away from the vertex towards the right or left M1 to activate the motor neurons and induce a muscle twitch. This twitch can be measured by electromyography (EMG) to record the motor evoked potential (MEP). Originally, a “motor hotspot” was defined as

the optimal TMS coil position over M1 that evokes MEPs of maximum amplitude and shortest latency in a target muscle [9]. However, due to practical issues, the motor hotspot is more commonly localized as the TMS coil position over M1 that evokes the largest and most consistent MEP amplitude from a target muscle, regardless of its latency [10][11]. In some cases, because of stroke or corticospinal tract injury, MEPs might be absent upon M1 stimulation. Still, the motor hotspot can be targeted using the mirror image of the unaffected hemisphere [12]. Another method to localize the M1 in TMS studies is by magnetic resonance imaging (MRI) based on specific anatomical landmarks of the M1, i.e., hand knob [13], or by functional MRI (fMRI) while performing a specific motor task [14]. However, the motor hotspot method is more commonly employed in the TMS literature [15].

Afterward, the motor threshold is measured to personalize the TMS intensity for each individual. Resting motor threshold (RMT) is defined as the lowest TMS intensity needed to evoke an MEP of ≥50 μV in 5 of 10 consecutive trials in the relaxed muscle. In comparison, active motor threshold (AMT) is the lowest TMS intensity required to elicit MEP ≥200 μV in 5 of 10 consecutive trials during an isometric contraction of the target muscle of 10–20% of its maximal strength [3]. In therapeutic applications, the TMS intensity is usually reported as a percentage of the RMT in conventional rTMS paradigms, and AMT in studies that employ TBS paradigms [15].

Following localization of the motor hotspot and determining the TMS intensity, the TMS coil is fixed over the M1 for the whole treatment session. Jung et al. found that marking the hotspot with a felt-tip pen yielded similar consistency of MEPs compared with using a neuronavigation system with MRI guidance [16]. Nonetheless, expert panels advise using a neuronavigation system to ensure higher accuracy while applying the TMS coil over the M1 [15]. Concerning the types of the TMS coils, a figure-of-eight coil is most commonly applied at the hand and face regions of the M1 as it produces focal and superficial stimulation. While non-focal coils, such as H-coils and double-cone coils, are used preferably to target the lower limb and pelvic representation of the M1 as it produces deeper stimulation [17].

2. Pain

Over the years, various brain stimulation techniques at M1 have been trialed with a promising analgesic efficacy, including invasive epidural motor cortex stimulation [18] and non-invasive techniques such as transcranial direct current stimulation (tDCS) [19] and rTMS [20].

The rationale behind the analgesic efficacy of M1 stimulation relies mainly, but not exclusively, on its interconnections with the endogenous opioid system. Positron emission tomography (PET) scans demonstrated that M1 stimulation directly potentiated the top-down opioid-mediated inhibition system [21][22]. In addition, blocking μ-opioid receptors with the drug naloxone significantly reduced the analgesic efficacy of M1 stimulation [23], further supporting the relation between M1-rTMS stimulation and the release of endogenous opioids. Therefore, recent evidence highlights the potential role of blood β-endorphin measurement as an objective response biomarker in treating chronic pain with rTMS [24][25].

Another putative mechanism pertains to the glutamate receptor, N-methyl-D-aspartate (NMDA). The drug ketamine, an NMDA receptor antagonist, significantly reduced the analgesic efficacy of high-frequency rTMS over M1, suggesting a shared pathway with the LTP-like plasticity mechanisms [26]. In addition, a disruption in the γ-aminobutyric acid (GABA)-mediated intracortical inhibition was noticeable in both acute [27] and chronic pain conditions [28]. In turn, high-frequency M1-rTMS was shown to restore the defective intracortical inhibition with a direct correlation between the analgesic effect and cortical excitability [29][30][31]. This notion highlights the principle of state dependency of TMS, where the facilitatory effect of high-frequency rTMS is reversed and the cortical excitability decreases if the high-frequency rTMS is applied during a state of enhanced cortical excitability [32][33].

On the neural network level, neuroimaging studies have shown that M1 stimulation modulated the excitability of other cortical and subcortical areas related to sensory, cognitive, and emotional components of pain, such as the thalamus, insular cortex, and anterior cingulate gyrus [34][35].

3. Fatigue

Fatigue is a frequent and disabling symptom experienced in various diseases and cannot be completely explained by conventional structural damage [36]. With the lack of effective treatments, M1-rTMS has been applied to relieve fatigue in patients with fibromyalgia syndrome [37], multiple sclerosis [38], amyotrophic lateral sclerosis [39], and chronic neuropathic pain [40]. The mechanism of action of rTMS in fatigue management remains unknown. However, applying rTMS at M1 might modulate the functional connectivity between the impaired neural networks in these patients, resulting in reduced fatigue perception [38].

4. Dysphagia

The rationale behind employing M1-rTMS in dysphagia management relies mainly on its effect on the corticobulbar projections to swallowing muscles [41]. Applying rTMS over the swallowing musculature hotspot at M1 has been trialed with promising results in dysphagia after stroke [42], Parkinson's disease [43], and in the context of aging, aka presbydysphagia [44].

5. Speech and Voice Impairments

As M1 receives input from Broca's area and projects through corticobulbar tracts to the muscles responsible for speech production [45], several clinical studies have investigated the potential to increase or decrease excitability in these tracts through rTMS protocols. These studies involved post-stroke aphasia [46] and dysarthria [47], Parkinson's disease-related hypokinetic dysarthria [48], Tourette syndrome [49], and adductor laryngeal dystonia [50].

6. Sleep Disorders

The therapeutic application of M1-rTMS in sleep disorders has been investigated in restless legs syndrome [51], sleep bruxism [52], obstructive sleep apnea [53], and sleep disturbances associated with neurological conditions, in particular Parkinson's disease and chronic pain [54].

Restless legs syndrome (RLS) is characterized by M1 disinhibition and CNS dopaminergic dysfunction [51]. In turn, high-frequency rTMS at M1 was shown to restore the intracortical inhibition since its mechanism is state-dependent on the cortical excitability prior to TMS stimulation [32][33]. In addition, M1-rTMS activates the corticostriatal projections leading to the endogenous release of dopamine [55].

On the other hand, reducing the nocturnal recurrence of motor symptoms and pain in PD and chronic pain conditions, respectively, can result in indirect improvement in sleep quality. In addition, inducing LTP-like plasticity in the M1 during wakefulness was found to modulate the slow-wave activity during sleep and could thereby regulate the sleep need [56][57].

7. Cognitive Dysfunction

The application of M1-rTMS has been investigated in a few studies of affected cognition in Parkinson's disease [58], stroke [59], and fibromyalgia syndrome [60]. The procognitive effect of M1 stimulation in these conditions can be rationalized by the increasingly identified roles of M1 in higher cognitive processes, such as attention, memory, motor imagery, and language comprehension, and the functional connectivity between M1 and parietal cortex that supports the planning and execution of goal-oriented movements [61][62][63][64][65].

8. Disorders of Consciousness

The mechanistic rationale for the therapeutic use of M1-rTMS in disorders of consciousness is related in part to EEG findings showing that high-frequency rTMS at M1 transiently increased neuronal oscillations in the α and β frequency [66]. In addition, fMRI studies demonstrated that high-frequency rTMS at M1 induced blood-oxygenation-level-dependent (BOLD) changes both locally and in remote brain regions, including the supplementary motor area, dorsal premotor area, putamen, cingulate motor area, and crucially, the thalamus [67]. The application of M1-rTMS was safe and utilized without any adverse effects in patients with disorders of consciousness, including minimally conscious state (MCS) and vegetative state/unresponsive wakefulness syndrome, and improved the coma recovery scale in a subset of comatose patients [68].

9. Anxiety and Depression

The mechanistic rationale behind the improvement in anxiety and depression following M1-rTMS might stem from its effect on the concomitant symptoms and consequently emotional improvement in mood and general behavior. On the other hand, a recent meta-analysis combined with resting-state fMRI reported a positive correlation between M1 and depressive disorders-regions of interest (ROI), hence proposing M1 as a potential therapeutic

target in depressive disorders [69]. In addition, M1-rTMS stimulation was found to alter the serum levels of kynurenine [70][71], a tryptophan metabolite and one culprit in the pathophysiology of depression [72]. Preliminary evidence of antidepressant efficacy of M1-rTMS has been reported in patients with Parkinson's disease [73], stroke [70], and chronic pain [74].

10. Bladder Dysfunction

The mechanistic rationale for the use of M1-rTMS in this condition relies on its influence on the corticospinal tract excitability and consequently detrusor/urethral sphincter functionality [75]. In addition, recent evidence has revealed an essential role of certain M1 neuronal subpopulations in issuing the "order" to initiate voiding via their projections to the pontine micturition center [76][77]. Preliminary evidence on the therapeutic potential of M1-rTMS on urinary symptoms has been reported in multiple sclerosis [75], Parkinson's disease [78], and bladder pain syndrome/interstitial cystitis [79].

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