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IS THIS FOR REAL?

THE ROLE OF ADVANCED PLACEBO TECHNOLOGY WHEN USING TRANSCRANIAL MAGNETIC STIMULATION IN CLINICAL PRACTICE

Georgios Mikellides, MD

Doctoral Thesis

IS THIS FOR REAL?

The role of advanced placebo technology when using Transcranial Magnetic Stimulation in clinical practice

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The role of advanced placebo technology when using Transcranial Magnetic Stimulation in clinical practice

Dissertation

to obtain the degree of Doctor at Maastricht University,

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Prof. dr. Pamela Habibović

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CHAPTER 1

General Introduction
& Outline of the thesis

We are currently witnessing a paradigm shift in Psychiatry and Applied Cognitive Neuroscience in which the accumulating insights into the functioning of the human brain and its relation to behavior and cognition increasingly find their ways into new approaches of diagnosing and treating various neuropsychiatric and psychological disorders. We are moving into an era where Psychiatry and Clinical Psychology join forces with Basic Brain and Neuroscience research, adopting new brain-based methodologies to develop innovative approaches to investigate the healthy and diseased human brain and to treat patients who are suffering from neuropsychiatric conditions. This is a much needed and welcomed development considering that the classical approaches of treating neuropsychiatric patients with medication and/or psychotherapy, although clinically effective for some patients, have proven to leave many patients behind who do not respond to these conventional therapies or who cannot or do not want to tolerate the side effects of pharmacological treatments (Conway et al., 2017; Khawam et al., 2006; Souery et al., 2006). It has become clear that we are on need of non-pharmacological treatment alternatives that capitalize directly from the growing knowledge about brain (mal)function and neuroplasticity changed associated with those neuropsychiatric disorders, to conceptualize those as brain disorders with a biological cause and to consequently treat them at their source: the human brain. In order to achieve this goal, researchers and clinicians need to work hand in hand in order to improve the wellbeing of all. Pioneering and innovation should be an integral part of our clinical and research work in order to offer the best possible treatment to each and every patient.

In the past almost 30 years, the field of neuromodulation and brain stimulation has developed into one of the prime examples how neuroscience research and neuroscientific techniques find their way into new clinical applications. Those brain stimulation technologies are increasingly used to help patients suffering from various neuropsychiatric disorders and start to establish themselves in the mental health care system as effective non-pharmacological treatment alternatives with minimal side effects.

Brain Stimulation

The modulation of brain function and plasticity through the application of electrical or magnetic fields, also known as brain stimulation, has been developed as a potential method for enhancing or inhibiting brain activity. Brain stimulation is a rapidly evolving field of neuroscience, with numerous techniques being developed to manipulate the activity of neural circuits in the brain. Such techniques are broadly categorized into invasive and noninvasive, depending on whether any invasive procedure is involved (Davis & van Koningsbruggen, 2013;

Purves et al., 2018). Brain stimulation techniques have the potential to revolutionize the treatment of neurological and psychiatric conditions as they can induce neuroplastic changes and thereby modulate various aspects of brain function through the selective targeting of specific brain regions.

INVASIVE BRAIN STIMULATION TECHNIQUES

In the field of neuroscience, invasive brain stimulation refers to the application of direct electrical or magnetic stimulation to specific areas of the brain through surgically implanted electrodes (Nguyen et al., 2011). This technique is often employed as a therapeutic intervention for neurological and psychiatric disorders such as Parkinson's disease, epilepsy, and obsessive-compulsive disorder (Goodman & Alterman, 2012). Typically, invasive brain stimulation is viewed as a last resort when other forms of treatment have failed, and it is only performed after careful evaluation and discussion with the patient.

Deep brain stimulation (DBS) and electroconvulsive therapy (ECT) are two of the most widely used forms of invasive brain stimulation. DBS involves the implantation of electrodes in specific regions of the brain, which are then stimulated by a device implanted in the chest or abdomen (Krauss et al., 2021). ECT, on the other hand, is a form of stimulation that involves the application of brief electrical pulses to the brain while the patient is under general anesthesia (Kellner et al., 2020). While these methods have demonstrated efficacy in treating a range of neuropsychiatric disorders, their invasiveness raises ethical and safety concerns, and ongoing research is aimed at minimizing their risks while optimizing their benefits.

Deep brain stimulation (DBS) is a brain stimulation method that was first developed in the 1980s to treat movement disorders (Dougherty, 2018). Over the years, DBS has demonstrated efficacy in the treatment of numerous neurological and psychiatric disorders, and it has been approved by the FDA as a therapeutic option for Parkinson's Disease, essential tremor, dystonia, obsessive-compulsive disorder (OCD), and epilepsy (Lee et al., 2019). In Parkinson's disease, DBS has been shown to reduce motor symptoms, improve quality of life, and reduce the need for medication (Groiss et al., 2009). Furthermore, DBS has shown promise in the treatment of a wide range of other disorders, including Tourette syndrome, major depressive disorder, eating disorders and obesity, substance abuse/addiction, chronic pain, Alzheimer's disease, tinnitus, post-traumatic stress disorder, and anxiety disorder (Lee et al., 2019). The use of DBS is typically considered when other treatments, such as medications, have failed to provide satisfactory relief of symptoms or when the side effects of medication are intolerable.

DBS is a neurosurgical procedure that involves the implantation of electrodes into specific areas of the brain to deliver electrical impulses. The procedure involves the insertion of thin wires or electrodes into specific brain areas such as the subthalamic nucleus, globus pallidus, or thalamus (Dougherty, 2018). The electrodes are connected to a device similar to a pacemaker, which is implanted under the skin in the chest or abdomen. The device delivers electrical impulses to the targeted brain region, which can help alleviate symptoms. Clinicians adjust stimulation parameters such as frequency and pulse width using a computer that communicates with the implantable pulse generator (Dougherty, 2018). The subthalamic nucleus (STN) and globus pallidus interna are the most commonly used targets for DBS in the treatment of movement disorders (Dougherty, 2018). Although DBS is generally considered a safe procedure, it does carry some risks. Possible complications include intracerebral hemorrhage and seizures (Lee et al., 2019). To ensure that patients are fully informed about the procedure's risks and benefits, they must undergo a comprehensive evaluation and counseling before the surgery.

Although the exact mechanisms underlying DBS are not fully understood, there are several hypotheses that may explain its therapeutic effects. According to Lee et al. (2019), numerous primary mechanistic theories have been proposed, including direct inhibition or excitation of neural activity, information interruption, and synaptic filtering. One possible hypothesis is that DBS works by disrupting pathological oscillatory activity in dysfunctional brain circuits (Hamani et al., 2008). Another proposed mechanism of action for DBS is that it enhances the release of neurotransmitters such as dopamine, serotonin, and glutamate, which are involved in the regulation of mood, movement, and cognition (Alosaimi et al., 2020). DBS may also work by modulating the plasticity of neuronal circuits, which is the ability of the brain to adapt to changes in its environment (van Hartevelt et al., 2014). However, the exact mechanisms underlying the therapeutic effects of DBS are still not fully understood. Further research is needed to optimize the clinical use of DBS in the treatment of neurological and psychiatric disorders and to fully elucidate its mechanisms of action. Nonetheless, the current evidence suggests that DBS has the potential to improve the quality of life of patients suffering from a range of disorders.

Electroconvulsive therapy (ECT) is a convulsive medical treatment involving the induction of generalized convulsive seizures in the central nervous system, first developed in the late 1930s (Kellner et al., 2020). ECT is considered a safe and effective treatment option for individuals who have not responded to other forms of therapy or medication (American Psychiatric Association, 2016). The procedure typically takes place in a hospital or outpatient setting. ECT involves passing a small electrical current through the brain to produce a controlled seizure that can lead to changes in brain chemistry and neural connectivity (Kellner et al., 2020; Pinna et al., 2018). During ECT, the patient is given a muscle relaxant and an anesthetic to minimize

discomfort and prevent injury during the seizure. The patient's vital signs, including blood pressure, heart rate, and oxygen saturation, are monitored throughout the procedure to ensure patients' safety. Electrodes are placed on the scalp, usually in a bilateral (on both sides of the head) or unilateral (on one side of the head) placement (Kellner et al., 2020; Pinna et al., 2018). The electrode placement is determined based on the patient's individual needs and medical history. Once the electrodes are in place, a controlled electrical current is applied to the brain for a few seconds. This causes a seizure to occur, which lasts for 20-60 seconds. The entire procedure typically takes 5-10 minutes. ECT is administered with a constant current of either 0.8 or 0.9 Ampere, delivered in short pulses that typically last between 0.25 and 1.5 milliseconds. The frequency and duration of the stimulus train may vary and usually lasts up to 8 seconds. (Fridgeirsson et al., 2021). After the seizure, the patient is monitored until they are alert and their vital signs have stabilized. The number of treatments required may vary depending on the patient's individual needs and response to the treatment.

Several theories have been proposed to explain the mechanism of action of ECT. These theories may be classified into neurophysiological hypotheses, neurobiochemical hypotheses, and neuroplastic changes (Ryan & McLoughlin, 2018; Singh & Kar, 2017). Neurophysiological hypotheses encompass alterations in cerebral blood flow and regional metabolism, changes in blood-brain barrier permeability, and electroencephalographic changes. Neurobiochemical hypotheses involve genetic modifications, alterations in neurotrophic factors, changes in the immune system, effects on hormones such as the hypothalamic-pituitary-adrenal (HPA) axis, modulation of monoaminergic neurotransmitters, and modulation of molecules such as serotonin, neuropeptide Y, and glutamate, among others (Singh and Kar, 2017).

ECT has been shown to be particularly effective in the treatment of depressive disorders, including severe and treatment-resistant forms (Pagnin et al., 2004). In fact, ECT is considered the gold standard treatment for treatment-resistant depression (American Psychiatric Association, 2016). Additionally, ECT has been found to be effective in treating all phases of severe and drug-resistant bipolar disorder (BD) (Perugi et al., 2017). Compared to pharmacotherapy, ECT has been found to be significantly more effective (ECT Review Group, 2003).

Despite its efficacy, ECT is not without potential risks and side effects. Some patients may experience short-term side effects such as headaches, dry mouth, nausea, myalgia, memory loss, and confusion (Andrade et al., 2016; Kellner et al., 2020). Nevertheless, these risks are considered minimal, and ECT is generally considered safe when carried out by a trained healthcare professional.

NONINVASIVE BRAIN STIMULATION TECHNIQUES

In contrast to invasive techniques, non-invasive brain stimulation (NIBS) refers to a variety of techniques that can modify the activity of brain regions without requiring surgery or implantation of electrodes (Davis & van Koningsbruggen, 2013). These interventions employ the application of a coil or electrode to the scalp, which does not physically penetrate the body (Davis & van Koningsbruggen, 2013). NIBS interventions hold great promise for the treatment of various neurological and psychiatric conditions with long-lasting effects (Cirillo et al., 2017). As our understanding of the underlying mechanisms and optimal treatment parameters continues to grow, NIBS may become an increasingly important tool in the mental health toolkit. In recent decades, two NIBS methods, namely transcranial current brain stimulation and transcranial magnetic stimulation, have been extensively studied in both healthy subjects and patients with various disorders. TMS uses electromagnetic fields to induce electrical currents in the brain, whereas tES delivers a weak electrical current directly to the scalp.

Transcranial current brain stimulation (tCS) is a non-invasive technique used to modulate neural activity in the brain. tCS involves the application of weak electrical currents via two or more electrodes placed on the scalp, with the aim of modulating cortical excitability and promoting brain stimulation (Reed & Cohen Kadosh, 2018; Ruffini et al., 2013). The technique is considered safe and well-tolerated and has shown promise as a therapeutic tool for a variety of neuropsychiatric conditions, including depression, schizophrenia, and chronic pain. tCS represents a promising avenue for the development of novel therapeutic interventions for a variety of neuropsychiatric conditions. While the technique is still relatively new and more research is needed to fully understand its potential, early studies suggest that tCS may offer a safe, effective, and non-invasive alternative to traditional pharmacological interventions. tCS techniques, such as transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS), have gained increasing attention in recent decades.

tACS is a non-invasive brain stimulation technique that involves the application of low-amplitude alternating current to the scalp to modulate neural activity in specific brain regions. tACS has been used to study the functional connectivity between brain regions, enhance cognitive processing, and treat various neurological and psychiatric disorders (Elyamany et al., 2021; Reed & Cohen Kadosh, 2018). During tACS, electrodes are placed on the scalp over the targeted brain region, and an alternating current with a specific frequency is delivered. The frequency of the current can be adjusted to match the frequency of the neural oscillations in the targeted brain region, which can enhance or disrupt neural activity depending on the phase of the current.

tRNS is a non-invasive brain stimulation technique that involves the application of low-frequency random noise to the scalp to modulate neural activity in specific brain regions (Reed & Cohen Kadosh, 2018). tRNS has been used to study the functional connectivity between brain regions, enhance cognitive processing, and treat various neurological and psychiatric disorders. During tRNS, electrodes are placed on the scalp over the targeted brain region, and a low-frequency alternating current with random amplitude and frequency is delivered. The random nature of the current is thought to stimulate a broad range of neural frequencies, which can enhance neural plasticity and improve cognitive performance.

tDCS is a non-invasive brain stimulation technique that involves the application of a low-intensity direct current to the scalp to modulate neural activity in specific brain regions, without impacting action potentials (Reed & Cohen Kadosh, 2018). During tDCS, electrodes are placed on the scalp over the targeted brain region, and a low-intensity direct current is delivered. The current is thought to modulate the resting membrane potential of neurons, leading to changes in cortical excitability and neural plasticity. tDCS has been used to study the functional connectivity between brain regions, enhance cognitive processing, and treat various neurological and psychiatric disorders. Anodal stimulation is associated with an increase in cortical excitability, while cathodal stimulation is associated with a decrease in cortical excitability (Brunoni et al., 2012). Neuroimaging studies have shown that tDCS induces changes in regional blood flow, glutamatergic neurotransmission, and membrane function in the brain (Rostami et al., 2013).

Transcranial Magnetic Stimulation (TMS) is the most well-known non-invasive medical therapy that relies on the principle of electromagnetic mutual induction, which was initially reported by Michael Faraday (1839) in 1831. This principle refers to the relationship between electrical current and magnetic fields. The first magnetic stimulator was developed by Anthony Barker and colleagues in the Department of Medical Physics at Sheffield University, United Kingdom in 1985 (Barker et al., 1985). This development marked a turning point in the history of transcranial magnetic stimulation, as the technique was used for the first time in an awake individual, and its effects on the motor cortex of the human brain were demonstrated.

TMS is a safe, non-invasive, and well-tolerated brain stimulation technique that utilizes rapidly changing short magnetic fields to induce weak electric currents in specific areas of the brain (Cirillo et al., 2017; Klomjai et al., 2015). TMS uses an insulated coil that is positioned tangentially to the scalp and generates a magnetic field through electromagnetic induction (Zewdie & Kirton, 2016). This magnetic field penetrates the skin, scalp, and skull, allowing for the induction of a short-lasting (150–300 μs) electric current in the brain (Burke et al., 2019; Zewdie & Kirton, 2016). TMS over the motor cortex can evoke motor-evoked potentials (MEPs), which are used to assess cortical and spinal excitability (Klomjai et al., 2015). MEP is defined as the resulting electromyography (EMG) deflection (increase) following TMS activation (Zewdie &

Kirton,2016). Despite significant research into TMS, the exact mechanisms underlying TMS-induced activation remain incompletely understood (Burke et al., 2019).

TMS has the capability to simultaneously activate both excitatory and inhibitory neurons beneath the coil using various stimulation patterns, including single, paired, or repetitive methods (Platz, 2016; Zewdie & Kirton,2016). Single-pulse TMS (spTMS) applies one pulse at a time, which is a safe technique to activate the human motor cortex (Zewdie & Kirton, 2016). In addition, spTMS is also a useful tool for evaluating the strength and excitability of the motor cortex (Zewdie & Kirton, 2016). The production of muscle contractions in response to spTMS makes it an effective method for identifying the resting motor threshold (rMT) of an individual. The rMT, which corresponds to the minimum amount of intensity required to elicit a motor-evoked potential (MEP) in at least 50% of all trials (Borckardt et al., 2006), is a reliable measure for determining the stimulation intensity during TMS therapy (Burke et al., 2019). Burke et al. (2019) reported that spTMS is a valuable tool to measure the cortical silent period (cSP), which represents a transient suppression of EMG activity during voluntary muscle contraction and is thought to reflect GABA B receptor-mediated cortical inhibition. Moreover, previous research has suggested that spTMS could serve as a potential treatment for migraines (Bhola et al., 2015; Lipton et al., 2010). According to Rotenberg et al. (2014), spTMS paradigms involve applying isolated and distinct pulses to a specific cortical area, while paired-pulse TMS (ppTMS) paradigms utilize two isolated pulses delivered in close succession. The ppTMS technique can be employed to investigate the excitatory and inhibitory interactions within the human motor cortex (Moliadze et al., 2005). During ppTMS, a conditioning stimulus and a test stimulus are applied in close succession, with different intervals and intensities (Bandeira et al., 2021; Burke et al., 2019). The various types of ppTMS, such as short interval cortical inhibition (SICI), long interval cortical inhibition (LICI), intracortical facilitation (ICF), interhemispheric inhibition (IHI), and short-latency afferent inhibition (SAI), are used to investigate different forms of excitatory and inhibitory interactions in the human motor cortex (Burke et al., 2019). Unlike spTMS and ppTMS, rTMS involves the administration of repetitive TMS pulses to a targeted brain area, resulting in prolonged effects that continue beyond the stimulation period (Klomjai et al., 2015). rTMS involves the application of three or more pulses at a minimum frequency of 0.5 pulses per second, using a variety of frequencies, length of trains, intertrain intervals, and durations (Burke et al., 2019). When using TMS, we often speak about "online" and "offline" effects. "Online" effects happen during the stimulation and generally a disruptive effect, but they can also modulate the function of the targeted area. On the other hand, "offline" effects are neuromodulatory and last beyond the stimulation period (Burke et al., 2019). Depending on the stimulation frequency, rTMS may reduce or increase cortical excitability of specific areas of the cerebral cortex, with long-term effects being referred to as "LTP-/LTD-like" plasticity based on whether rTMS increases or decreases cortical excitability (Platz, 2016). Generally, in most individuals, Low Frequency rTMS (LF-rTMS) (≤1 Hz) is inhibitory and decreases cortical

excitability, whereas High Frequency rTMS (HF-rTMS) (≥5 Hz) is excitatory and increases cortical excitability (Klomjai et al., 2015; Maeda et al., 2000). This observation is mainly based on motor cortex and may not always hold true for other cortical regions.

Theta Burst Stimulation (TBS) is a novel form of rTMS protocols that differs from the classical rTMS protocols by using burst patterns of stimuli at different frequencies (Braga et al., 2021). TBS has emerged as a promising technique to induce long-term changes in cerebral cortex excitability in a shorter period of time, compared to traditional rTMS protocols, leading to significant interest in research (Chung et al., 2015; Huang et al., 2005). TBS protocols provide a noteworthy advantage in terms of time-efficiency as they offer a quicker alternative (typically lasting 1 to 3 minutes) compared to standard rTMS protocols (which typically last between 20 and 45 minutes). TBS protocols involve shorter stimulation durations and fewer total pulses delivered, and also exhibit lower interindividual variability compared to standard rTMS (Chung et al., 2015). TBS involves a burst pattern containing three 50-Hz pulses at 5 Hz, and different types of TBS protocols have been developed and can be used in rTMS therapy (He et al., 2020). These include Intermittent Theta Burst Stimulation (iTBS), which increases cortical excitability, and Continuous Theta Burst Stimulation (cTBS), which reduces cortical excitability, similar to High Frequency rTMS (HF-rTMS) and Low Frequency rTMS (LF-rTMS) (Huang et al., 2005).

TMS offers a wide range of stimulation parameters, such as frequency, intensity, latency, targeted area, coil position, and direction, among others, which have a significant impact on the cortical outcome of TMS (Braga et al., 2021; Brihmat et al., 2022). Different combinations of these parameters and targeted areas have been developed to achieve optimal TMS outcomes (Peng et al., 2018). Over the years, numerous coils, such as figure-of-eight, circular, H-coil, double cone, have been designed for magnetic stimulation of the brain (Rossi et al., 2009). The figure-eight coil is the most commonly used TMS coil and consists of two loops in opposite directions, providing focal stimulation of cortical regions beneath the central part of the coil. This design generates a relatively focused and superficial magnetic field, penetrating up to 2-3 centimeters into the brain, making it ideal for stimulating cortical areas near the surface. The efficiency and focality of the coil are influenced by the relative angle between the wings, with coil elements that are not tangential to the scalp resulting in a decrease in coil efficiency (Rossi et al., 2009). On the other hand, circular coils of various sizes enable more direct stimulation of deeper brain regions as the diameter of the coil increases. However, they generate a more diffuse magnetic field compared to the figure-eight coil, making them useful for stimulating larger areas of the brain but limiting their penetration depth to 1-2 centimeters. H-coils, or Hesed coils, consist of two rectangular-shaped coils that are joined at their bases, allowing for a deeper and more focal stimulation of the targeted brain area, with penetration up to 5-6 centimeters into the brain (Zangen et al., 2005). Lastly, the double cone coil is a newer TMS coil type with two adjacent circular wings at an angle of 95 degrees, providing a stronger but less

focal electric field than the figure-of-eight coil. This coil type enables direct stimulation of deep brain regions and is capable of penetrating to a greater depth (Rossi et al., 2009).

In recent years, several randomized studies have investigated the effectiveness of rTMS therapy as a non-invasive alternative in comparison to invasive techniques such as ECT. One such study, conducted by Eranti et al., compared the effectiveness of rTMS with ECT in treating depression (Eranti et al., 2007). The results showed that the Hamilton Depression Rating Scale (HAM-D) scores of the ECT group were significantly lower than those of the rTMS group at the end of the treatment. However, no significant differences were observed between the ECT and rTMS groups in HAM-D scores at the 6-month follow-up. The authors concluded that ECT is more effective than rTMS, especially in the short-term treatment of depression. Another meta-analysis conducted by Berlim et al. also suggested that ECT is more effective in treating major depressive disorder (MDD) compared to HF-rTMS, although no significant differences were observed in dropout rates (Berlim et al., 2013b). A systematic review and meta-analysis by Chen et al. investigated the effects of different treatments, including ECT, Bilateral repetitive transcranial magnetic stimulation (B-rTMS), Left prefrontal rTMS (L-rTMS) and Right prefrontal rTMS (R-rTMS), on patients with MDD (Chen et al., 2017). The study found that while ECT was the most effective treatment, it was the least tolerated by patients. However, R-rTMS was found to be the most tolerable treatment for patients with MDD, and B-rTMS was found to have the best balance of efficacy and acceptability. A recent retrospective study showed that HF-rTMS can alleviate the cognitive side effects induced by ECT in patients with MDD (Chen et al., 2022). Unlike ECT, rTMS therapy does not require the intentional induction of seizures, which is considered a positive aspect of the therapy (Micallef-Trigona, 2014).

Overall, brain stimulation techniques, including both invasive and non-invasive methods, have been shown to modulate neural activity in the brain, leading to changes in brain function and behavior. These changes are thought to be mediated by the concept of neuroplasticity, which refers to the brain's ability to reorganize itself in response to changes in the environment or experiences. Neuroplasticity is a fundamental property of the brain, allowing it to adapt to new situations, learn new skills, and recover from injury or disease. Brain stimulation techniques can promote neuroplasticity by inducing changes in synaptic plasticity, the formation of new neural connections, and the activation of various neurotransmitters and growth factors. With the increasing understanding of the fundamental mechanisms of neuroplasticity, brain stimulation methods may gain significance as potential instruments for treating different neurological and psychiatric disorders.

Neuroplasticity

In the late nineteenth century, William James introduced the concept of "plasticity" in "The Principles of Psychology", emphasizing the importance of plasticity in the brain and nervous system and the brain's ability to change (James, 1890). Later, in 1948, neuroscientist Jerzy Konoski defined the term "neural plasticity" in his book, highlighting the relationship between plastic changes and the formation and multiplication of new synaptic junctions between nerve cells (Konoski, 1948). Subsequently, Canadian psychologist Donald Hebb introduced the "Hebb Synapse" theory in 1949, which explains the neural pathways involved in learning and memory, including synaptic changes, cell assemblies, and phase sequences (Hebb, 1949).

Neuroplasticity, also known as brain plasticity or neural plasticity, refers to the nervous system's ability to reorganize its structure, function, and connections in response to internal or external stimuli (Cramer et al., 2011). This complex phenomenon encompasses morphological changes, as well as biochemical and pharmacological adaptations such as alterations in intracellular pathways, receptors, and synaptic proteins. Additionally, changes in neuronal networks such as modifications in connectivity, dendritic remodeling, and dendritic spines, as well as the emergence of new neurons through adult neurogenesis, are also involved (de Oliveira, 2020). The capacity of the brain to change and adapt may arise during development, learning, adaptive behavior, memory, as well as in response to disease or therapy (Cramer et al., 2011; Gulyaeva, 2017). These changes in brain structure and function may occur throughout an individual's life.

The term "neuroplasticity" encompasses two types of changes in the nervous system: structural neuroplasticity and functional neuroplasticity. Structural neuroplasticity comprises synaptic plasticity and neurogenesis, which refer to the capacity of synapses to alter their strength and the ability of the nervous system to generate new neurons and neuronal connections, respectively (Demarin et al., 2014). In contrast, functional neuroplasticity refers to modifications in the functional properties of neurons, which involve alterations in synaptic efficacy that can result in the strengthening or weakening of postsynaptic neuronal responses (Bandeira et al., 2021). Both structural and functional neuroplasticity are essential for learning and memory, as they lead to persistent changes in synaptic relationships between neurons (Bandeira et al., 2021; Demarin et al., 2014). Neuroplasticity is a critical component for comprehending the pathophysiology and treatment of neuropsychiatric disorders because such disorders are linked to alterations in the structure and function of the brain (de Oliveira, 2020).

LONG-TERM POTENTIATION (LTP) AND LONG-TERM DEPRESSION (LTD)

One of the most studied mechanisms of neuroplasticity is long-term potentiation (LTP) and long-term depression (LTD), which are responsible for strengthening or weakening the connections between neurons. LTP and long-term depression LTD are well-described phenomena in the mammalian brain, occurring at excitatory synapses and activated by N-methyl-D-aspartate (NMDA)-type glutamate receptors in pre- and postsynaptic neurons. LTP and LTD are key cellular processes contributing to neuroplasticity, although their neurobiological mechanisms are not yet fully understood. LTP is associated with an increase in synaptic strength, while LTD results in a decrease in synaptic strength (Klomjai et al., 2015; Platz, 2016), corresponding to a weakening of synaptic connection (Bandeira et al., 2021). The induction of LTP requires intensive synaptic activity and alterations in glutamate receptor activity (Bandeira et al., 2021).

LTP is considered a significant mechanism of neuroplasticity as it is believed to play a critical role in learning and memory (Gulyaeva, 2017). The induction of LTP is characterized by the influx of Na+ through the AMPA channel in response to large glutamate stimuli on the synaptic fend, which leads to the depolarization of the neuron and the removal of the voltage-dependent magnesium block on the NMDA receptor. Subsequently, calcium on the synaptic fend passes through the NMDA receptors, triggering a cascade that activates intracellular factors and contributes to both early and late-stage LTP (Bandeira et al., 2021). The NMDA receptor, which also binds to glutamate, facilitates this process. In the induction of LTD, a low level of depolarization is produced which is insufficient to completely remove the Mg++ ion from the NMDA receptor but is still capable of permitting some Ca++ ions to enter the cell. This initiates a cascade that reduces the expression of AMPA receptors, making it more difficult for the two neurons to establish a connection. The reduction in AMPA receptors leads to decreased excitability of the postsynaptic neuron (Bandeira et al., 2021).

In mammalian brains, the early phases of LTP and LTD involve changes in the distribution of AMPA-type glutamate receptors. During LTP, more receptors are added to strengthen the synapse, while during LTD, receptors are removed to weaken the synapse. These structural changes require the synthesis of new proteins and are thought to be involved in the cellular substrates of learning and memory. Long-term synaptic plasticity is a term used to describe long-lasting changes in the efficacy of synaptic transmission that result from experience-dependent modifications in neural circuits (Luscher & Malenka, 2012).

NIBS techniques have been found to modulate synaptic plasticity through the induction of LTP and LTD. Specifically, tDCS, tACS, and TMS have been shown to induce LTP and LTD-like effects in various brain regions.

NEUROPLASTICITY AND NON-INVASIVE BRAIN STIMULATION

NIBS therapies have the potential to modify cortical brain activity and thus offer therapeutic options for neuropsychiatric disorders (Cramer et al., 2011; Gulyaeva, 2017). These techniques are capable of inducing long-term changes in cortical synapses (Huerta & Volpe, 2009; Klomjai et al., 2015) and can trigger LTP-like and LTD-like plasticity mechanisms (Bandeira et al., 2021). rTMS has been demonstrated to induce "offline" neuromodulatory effects, which are related to LTD and LTP mechanisms (Burke et al., 2019). LTP is typically induced by prolonged low-intensity stimulation such as in LF-rTMS protocols, while spaced protocols consisting of repeated short-duration stimulations have been found to be associated with late-phase plasticity (Bandeira et al., 2021).

Bandeira et al. (2021) have reported that TMS can modulate neuroplasticity at the genetic level. Specifically, a single TMS session has the ability to increase mRNA expression, induce gene expression, and activate enzymes, providing an explanation for the long-lasting effects of TMS. rTMS is a therapeutic technique that can modulate cortical excitability in specific brain regions of patients with neuropsychiatric disorders, such as depression, thereby promoting neuroplasticity (Kumar et al., 2018). Additionally, rTMS can influence neural processes involved in the initiation and maintenance of synaptic plasticity, including the gene and protein expression associated with N-methyl-D-aspartate (NMDA) receptor function (Peng et al., 2018).

In the context of brain injury and stroke recovery, the brain's remarkable capacity for neural plasticity has been identified as a crucial factor, as it allows for the creation of new connections between neurons (Gulyaeva et al., 2017). The phenomenon of motor and non-motor deficit recovery following stroke has been extensively investigated, with a range of treatments including pharmaceutical, biological, and electrophysiological interventions being studied in the context of post-stroke rehabilitation (Dimyan & Cohen, 2011). The goal of these therapies is to improve neuroplasticity in individuals who have experienced a stroke. One such approach is the use of non-invasive brain stimulation (NIBS), which has been examined in numerous clinical trials. These studies have demonstrated that stimulating the primary motor cortex (M1) using NIBS can improve motor rehabilitation in stroke patients (Dimyan & Cohen, 2011). Furthermore, cognitive training has been shown to be effective in treating non-motor deficits such as neglect and language impairment (Cramer et al., 2011). NIBS has also been investigated as a means of enhancing neuroplasticity following brain injury. A review by Villamar et al. (2012) indicated that NIBS can reduce the extent of injury and promote plastic changes following traumatic brain injury.

rTMS AND Neuropsychiatric Disorders

TMS has gained popularity in clinical practice due to its safe nature, favorable tolerability, and minimal side-effect profile. In recent years, numerous studies have investigated the effectiveness of rTMS in treating various neuropsychiatric conditions, including but not limited to depression, schizophrenia, bipolar disorder, anxiety disorders, obsessive-compulsive disorder, addiction disorders, post-traumatic stress disorder, chronic pain, epilepsy, fibromyalgia, and dementia.

rTMS IN PSYCHIATRY

Recent scientific evidence suggests that rTMS is a well-tolerated, effective, and safe treatment option for various psychiatric disorders such as major depressive disorder, obsessive-compulsive disorder, schizophrenia, bipolar disorder, addictions, and anxiety-related disorders. The pathophysiology, mechanisms of action, and use of rTMS for treating depression and addictions will be discussed in detail.

<u>TMS & Depression</u>

Depression is a prevalent mental disorder that affects approximately 5% of the global adult population (WHO, 2021). The underlying pathophysiology of depression has been widely studied through various single models and mechanisms (Malhi & Mann, 2018). The monoamine hypothesis postulates that reduced levels of major monoamine neurotransmitters, including serotonin, norepinephrine, and dopamine, may contribute to the development of depression (Jesulola et al., 2018). Moreover, the involvement of genetic factors in depression has been extensively discussed in the literature (Gonda et al., 2019; Jesulola et al., 2018; Malhi & Mann, 2018). Several genes have been proposed to be associated with depression, including apolipoprotein E, guanine nucleotide-binding protein, methylenetetrahydrofolate reductase, dopamine transporter, serotonin transporter, and dopamine receptor genes (Jesulola et al., 2018). The role of environmental factors in the development of depression has been investigated (Gonda et al., 2019). Stressful events, such as death, divorce, chronic illness, financial difficulties, and social isolation, have been shown to be associated with depression (Jesulola et al., 2018; Malhi & Mann, 2018). Additionally, neurogenesis, the process of generating new neurons, has been increasingly recognized as a potential factor in the development and treatment of depression (Jesulola et al., 2018; Malhi & Mann, 2018). According to Hanson et al. (2011), "The neurogenesis hypothesis of depression posits that (1) neurogenesis in the subgranular zone of the dentate gyrus is negatively regulated by stressful experiences and positively regulated by treatment with antidepressant drugs and (2) alterations

in the rate of neurogenesis play a fundamental role in the pathology and treatment of major depression."

Antidepressants are a pharmacological class of drugs used to alleviate depressive symptoms. The first-generation antidepressants utilized to treat depression were tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) (Chockalingam et al., 2019). Subsequently, newer classes of antidepressants with more favorable side effect profiles were developed during the 1980s and 1990s (Chockalingam et al., 2019; Gonda et al., 2019). These new classes of antidepressants include selective serotonin reuptake inhibitors (SSRIs), selective serotonin and noradrenaline reuptake inhibitors (SNRIs), noradrenaline/dopamine reuptake inhibitors (NDRIs), noradrenaline reuptake inhibitors (NRIs), noradrenergic and selective serotonergic antidepressants (NaSSAs), and serotonin antagonist and reuptake inhibitors (SARIs) (Gonda et al., 2019). SSRIs are frequently the initial treatment of choice for depression, however, a subset of patients (15%) may discontinue use of SSRIs due to adverse effects (Khawam et al., 2006). The most commonly reported side effects include gastrointestinal effects, sexual dysfunction, central nervous system effects, bleeding, hyponatremia, serotonin syndrome, and discontinuation syndrome (Khawam et al., 2006). Additionally, approximately 30% of patients with depression do not respond to antidepressant medications and suffer from treatment-resistant depression (TRD) (Souery et al., 2006), leading them to explore alternative treatment options such as rTMS or ketamine therapy.

The DLPFC has been demonstrated to play a significant role in the etiology and treatment of depression in multiple studies (Koenigs & Grafman, 2009). The DLPFC is considered the most frequently targeted area for the treatment of MDD. The DLPFC is a frontal brain region that is implicated in a variety of cognitive and behavioral processes such as planning, decision-making, and reward processing (Berlim et al., 2014; Tik et al., 2017). Depressed individuals are found to have hypoactivity in the left DLPFC, which is linked to several symptoms of depression, including negative emotional bias, rumination, appetite changes, and reduced energy levels. HF-rTMS over the left DLPFC can activate this brain region and produce antidepressant effects. Furthermore, LF-rTMS over the right DLPFC has been shown to decrease local activity and produce antidepressant effects (Baeken et al., 2019; Janicak & Dokucu, 2015). Notably, rTMS has been identified as a promising treatment option for patients who do not respond to antidepressant medication (Carpenter et al., 2012). Additionally, a recent case study demonstrated the potential of rTMS as a treatment for patients with TRD who had previously received ECT without success (Mikellides & Tantele, 2018). However, since these findings are based on a single case study, they cannot be generalized.

Blumberger et al. (2018) conducted a study that compared the efficacy and safety of a standard HF-rTMS protocol, which lasts over 30 minutes, with an iTBS protocol that lasts for only 3 minutes. The study found that iTBS had similar or even better effects on brain activity

compared to the standard HF-rTMS protocol. As a result of these findings, in August 2018, the US FDA approved MagVenture's TBS protocol for the treatment of depression. The studies presented in Chapter 2 and Chapter 3 used MagVenture's FDA-approved iTBS protocol. In September 2022, the SAINT (Stanford accelerated intelligent neuromodulation therapy) Neuromodulation System received FDA clearance for the treatment of MDD in adults who did not respond to prior antidepressant medications in the current episode. The system uses an accelerated iTBS protocol that can be completed in just 5 days, which is much faster than traditional approaches that required 6 weeks of treatment. The protocol involves the delivery of 50 iTBS sessions over the 5-day period, with 10 sessions given each day (Cole et al., 2020; Cole et al., 2022).

Apart from rTMS, in recent years, the potential antidepressant effects of ketamine in humans have gained significant attention as an alternative treatment for depression. Ketamine, a racemic mixture of S-ketamine (esketamine) and R-ketamine, can be administered via several routes, including intravenous (IV), intranasal, oral, sublingual, subcutaneous, and intramuscular (IM) administration (Iqbal & Mathew, 2020). Studies have shown that IM ketamine can reduce depressive and anxiety symptoms, with comparable efficacy to IV ketamine (Ahuja et al., 2022; Bonnett et al., 2021).

In the treatment of *obsessive-compulsive disorder* (OCD), rTMS has been identified as an effective method for reducing some of the symptoms. Recent meta-analyses suggest that LF-rTMS over the supplementary motor area or the orbitofrontal cortex may offer the greatest improvement in OCD symptoms (Berlim et al., 2013a; Rehn et al., 2018). Additionally, HF-rTMS over the DLPFC has been found to be more effective than sham rTMS (Liang et al., 2021). In 2018, the Brainsway Deep Transcranial Magnetic Stimulation System using the H-coil was approved by the FDA for the treatment of OCD (FDA, 2018). Then in 2020, based on the results of a multicenter randomized controlled trial conducted by Carmi et al. (2019) in adult patients, the FDA cleared MagVenture TMS Therapy for use as an adjunct treatment for OCD (K193006). In contrast to the OCD treatment methods outlined in existing literature, the recently FDA-approved protocol for treating OCD involves administering TMS bilaterally over both the left and right dorsomedial prefrontal cortex (DMPFC) using a double-cone coil designed to penetrate deeper, while applying a high-frequency 20-Hz repetitive TMS sequence for about 18 minutes. Despite these promising results, the optimal target area and stimulation frequency remain controversial.

TMS has also been shown to be an effective method in decreasing negative symptoms and auditory hallucinations in *schizophrenia*. Patients with negative symptoms of schizophrenia have been found to have reduced activity in their prefrontal cortex (PFC), and HF-rTMS over the

PFC has been shown to increase local activation and lead to significant improvements in negative symptoms (Linsambarth et al., 2019). Additionally, Kubera et al. (2015) applied rTMS over the superior temporal cortex (STC) in patients with auditory verbal hallucinations (AVH), which is a brain area associated with increased cortical activity in patients who suffer from positive symptoms of schizophrenia, such as AVH. A meta-analysis by Zhang et al. (2013) suggested that LF-rTMS over the left temporoparietal cortex may be an effective treatment for patients with auditory hallucinations in schizophrenia spectrum disorders, leading to a reduction in the severity of auditory hallucinations. Furthermore, the combination of HF-rTMS over the left DLPFC with LF-rTMS over the Wernicke's area on the left temporoparietal cortex or over the right DLPFC has been found to be effective in reducing negative symptoms, delusions, and auditory hallucinations in schizophrenia patients (Mikellides & Tantele, 2020).

rTMS has emerged as a promising treatment option for *anxiety symptoms*, with evidence suggesting its efficacy and safety in treating generalized anxiety disorder (Cui et al., 2019). In particular, the application of rTMS over the right DLPFC has been found to be effective in treating post-traumatic stress disorder (PTSD) (Kan et al., 2020), leading to reductions in PTSD, anxiety, and depressive symptoms after 10 daily sessions (Berlim et al., 2014). Similarly, LF-rTMS over the right DLPFC has been shown to significantly improve panic symptoms in patients with panic disorder (Mantovani et al., 2007). Nonetheless, further research is required to establish the effectiveness of rTMS for anxiety disorders, and to identify the optimal stimulation parameters and brain targets for this purpose.

Finally, rTMS has emerged as a promising treatment option for patients with *monopolar and bipolar depression* (Phillips et al., 2020). In individuals with bipolar disorder (BD), the application of HF-rTMS over the left DLPFC resulted in significant cognitive improvements, including working memory and processing speed, without any reported adverse side effects (Yang et al., 2019). Although rTMS has been shown to be a well-tolerated and safe treatment for BD, the efficacy of rTMS for episodes of mania, depression, and mixed state is mixed, and the studies do not demonstrate a significant advantage of rTMS over sham stimulation (Kozel, 2018). Therefore, additional randomized controlled trials are needed to determine the efficacy of rTMS for BD (Kozel, 2018).

TMS & Addiction

In 2020, approximately 40 million adults in the United States, equivalent to 12.5% of the population, were reported to be cigarette smokers according to the Centers for Disease Control and Prevention (CDC) (CDC, 2022). Nicotine, a tertiary amine found in tobacco products (Benowitz, 2009; Tiwari et al., 2020), acts as a binder to nicotinic acetylcholine receptors (nAChRs) in the brain (Brunzell et al., 2015). Nicotine addiction induces alterations in

dopaminergic and cholinergic systems, such as the ventral tegmental area (VTA), nucleus accumbens (NAc), hippocampus, and prefrontal cortex (PFC) (Subramaniyan & Dani, 2015). Furthermore, nicotine is associated with the release of dopamine in the mesolimbic area, the corpus striatum, and the frontal cortex (Benowitz, 2009). In the field of smoking cessation, three classes of medications are currently employed as first-line pharmacotherapies: nicotine replacement therapy, bupropion, and varenicline (Benowitz, 2009). Yilmazel Ucar et al. (2014) conducted a retrospective study which reported the success rates of these medications for smoking cessation. The success rates were 32.5% for varenicline, 23% for bupropion, and 52.8% for nicotine replacement therapy, with an overall success rate of 35%. More recently, there has been a growing interest in exploring new, alternative, and effective treatments for smoking cessation.

Barr and colleagues (2011) investigated the effectiveness of HF-rTMS over the DLPFC as a treatment option for addiction. They found that active HF-rTMS significantly decreased craving levels in patients addicted to tobacco, alcohol, and cocaine. Active HF-rTMS over the DLPFC was effective in reducing smoking craving, the number of cigarettes, cigarette consumption, and nicotine dependence compared to sham rTMS. For alcohol addiction, active HF-rTMS was also effective in reducing the level of alcohol craving and alcohol consumption compared to sham rTMS. In cocaine addiction, HF-rTMS over the DLPFC was found to decrease the level of cocaine craving. The DLPFC was identified as the preferable rTMS target area for treating nicotine, alcohol, and cocaine addiction, although for cocaine addiction, it is unclear whether rTMS over the right or left DLPFC is more effective.

A recent study suggests that daily MRI-guided rTMS targeting the left DLPFC for 10 days may reduce cigarette consumption and the desire to smoke for up to a month and increase the likelihood of smoking cessation (Li et al., 2020). Additionally, HF-rTMS (20Hz) targeting the left DLPFC for 10 daily sessions has been found effective in reducing cigarette consumption, craving, and dependence while improving symptoms of anxiety and depression (Abdelrahman et al., 2021). In 2020, the US FDA approved the BrainsWay deep TMS system as an aid in short-term smoking cessation in adults.

Despite the promising results of existing smoking cessation treatments, there is still a lack of well-established options that demonstrate significant immediate or long-term abstinence rates. While iTBS is an FDA-approved protocol widely used for depression, its use in smoking cessation has not been extensively researched.

rTMS IN NEUROLOGY

A substantial and expanding body of research recognizes the significance of rTMS in the treatment of a range of neurological disorders, including but not limited to neuropathic pain, dementia, epilepsy, Parkinson's disease, and post-stroke rehabilitation.

Yang and Chang (2020) have highlighted the potential of rTMS as a treatment option for various types of *neuropathic pain*, including central pain, peripheral nerve disorders, fibromyalgia, and migraine. Notably, a recent study demonstrated that four consecutive HF-rTMS sessions (at 20 Hz) applied every 3 weeks over the primary motor cortex yielded a sustained analgesic effect (Quesada et al., 2020). Moreover, HF-rTMS over the primary motor cortex has been shown to lead to long-lasting improvement in quality of life and reduction of chronic pain in patients with fibromyalgia, without adversely affecting pain and mood levels (Boyer et al., 2014; Passard et al., 2007).

rTMS applied over the DLPFC has been found to enhance behavioral and psychological symptoms in patients with *dementia*. A recent meta-analysis of randomized controlled trials has revealed that rTMS is an effective treatment for cognitive impairment in patients with Alzheimer's disease (Wang et al., 2020). Moreover, Chou et al. (2020) reported that rTMS led to significant improvement in the cognitive performance of patients with Alzheimer's disease. The effectiveness of rTMS in improving the cognitive ability of patients with Alzheimer's disease was further demonstrated in a study by Lin et al. (2019), where bilateral DLPFC stimulation in combination with long-term treatment was found to be the most effective approach.

A recent meta-analysis demonstrated that rTMS is effective in reducing both seizure frequency and interictal epileptiform discharges in drug-resistant *epilepsy* (DRE) (Mishra et al., 2020). Fregni et al. (2006) conducted a randomized controlled trial which showed that active LF-rTMS leads to a significant reduction in the number of seizures compared to sham rTMS. This effect persisted for at least 2 months. Similarly, 0.5 Hz rTMS over the epileptic focus is associated with a decrease in the number of seizures in focal epilepsy patients (Santiago-Rodríguez et al., 2007). However, despite these limited positive results, the clinical role of TMS in epilepsy requires further investigation.

A number of studies have explored the impact of rTMS on both motor and nonmotor symptoms of *Parkinson's Disease* (PD). Research findings suggest that HF-rTMS has a positive effect on voice and speech (Dias et al., 2006) as well as depression (Shin et al., 2016) in PD patients. Meanwhile, LF-rTMS has been found to alleviate parkinsonism (Chou et al., 2015; Shimamoto et al., 2001). These results are particularly significant as the improvement of motor and mood symptoms of PD could enhance patients' quality of life. The motor cortex (M1) is frequently targeted in PD treatment. Yang et al. (2018) showed in their study that multi-session HF-rTMS of the M1 was the most effective protocol for treating PD. Additionally, in Lefaucheur et al.'s

review (Lefaucheur et al., 2020), HF-rTMS was recommended in the M1 contralateral to the pain side for patients with neuropathic pain. They also reported that left DLPFC HF-rTMS can be used to alleviate depressive symptoms in PD. Moreover, bilateral M1 stimulation (Aftanas et al., 2020; Lefaucheur et al., 2020) and left DLPFC stimulation with HF-rTMS were found to be potentially effective in improving parkinsonism symptoms (Aftanas et al., 2020).

Levels of evidence of rTMS efficacy

In 2020, a group of European experts in 2020 (Lefaucheur et al., 2020) published a paper entitled "Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018)" which provided updated information on the therapeutic use of rTMS for several neuropsychiatric disorders. The level of evidence regarding the efficacy of rTMS was determined for each disorder based on the results of all studies and classified into three levels: Level A ("definitely effective or ineffective"), Level B ("probably effective or ineffective"), and Level C ("possibly effective or ineffective"). Table 1 displays the classification of the evidence for psychiatric and neurological disorders into these three levels.

Table 1: Classification of rTMS efficacy evidence for psychiatric and neurological disorders

Psychiatric Disorders			
	Level A	Level B	Level C
Major depressive disorder	HF-rTMS over the left DLPFC (with either the figure of 8 or H1-coil)	LF-rTMS over the right DLPFC	
		Bilateral LF-rTMS over the right DLPFC	
		HF-rTMS over the left DLPFC	
Major unipolar depression		Bilateral cTBS over the right DLPFC	
		iTBS over the left DLPFC	
Post traumatic stress disorder		HF-rTMS of the right DLPFC	
Schizophrenia			LF-rTMS over the left TPC in auditory hallucinations
			HF-rTMS over the left DLPFC on negative symptoms
Obsessive compulsive disorder			LF-rTMS of the right DLPFC

Cigarette craving and consumption			HF-rTMS of the left DLPFC

Neurological Disorders

	Level A	Level B	Level C
Neuropathic pain	HF-rTMS of M1 contralateral to pain side		
Fibromyalgia		HF-rTMS of the left M1 in improving quality of life	
		HF-rTMS of the left DLPFC in relieving pain	
Parkinson's disease		HF-rTMS of the left DLPFC for treating depressive symptoms	
		HF-rTMS of bilateral M1 regions in improving motor symptoms	
Multiple sclerosis		iTBS of the leg motor cortex in relieving lower limb spasticity	
Complex regional pain syndrome - type I			HF-rTMS of M1 contralateral to pain side
Chronic epilepsy			LF-rTMS of the epileptic focus
Chronic tinnitus			LF-rTMS of the auditory cortex of the left hemisphere (or contralateral to the affected ear)
Alzheimer's disease			Multisite rTMS-COG to improve cognitive function, memory and language level
Stroke	LF-rTMS of contralesional M1 in hand motor recovery at the post-acute stage of stroke	HF-rTMS of ipsilesional M1 in promoting hand motor recovery at the post-acute stage of stroke	cTBS of the contralesional left PPC in visuospatial hemineglect recovery at the post-acute stage of stroke
		LF-rTMS of right IFG in promoting non-fluent aphasia recovery at the chronic stage of stroke	

Despite the promising clinical effects of rTMS in treating various neuropsychiatric and neurological diseases, several RCTs have revealed that sham or placebo rTMS can also lead to significant positive clinical benefits. Although the real rTMS was generally significantly stronger than the placebo condition, the appropriate use of placebo controls in clinical studies is a key question that needs to be addressed.

Placebo Effect

The placebo effect is a psychological phenomenon that refers to the health benefits experienced by patients who receive an inert substance without any medical effects due to their belief that the substance is effective (Pozgain et al., 2014). On the other hand, the nocebo effect is defined as the negative health effects experienced by patients taking an inert substance that worsen their health status due to their negative beliefs and expectations about the substance (Pozgain et al., 2014). Neither the placebo nor nocebo effects have a direct therapeutic effect (Turi et al., 2018). Placebo is typically an inert substance or procedure/treatment, and the placebo effect is the phenomenon that occurs after the administration of an inert substance or a sham physical treatment such as sham surgery, which may be associated with the psychological context of the inert substance or sham treatment (Benedetti et al., 2011; Finniss et al., 2010). The use of placebo in medical practice dates back to the 18th century, when it was prescribed to meet patients' expectations and demands (Jutte, 2013).

The mechanisms underlying the placebo effect are not fully understood; however, researchers have classified them into psychological and neurobiological. The placebo response is driven by various psychological factors and mechanisms, including expectancy, learning memory, conditioning, somatic focus, reward, anxiety reduction, meaning, past experiences, social observation, and motivation (Benedetti et al., 2011; Finniss et al., 2010; Quattrone et al., 2018). Expectancy and classical conditioning are among the most studied psychological mechanisms (Finniss et al., 2010). Expectancy refers to the belief that an event is likely to happen and describes its impact on health and neurochemical reactions in the body (Braga et al., 2021; Pozgain et al., 2014). These beliefs are associated with hormonal and immunological responses and can regulate cognitive processes such as perception, motor control, and working memory (Braga et al., 2021; Pozgain et al., 2014). Expectations prepare the body to anticipate an event to better cope with it (Benedetti et al., 2011). In the context of clinical practice, expectancy is a crucial factor in understanding the influence of explicit and implicit contextual elements on the placebo effect (Braga et al., 2021; Finniss et al., 2010). Additionally, the placebo effect can be

described using Pavlov's conditioned reflex theory as a learned response to previous experience with medications or procedures (Heeg et al., 1997; Pozgain et al., 2014). This response is often rapid, automatic and unconscious (Heeg et al., 1997). With repeated pairings of an active medicine or procedure with a neutral stimulus, the neutral stimulus alone can elicit a response that was previously elicited by the active intervention (Finniss et al., 2010). Neurobiological factors that contribute to the placebo effect include neurotransmitters such as endorphins, cannabinoids, and dopamine, as well as activation of specific brain regions including the prefrontal cortex, anterior insula, rostral anterior cingulate cortex, and amygdala in placebo analgesia (Kaptchuk & Miller, 2015).

PLACEBO EFFECT IN CLINICAL PRACTICE

There is a growing body of evidence indicating that the placebo effect plays a crucial role in clinical practice. The psychosocial context of the patient includes both individual patient and clinical factors, as well as the interaction between the patient, clinician, and treatment environment (Finniss et al., 2010). Factors such as enthusiasm for a new treatment, doctor-patient interactions, increased expectations of treatment effects, and decreased negative emotions such as anxiety, may enhance treatment outcome (Kjaer et al., 2020). However, it should be noted that placebo effects primarily address the subjective and self-reported symptoms of a disease, such as those in cancer, gastrointestinal, and urogenital disorders, and do not alter the underlying pathophysiology of the disease (Kaptchuk & Miller, 2015).

Placebo effects have been previously observed in pharmacological treatments (Kjaer et al., 2020). These effects are dependent on complex neurobiological mechanisms, involving neurotransmitters and the activation of specific, quantifiable, and relevant brain regions (Kaptchuk & Miller, 2015). Moreover, it has been suggested that several medications are also associated with these neurobiological mechanisms (Kaptchuk & Miller, 2015).

The placebo effect has been observed to produce significant effects in various disorders such as pain, depression, multiple sclerosis and Parkinson's disease (Quattrone et al., 2018). Parkinson's disease is a neurological disorder that exhibits high rates of placebo response. A recent systematic review by Quattrone et al. (2018) on the neurobiological basis of the placebo effect in Parkinson's disease suggests that dopamine release in the dorsal striatum can activate the entire nigrostriatal pathway, leading to motor improvement. Expectancy of improvement, prior exposure, and learning strategies also appear to play a key role in the placebo response in Parkinson's disease (Quattrone et al., 2018). Placebo effect has also been found to be a significant factor in the treatment of depression (Pozgain et al., 2014). The amount and effect of antidepressant commercials may create higher expectations, thereby affecting the placebo effect (Pozgain et al., 2014).

In medical practice, the administration of deceptive placebos to induce symptom relief raises ethical concerns regarding patient autonomy and informed consent (Annoni, 2018). The ethical principles that guide the use of placebo effects in clinical practice necessitate careful consideration. Annoni (2018) proposed three strategies for ethical administration of placebos: (1) the use of deceptive placebos may be justified in cases where the potential benefits outweigh concerns about autonomy, trust, and non-maleficence; (2) exploring the use of non-deceptive placebos; and (3) harnessing placebo effects through skillful use of verbal communication.

PLACEBO EFFECT IN RCTs

In scientific research, placebo effects can be studied using two types of methods: randomized controlled trials (RCTs) using drugs or procedures, and laboratory experiments (Miller et al., 2009). In RCTs, researchers aim to determine whether subjects receiving real treatment exhibit greater improvements compared to those receiving a placebo (Benedetti et al., 2011). Thus, placebo controls are used to distinguish the effects of real treatment (Kjaer et al., 2020). To ensure that the effects of a real condition are distinguishable from those of a placebo, a proper placebo control condition is necessary. This condition requires that both the real and placebo treatments look identical, except for the presence of the active component of the real treatment. By doing so, the patient is unaware of which treatment they are receiving (Davis et al., 2013; Kjaer et al., 2020). Furthermore, a placebo control condition ensures that any observed changes or improvements are truly due to the real treatment, rather than being influenced by other factors (Davis et al., 2013).

Finniss et al. (2010) have demonstrated that the active treatment's efficacy is influenced by both the treatment itself and the context surrounding it. However, subjects assigned to the placebo/sham groups frequently experience symptom improvements (Miller et al., 2009), which may be attributed to the placebo intervention and the clinical environment (Miller et al., 2009). The occurrence of the placebo effect in randomized controlled trials may be associated with several factors, including the natural progression of the disease, symptom fluctuations, regression to the mean, and response bias (Finniss et al., 2010). Expectancy and prior beliefs have been identified as significant factors for researchers to consider when evaluating the overall impact of a treatment or procedure (Braga et al., 2021). The size of the placebo effect varies considerably depending on the context in which it is employed. The placebo effect is more prominent in studies that explore placebo mechanisms than in studies that use placebo as a control condition (Finniss et al., 2010).

In recent decades, researchers have dedicated significant attention to reducing the placebo effect in RCTs. The use of a double-blind design has been suggested as a strategy to minimize

expectation bias and reduce the potential for improvement due to the placebo intervention in clinical trials (Heeg et al., 1997; Kjaer et al., 2020; Miller et al., 2009). With a double-blind design, patients are unaware of their treatment condition, meaning that they do not know whether they are receiving an active or placebo intervention and are therefore less likely to have expectations about the treatment (Heeg et al., 1997). Additionally, in a double-blind design, neither the patients nor the healthcare providers are aware of whether an active or sham intervention is being administered, further reducing the potential for bias (Kjaer et al., 2020).

In RCTs, the use of a placebo intervention raises significant ethical concerns related to deception. In some cases, study participants are not informed that the research aims to evaluate the placebo effect in order to create a reliable placebo intervention (Miller et al., 2009). Evers et al. (2018) have provided several ethical recommendations for the use of placebo interventions in clinical practice, including (1) considering placebo effects as a standard part of treatment, (2) informing patients about placebo interventions in a manner that maximizes treatment effects and minimizes side effects, (3) establishing a patient-clinician relationship characterized by trust, warmth, and empathy to maximize placebo effects, (4) training healthcare providers in patient-clinician communication to maximize placebo effects, and (5) preferring open-label placebo prescriptions over hidden ones where there is evidence for efficacy and prescribing a placebo is legal.

PLACEBO EFFECT & NIBS

In studies that utilize NIBS, several factors may contribute to positive or negative outcomes, including the participant's beliefs and expectations, the interaction between the researcher and participant, and changes in emotional state or motivation (Braga et al., 2021). These factors can introduce confounds that must be carefully controlled to assess the true effects of active stimulation (Braga et al., 2021). Additionally, some sensations that can occur during NIBS, such as acoustic or tactile sensations, may influence participants' blinding to the treatment condition (Braga et al., 2021). Furthermore, NIBS interventions combined with placebo-inducing written instructions have been shown to reinforce reward learning in healthy individuals (Turi et al., 2017). Expectancy can also play a role in maintaining blinding in double-blind NIBS studies, as evidenced by a study by Turi et al. (2018) which found that experimentally induced expectancy impacted the cognitive functions of healthy individuals.

Braga et al. (2021) conducted a review on NIBS and reported that the outcomes of NIBS can be influenced by participants' beliefs about the type of stimulation received and their expectations and prior beliefs about the effects of the stimulation. Specifically, they found that active stimulation was superior to sham when positive expectations were presented in the sham

group and not in the active group. In contrast, active stimulation was significantly superior to sham when positive expectations were presented in the active group and not in the sham group.

Turi et al. (2018) proposed several reasons why sham protocols in NIBS studies are effective in inducing placebo effects. Firstly, as NIBS techniques are medical devices, they have the potential to induce placebo effects. Additionally, NIBS techniques have been shown to induce higher placebo effects than medication (Braga et al., 2021). Secondly, both active and placebo effects can be studied with NIBS as active stimulation is associated with minor adverse events, whereas no adverse events occur with sham stimulation. Finally, NIBS protocols can be useful in assessing the efficacy of blinding in NIBS studies.

In the context of NIBS studies, the use of sham interventions is a commonly employed form of placebo control (Kjaer et al., 2020). A variety of sham control protocols have been developed in order to simulate the sensations and treatment context of active stimulation without actually delivering the stimulation (Braga et al., 2021; Kjaer et al., 2020). Davis et al. (2013) found that the two most commonly used methods for controlling effects in NIBS studies are sham control stimulation and off-target active stimulation. In sham control stimulation, participants receive little or no stimulation, whereas in off-target active stimulation, a full amount of stimulation is delivered to an area of the scalp that is not related to the process being studied.

PLACEBO EFFECT IN TMS

In the history of TMS, the placebo effect has been recognized as a crucial factor in evaluating treatment outcomes, given its high potential to induce such an effect. Consequently, placebo effect must be considered a major source of bias in rTMS efficacy assessment (Dollfus et al., 2016). Previous studies have indicated that the placebo effect could be a component of the therapeutic efficacy of rTMS (Jin et al., 2021; Razza et al., 2018). Razza et al. (2018) conducted a systematic meta-analysis, which revealed that large placebo effects were present in depressive trials. Moreover, these placebo effects were linked to improvements in depressive symptoms observed in the active treatment group. In addition, both active HF-rTMS and sham stimulation have been shown to lead to improvements in headache characteristics and related disability (Granato et al., 2019). Several factors have been identified that may augment the placebo effect, including the use of a medical device, positive interactions with research staff, participant motivation, and expectations (Granato et al., 2019; Jin et al., 2021; Razza et al., 2018).

As mentioned earlier, the use of sham control stimulation and off-target active stimulation are standard techniques for controlling effects in NIBS. However, challenges are encountered with

both of these placebo methods. Firstly, off-target stimulation can cause psychiatric effects that may be difficult to distinguish from the effects of active stimulation. Secondly, the development of a satisfactory sham control condition in TMS is hindered by the production of the clicking sound during TMS and the somatic sensations such as muscle contractions in the scalp, face, or neck (Davis et al., 2013).

The effectiveness of placebo is affected by the type of sham condition used (Dollfus et al., 2016). However, finding the appropriate placebo control conditions remains challenging for the TMS community (Kjaer et al., 2020). According to Loo et al. (2000), an "ideal" sham for TMS should meet the following criteria: 1) the use of a TMS coil identical to that used for treatment to ensure visual and tactile equivalence with "real" treatment; 2) the stimulation of superficial nerves and muscles leading to similar scalp sensations; 3) the presence of a similar acoustic artifact of TMS, time-locked to the scalp sensation; and 4) the absence of any physiological effects on the cortex.

In TMS research, several types of sham protocols have been developed over the last few decades to improve blinding and minimize the likelihood that participants will be able to differentiate between the different types of stimulation (Braga et al., 2021). One way to apply sham protocols is by changing the coil position, such as tilting the coil 45 to 90 degrees from the scalp to reduce brain stimulation, which is one of the most commonly used methods in TMS randomized controlled trials (Mennemeier et al., 2009). Loo et al. (2000) conducted a study to examine the effects of different coil positions, specifically Condition A (front edge at 45°) and Condition B (lateral edge at 45°), on cortical activation and scalp sensation using a figure-eight stimulating coil. However, they found that none of the coil positions investigated satisfied the criteria for an ideal sham. In 2001, Lisanby et al. conducted a study comparing different sham manipulations, including one-wing 45° and 90° and two-wing 45° and 90° tilt, on their thresholds for MEPs and intracerebral measurements of voltage induced in the prefrontal cortex of a rhesus monkey. They found that one-wing 45° and 90° and two-wing 90° tilt induced significantly lower voltage in the brain compared to active TMS. Another method to avoid active stimulation is to use regular coils that are turned upside-down (Braga et al., 2021). In "tilting the coil" approaches, similar to active stimulation sound is produced, and the amount of magnetic field produced can generate somatosensory effects, depending on the orientation (Duecker & Sack, 2015; Mennemeier et al., 2009).

A purpose-built sham TMS coil is another method to provide sham stimulation (Braga et al., 2021; Duecker & Sack, 2015). This type of coil resembles a regular TMS coil but has the ability to attenuate the magnetic field. When positioned over the area of interest, the coil produces a sound similar to active stimulation, but no brain stimulation occurs due to the attenuation of the magnetic field (Braga et al., 2021; Duecker & Sack, 2015). However, the limitation of this approach is that it does not produce the somatosensory effects and peripheral nerve

stimulation of active stimulation (Duecker & Sack, 2015). To address this issue, Mennemeier et al. (2009) used a matched, air-cooled sham TMS coil that is combined with two large rubber electrodes placed over selected scalp muscles to simulate the look, sound, and feel of active stimulation at 1Hz without generating a significant magnetic field.

In order to minimize the placebo effect in TMS, there is a need to develop more efficient and improved control procedures and sham coils (Braga et al., 2021; Razza et al., 2018). In recent years, sham controls in RCTs have attempted to mimic the sensory artifacts of active TMS, such as sound and sensation, which is a shift from the previous years (Razza et al., 2018). One of the best approaches to sham TMS may be the use of a sham coil in combination with electrical stimulation (Duecker & Sack, 2015). These sham coils are designed to look like regular TMS coils and can be positioned exactly like active TMS coils. A strong magnetic shield attenuates the magnetic fields, thereby preventing brain stimulation. Additionally, surface electrodes can be used to provide electrical stimulation of the skin, thus mimicking the somatosensory experience of active TMS. However, there is still a need to continue developing better sham controls to further reduce placebo effects in TMS.

In addition to the placebo effect, the safety of repetitive rTMS is also an important aspect to consider when assessing its efficacy in treating neuropsychiatric disorders. Although the placebo effect can impact the perceived effectiveness of rTMS, ensuring the safety of rTMS is critical in determining its suitability as a treatment option for neuropsychiatric disorders. Therefore, evaluating the effectiveness of rTMS in these disorders should take into account both the placebo effect and safety concerns.

Safety

PRECAUTIONS

In the course of administering rTMS therapy, special consideration must be given to patients with implanted electronic or magnetic devices, such as cochlear implants, drug pumps, and pacemakers, as exposure to magnetic fields may cause interference with the proper functioning of these devices (Rossi et al., 2009; Rossi et al., 2021). In addition, individuals with a history of syncope or epilepsy should be closely monitored and precautions taken during rTMS treatment (Rotenberg et al., 2014). With respect to rTMS application in pregnant patients, the potential risks to both the mother and fetus are minimal (Rossi et al., 2021).

ADVERSE EVENTS

rTMS is considered as a therapeutic option in cases where medication has been insufficiently effective, or the patient declines medication due to medication-related adverse effects or pregnancy-related concerns, among other reasons. In comparison to standard medication, rTMS appears to be associated with a lower incidence of adverse events (AEs). Notably, standard antidepressant medication may lead to AEs such as weight gain, sexual dysfunction, gastrointestinal disorders, sedation, blurry vision, or xerostomia (Khawam et al., 2006). On the other hand, the most commonly reported AEs of rTMS include headaches (5-23%), local discomfort at the site of stimulation (20-40%), and facial muscle twitching, while seizures are an infrequent occurrence (<0.1%) (Dobek et al., 2015; Rossi et al., 2009).

The induction of seizures is considered the most severe adverse event (AE) associated with TMS (Rossi et al., 2021), albeit its incidence is rare (Rossi et al., 2009; Rossi et al., 2021). In a survey assessing the risk of seizures, the likelihood of seizure occurrence in individuals without any risk factors was found to be less than 1 in 60,000 sessions (Lerner et al., 2019). The majority of seizures were reported in individuals with preexisting risk factors, such as congenital epilepsies or structural/functional brain abnormalities (Lerner et al., 2019). The 2021 "Expert Guidelines for TMS Use in Healthy Subjects and Patient Populations, with Updates on Training, Ethical and Regulatory Issues" report that certain medical conditions and pharmacological agents may lower the seizure threshold and increase the risk of provoking seizures (Rossi et al., 2021). Medical conditions and pharmacological agents that may increase the likelihood of provoking seizures during TMS include the presence of neuropsychiatric disorders, as well as general factors such as sleep deprivation, stress, depression/anxiety, increased alcohol intake, and medical factors such as metabolic abnormalities and alcohol withdrawal (Rossi et al., 2021). With respect to stimulation frequency, the incidence of seizures was found to be similar among HF-rTMS, LF-rTMS, and single/paired-pulse TMS. Notably, seizures were more frequently observed during the initial TMS sessions (Lerner et al., 2019). Therefore, precautionary measures should be taken in patients with a history of seizures, as well as in individuals with elevated risk factors (Lerner et al., 2019; Rossi et al., 2009; Rossi et al., 2021).

The rapid mechanical deformation of the TMS stimulation coil generates an acoustic artifact that is broad in frequency and may exceed 140 dB, which is above the recommended safety levels for the auditory system as per previous studies (Rossi et al., 2009; Rossi et al., 2021). Despite this, only a small proportion of individuals have reported experiencing hearing difficulties. To mitigate the potential for TMS-induced hearing problems, a number of preventative measures have been proposed, such as using hearing protection in the form of earplugs (Rossi et al., 2009; Rossi et al., 2021).

When applying rTMS to treat neuropsychiatric disorders, it is crucial to consider both its safety and effectiveness. Despite the extensive research that has been conducted, evaluating the efficacy of rTMS in treating neuropsychiatric disorders remains a vital area of investigation. These disorders, including but not limited to depression, addiction, epilepsy, and Parkinson's Disease, affect a significant portion of the population and can severely compromise an individual's quality of life. Pharmacotherapy and psychotherapy are current treatments for neuropsychiatric disorders, but they may not be effective for all individuals. rTMS has emerged as a promising alternative or adjunctive treatment option, but its effectiveness needs to be evaluated further. Moreover, identifying and standardizing optimal stimulation parameters such as frequency, intensity, and duration is essential for treating different neuropsychiatric disorders. Evaluating the effectiveness of rTMS in these disorders will establish its role in clinical practice and enhance patient outcomes. It is crucial to continue researching rTMS to better understand its potential benefits and limitations for treating neuropsychiatric disorders and refining its use accordingly.

Although rTMS exhibits potential in treating various neurological disorders, additional research is necessary to determine its efficacy in addressing epilepsy and Parkinson's disease specifically. Epilepsy is a chronic neurological disorder characterized by recurrent seizures that can severely impair a person's quality of life. Although medication can effectively control seizures in some people, up to one-third of individuals with epilepsy are refractory to drug treatment. For these individuals, rTMS may offer a promising alternative or adjunctive treatment. Studies have suggested that rTMS may modulate cortical excitability and reduce seizure frequency in some people with epilepsy, but the evidence is limited, and more research is needed to fully understand the potential of rTMS in this population. Additionally, PD is a progressive neurodegenerative disorder that affects millions of people worldwide. While there are various treatments available for PD, such as medication and surgery, there is still a need for more effective and long-lasting treatments. rTMS has shown promising results as a potential therapeutic tool for PD, with studies suggesting that it can improve motor symptoms and quality of life in PD patients. However, more research is needed to fully understand the potential of rTMS as a treatment for PD, including the optimal stimulation parameters, and the long-term effects of rTMS. Given that epilepsy and PD are chronic conditions, it is imperative to maintain ongoing assessments of the effectiveness of rTMS in these populations and to investigate its potential as a treatment option that is safe, non-invasive, and well-tolerated.

Summary

rTMS has been investigated as a potential therapy for several psychiatric disorders. Among these, depression has been the most thoroughly investigated in the context of rTMS. Depression remains a widely prevalent and incapacitating mental health condition that affects millions of individuals globally. While traditional pharmacological and psychotherapeutic treatments are available, a significant number of patients remain resistant to these interventions, highlighting the need for alternative and more effective treatments. rTMS has shown promise in treating depression, particularly in patients who have failed to respond to traditional treatments. Given the significant burden of depression on individuals, families, and societies, and the potential of rTMS to offer a safe and effective alternative to traditional treatments, it is crucial to continue to investigate the effectiveness of rTMS in depression. Furthermore, it is important to compare rTMS with other existing treatments to establish its effectiveness and safety in managing depression.

Furthermore, addiction, including nicotine addiction, is a significant public health issue, as quitting smoking can be a challenging process due to the addictive properties of nicotine. rTMS has been examined as a possible therapy for smoking cessation, and while some research has shown promising outcomes, further investigation is needed to assess the effectiveness of rTMS in this area. Effective smoking cessation interventions are urgently needed due to the high prevalence of smoking and associated health risks. Therefore, it is essential to study the optimal parameters of rTMS treatment for smoking cessation, such as frequency, intensity, and duration of stimulation. This investigation is a critical research area with the potential to have a significant impact on public health.

Despite TMS showing potential in treating various neurological conditions, its effectiveness needs further exploration in other disorders like epilepsy and Parkinson's disease. Nevertheless, present research on these ailments is limited and inconsistent. Further investigation is needed to determine the optimal stimulation parameters and targeted brain regions for each disorder, as well as the long-term effects. Such research could ultimately lead to the development of more effective and targeted treatments for these neurological disorders.

Finally, in evaluating the effectiveness of rTMS in treating neuropsychiatric disorders, it is important to consider two key factors: the placebo effect and safety considerations. The placebo effect can influence the perceived efficacy of rTMS, making it challenging to determine its actual effectiveness. Furthermore, safety is paramount when evaluating rTMS as a treatment option for neuropsychiatric disorders. It is necessary to ensure that the treatment is safe and does not cause any adverse effects for patients. Hence, both placebo effect and safety should be taken into account when evaluating the effectiveness of rTMS in neuropsychiatric disorders, to ensure that the treatment is both effective and safe. In order to gain a better understanding

of the potential benefits of rTMS in treating various neuropsychiatric conditions, further research is needed to address the impact of placebo effects and ensure the safety of rTMS. Ongoing research efforts must prioritize the investigation of both placebo effect and safety in rTMS, to advance the field and improve patient outcomes.

Outline of the Thesis

The main objective of this thesis is to investigate the use of rTMS in the field of neuropsychiatry. This objective was accomplished through various studies with different designs, including a literature review, randomized controlled trials, case-control studies, and a retrospective study. These studies examined various aspects of rTMS, such as its effectiveness, safety, tolerability, and potential applications in neuropsychiatry. Additionally, the importance of considering placebo effects and safety parameters when evaluating the efficacy of rTMS was also discussed.

In **Chapters 2** and **3** of this thesis, randomized double-blind controlled trials were conducted to assess the efficacy of accelerated intermittent theta-burst stimulation on the left DLPFC as a potential treatment for smoking cessation. As current smoking cessation treatments have high relapse rates and limited success rates, new and effective approaches are necessary. These chapters also discussed the placebo response induced by TMS and explored the potential impact of advanced placebo coil technology. Specifically, Chapter 2 evaluated the short-term effects of TMS on smoking cessation, both immediately after treatment and one-week post-treatment, while Chapter 3 assessed the long-term effects up to 6 months after treatment.

While Chapter 2 and 3 have focused on craving and addiction and the role of placebo in the clinical improvements often reported, in **Chapter 4**, the focus shifts to depression, which is the most investigated and popular clinical application of TMS. Although placebo effects have been reported in depression, significant effects of real TMS have been found in many multi-center large RCTs in comparison to placebo groups. Therefore, it has been established that the clinical benefits of TMS in depression are not solely due to placebo. In clinical practice, the efficacy of rTMS in treating depression is well established and is generally regarded as more effective than placebo. Nevertheless, the effectiveness of rTMS compared to other rapidly acting interventions such as ketamine in a naturalistic setting is still unknown. Chapter 2 of this thesis aimed to assess and compare the acute antidepressant effects of intramuscular ketamine and rTMS in a naturalistic clinical mental health setting for patients with depression.

Chapter 5 and 6 comprises two case reports that sought to assess the efficacy of rTMS in addressing two prevalent and persistent neurological disorders: epilepsy and Parkinson's Disease. In **Chapter 5**, a patient with frontal lobe epilepsy was treated with LF-rTMS over the bilateral orbitofrontal cortex. Existing research has indicated the potential of TMS in mitigating epilepsy symptoms and reducing seizure frequency. This chapter highlights the importance of adjusting different research findings into clinical practice with the ultimate aim to benefit the patient after all with positive results and outcomes. Additionally, **Chapter 6** describes the case of a patient with Parkinson's disease who underwent an accelerated form of HF-RTMS targeting the contralateral side to the patient's primary difficulties.

Finally, **Chapter 7** of the thesis addresses the safety concerns related to TMS, which have become increasingly important due to the development of new TMS coil technology and advanced placebo TMS coils. Despite the fact that TMS is generally considered a safe and well-tolerated treatment, the safety of these new coil geometries has not been fully established. This chapter presents a case report of a patient with OCD who experienced a seizure during the seventh session of her rTMS treatment using the FDA-approved bilateral DMPFC 20-Hz protocol with a double-cone TMS coil. Therefore, when selecting treatment protocols, it is essential to consider various factors and make appropriate arrangements for patients who may have unique characteristics that could either benefit or require additional precautions. The chapter highlights the need for caution and careful consideration when administering rTMS to ensure patient safety.

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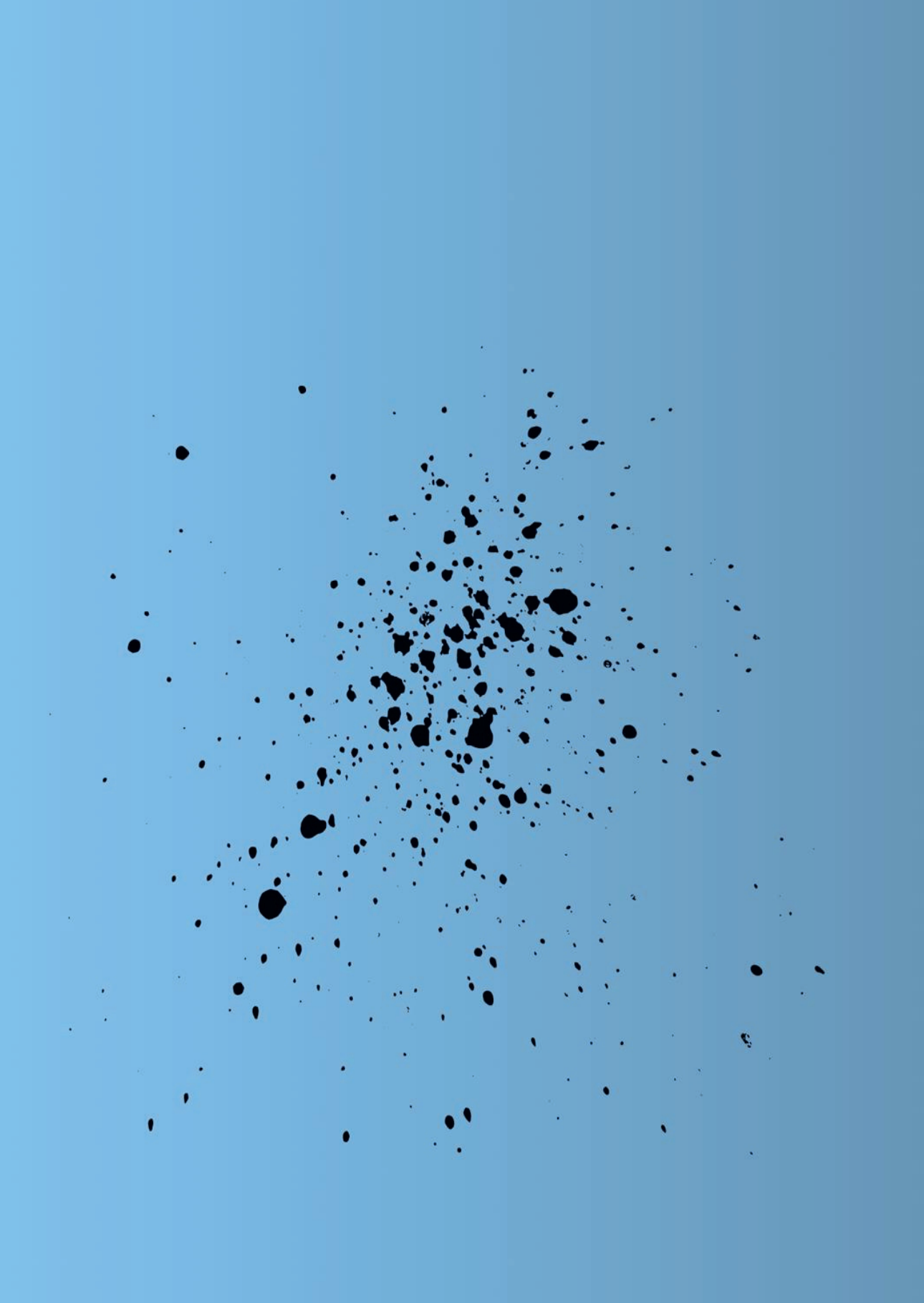
PART 1

TRANSCRANIAL MAGNETIC
STIMULATION IN PSYCHIATRY

CHAPTER 2

Accelerated intermittent theta burst stimulation in smoking cessation: placebo effects equal to real stimulation when using advanced placebo coil technology

Abstract

Smoking is currently one of the main public health problems. Smoking cessation is known to be difficult for most smokers because of nicotine dependence. Repetitive transcranial magnetic stimulation (rTMS) over the left dorsolateral prefrontal cortex (DLPFC) has been shown to be effective in the reduction of nicotine craving and cigarette consumption. Here, we evaluated the efficacy of accelerated intermittent theta burst stimulation (aiTBS; four sessions per day for 5 consecutive days) over the left DLPFC in smoking cessation, and we investigated whether the exposure to smoking-related cues compared to neutral cues during transcranial magnetic stimulation (TMS) impacts treatment outcome. A double-blind, randomized, controlled study was conducted in which 89 participants (60 males and 29 females; age 45.62 ± 13.42 years) were randomly divided into three groups: the first group received active aiTBS stimulation while watching neutral videos, the second group received active aiTBS stimulation while watching smoking-related videos and the last group received sham stimulation while watching smoking-related videos. Our results suggest that aiTBS is a tolerable treatment. All treatment groups equally reduced cigarette consumption, nicotine dependence, craving and perceived stress. The effect on nicotine dependence, general craving and perceived stress lasted for at least 1 week after the end of treatment. Active aiTBS over the left DLPFC, combined with smoking related cues, is as effective as active aiTBS combined with neutral cues as well as placebo aiTBS in smoking cessation. These findings extend the results of previous studies indicating that TMS therapy is associated with considerably large placebo effects and that these placebo effects may be further increased when using advanced placebo coil technology.

Introduction

Cigarette smoking is one of the foremost causes of preventable disease and premature death (Kondo et al., 2019; Sasco et al., 2004; Teo et al., 2006; Warren & Cummings, 2013; WHO, 2021). According to the World Health Organization (WHO), in 2020, 22.3% of the global population used tobacco (WHO, 2021). Nicotine is a highly addictive chemical compound (FDA, 2022) in tobacco and is released directly in the mesolimbic dopamine pathways where reward processing takes place (De Biasi & Dani, 2011). In 2014, 68% of US adult smokers wanted to quit smoking and in 2017, 55.1% of US adult smokers had made an attempt to quit smoking (Babb et al., 2017; CDC, 2022; Creamer et al.,2019). However, only a small percentage of adult smokers (7.4%) actually achieved to quit smoking (Creamer et al., 2019). To support smokers in smoking cessation, behavioral, psychological and pharmacological interventions as well as nicotine replacement therapy are some of the most used interventions (Lancaster et al., 2000) with medium to low success rates (Lancaster et al., 2000). Recently, there has been growing interest in new, alternative, and effective treatments for smoking cessation.

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation therapy (Klomjai et al., 2015; Pell et al., 2011) that delivers magnetic pulses to a brain region, inducing an electric current that can depolarize neurons and induce action potentials (Klomjai et al., 2015). Repetitive (r)TMS protocols have been found to have lasting effects on excitability that can either be (generally) inhibitory (1Hz) or excitatory (10Hz) in nature by engaging synaptic plasticity mechanisms, such as long-term potentiation (LTP) and long-term depression (LTD) (Gersner et al., 2011). Theta Burst Stimulation (TBS) is a more recent TMS protocol that delivers a comparable number of pulses in a very short time (Blumberger wt al., 2018; Chung et al., 2015). Two different patterns of TBS were developed: intermittent TBS (iTBS) and continuous TBS (cTBS) which generally increases and decreases cortical excitability, respectively (Chung et al., 2015).

The dorsolateral prefrontal cortex (DLPFC) is a frontal brain region that plays a crucial role in meso-cortico-limbic and serotonergic systems (Tik et al., 2017) and is involved in executive functions such as inhibitory control, as well as emotion regulation and decision making; processes modified by substance use and dependence (Amidfar et al., 2019; Hauer et al., 2019; Tik et al., 2017). Mesolimbic dopamine reward circuits and frontoparietal networks are associated with craving and are activated by addictive drugs (Due et al., 2002). Exposure to cigarette-related cues has been associated with activation in the DLPFC (Amiaz et al., 2009; Brody et al., 2002). Smoking related cues provoke activation of these brain circuits of smokers (Amiaz et al., 2009; Li et al., 2017). The combination of rTMS with smoking related cues has been found to be more effective compared to the combination of rTMS alone (Dinor-Klein et al., 2014).

Several lines of evidence support the efficacy of high frequency (HF)-rTMS over the left DLPFC in the reduction of nicotine craving and cigarette consumption (Amiaz et al., 2009; Hauer et al., 2019; Li et al., 2020) and cue-induced smoking craving (Li et al., 2013). A recently published double blind RCT showed that HF-rTMS (20Hz) over the left DLPFC for 10 daily sessions is effective in reducing cigarette consumption, craving, dependence as well as in improving anxiety and depressing symptoms (Abdelrahman et al., 2021). According to a recent systematic review, multiple target HF-rTMS may be effective in smoking cessation (Hauer et al., 2019). Accelerated TMS (aTMS), is used increasingly in research and clinical practice and has been shown to be as effective as a standard TMS procedure (Baeken et al., 2013; Holtzheimer et al., 2010; Theleritis et al., 2017). Recently, an accelerated, high-dose, iTBS protocol has shown promising results in patients with treatment resistant depression (Cole et al., 2020).

A growing body of research highlights the importance of determining the efficacy of TMS in neuropsychiatric disorders using randomized controlled trials (RCT) with placebo controlled groups. Placebo effects in TMS are a very common phenomenon (Dollfus et al., 2016; Jin et al., 2021; Mansur et al., 2011; Razza et al., 2018) and can have a big influence on the results of a study (Kaptchuk et al., 2000). Several studies indicated that the placebo effect may be a component of the therapeutic response to rTMS in neuropsychiatric disorders like major depressive disorder, and stroke rehabilitation (Jin et al., 2021; Razza et al., 2018).

Considering current knowledge of the efficacy of iTBS in substance use disorders, we investigated in a double-blind randomized control trial efficacy of four iTBS sessions per day during five consecutive days over the left DLPFC in smoking cessation, using the Cool-B65 Active/Placebo (A/P) coil, an advanced coil that is designed to support true "double blinded" clinical trials. Moreover, we wanted to investigate whether the exposure to smoking-related cues during the rTMS treatment, compared to neutral cues impacts cigarette craving. We hypothesized that 20 sessions of accelerated theta burst simulation over the left DLPFC while exposed to smoking-related cues, would reduce cigarette consumption and cigarette cravings, accompanied by reduced stress and motivation to quit smoking to a greater extent than active stimulation combined with neutral cues and sham stimulation with smoking-cues.

Materials and Methods

PARTICIPANTS

One hundred fifty-nine cigarettes smokers, who wanted to quit smoking, were recruited via internet advertisements and printed flyers in the period of April 2019 to December 2020 in Cyprus. Potential participants were screened in a short telephone interview where a total of

104 participants were eligible to participate. Inclusion criteria were the following: (a) aged 18–70, (b) native or fluent Greek speaker. Exclusion criteria were the following: (a) mental objects or implants in the brain, skull or near head (e.g., pacemakers, metal plates), (b) past or current of diagnosis of neurological or psychiatric disorder, (c) use of psychiatric medication, (d) past or current drug or alcohol abuse, other than nicotine, (e) use of IQOS ("I Quit Original Smoking") or electronic cigarettes (e-cigarettes). A total of 89 participants were included in the final analysis (60 males and 29 females; age 45.62 ± 13.42 years), excluding dropouts (n = 15). The minimum number of participants required was determined by an a priori power analysis where at least a sample size of 100 participants was suggested. [∗Measures that suggested this sample size were determined by the mixed model, a small to medium effect size (0.4), at an alpha level of probability of 0.05]. The experiment was carried out in the Cyprus rTMS Center in Larnaca, Cyprus. This study was approved by the Cyprus National Bioethics Committee and written informed consent was obtained from all participants (EEBK/E5/2019/08).

EXPERIMENTAL DESIGN

A multi-arm parallel group, double-blind, randomized, controlled study was conducted in which participants were randomly divided into three groups: the first group received active iTBS stimulation while watching neutral videos (TMS&N group), the second group received active iTBS stimulation while watching smoking-related videos (TMS&S group) and the last group received sham stimulation while watching smoking-related videos (Sham group). The Latin square design was used for the randomization. Both participants and the investigator who applied the rTMS and administered the self-reported measurements to the participants were blinded to the treatment condition. A second investigator was not blinded to the procedures to be able to set-up the appropriate stimuli. Four iTBS sessions (active or sham) were administrated every day, with 30min break between them over a 5-day period. Both active iTBS stimulation and sham stimulation were applied over the left DLPFC.

rTMS PROCEDURE

Stimulation was performed using a MagPro X100 (MagVenture, Farum, Denmark) and a figure-of-eight coil (Coil Cool-B65 A/P) for both active and sham stimulation. The Cool-B65 Active/Placebo (A/P) coil is designed to support true "double blinded" clinical trials as it can produce active and placebo stimulation by flipping the coil and can mimic a tapping sensation during placebo condition (MagVenture, 2018) (see The MagVenture Cool-B65 Active/Placebo (A/P) Coil in Supplementary Material for additional information).

Before the first session, the resting Motor Threshold (rMT) was determined by placing the coil over the left primary motor cortex (Borckardt et al., 2006) (see Resting Motor Threshold (rMT) in Supplementary Material for additional information). Stimulation was performed at 100% of rMT. Two experimenters were in the treatment room with the participant. The TMS operator (blinded experimenter) avoided watching the video while it was playing to remain blinded to the procedure and was only looking into the patients' direction. The videos were played by the second researcher.

In both active and sham conditions, an accelerated iTBS (aiTBS) treatment (four sessions with 30min break between them) was administered daily for a 5-day period over the left DLPFC. Beam_F3 Locator software was used to locate the left DLPFC (Beam et al., 2009) (see Beam_F3 Locator Software in Supplementary Material for additional information). The stimulation coil was placed at a 45◦ angle of the midline. iTBS was administrated at 5Hz and each session included 20 trains with 8 s inter train interval (10 pulses per train at 50Hz). A total number of 600 pulses was given per session.

DATA COLLESTION AND MEASUREMENTS

Demographic information as well as smoking-habits profile information were collected (Table 1). Participants were asked to report the number of cigarettes usually smoked during a day as well as the type of cigarettes, years of smoking and whether they ever quit smoking and if yes, how many times, to record smoking habits (Table 1).

Smoking-Related and Neutral Video Cues

During the rTMS treatment, participants were instructed to pay attention to videos that were presented on a monitor (Height: 20 cm; Width: 35 cm) placed opposite the treatment chair. Two different forms of videos were used (smoking related videos e.g., a person smoking cigarette in a restaurant and neutral videos e.g., a man cleaning his shoes) in order to elicit craving at the time of stimulation. Each video was presented for approximately 3min during the stimulation.

Primary Measures

i. Cigarette consumption: (a) Self-reported nicotine consumption: Participants had to daily record the number of cigarettes smoked from the completion of the four sessions until their next treatment visit. Participants were asked not to smoke during the breaks of the four daily

rTMS sessions; (b) Carbon monoxide (CO)- evaluated nicotine consumption: CO levels were measured using the piCO Smokerlyzer breath carbon monoxide meter device

ii. Nicotine dependence: Fagerström test for Nicotine Dependence (FTND) (Heatherton et al., 1991) is a short, self-report measure that assesses nicotine dependence. It contains six questions, and the total score is calculated as a sum of these six questions. The total scores of the questionnaire vary from 0 to 10, with lower scores indicating lower dependence on nicotine. This scale has been used previously in Cypriot samples and has been translated into Greek, showing good internal consistency (Demosthenous et al., 2019; Karekla et al., 2010).

iii. Craving: (a) Momentary Craving: The Visual Analog Scale (VAS) is a psychometric measurement instrument that measures symptom severity on a continuous scale (Klimek et al., 2017).We used the VAS to assess smoking craving by asking participants to respond to the question "How much do you want to smoke right now?", on a scale from0 "no craving" to 100 "most craving ever experienced"; (b) General Craving: Tobacco Craving Questionnaire–Short Form (TCQ-SF) (Heishman et al., 2008) is a self-report measure that assesses tobacco craving in four dimensions: emotionality, craving in anticipation of relief from withdrawal or negative mood; expectancy, craving in anticipation of positive outcomes from smoking; compulsivity, craving in anticipation of an inability to control tobacco use; and purposefulness, craving coupled with intention and planning to smoke. Each factor scale contains three items. TCQ-SF items were rated on a Likert scale of 1 (strongly disagree) to 7 (strongly agree). Total scores vary from 12 to 84, by summing the 12 items and the scores for each factor scale vary from 3 to 21 by summing the three items in each factor scale. A high score indicates high tobacco craving. We translated the TCQ-SF into Greek using the forward and backward translation procedure (Cronbach's α = 0.90, see Cronbach's alpha in Supplementary Material for additional information).

Secondary Measures

i. Perceived Stress: Perceived Stress Scale-4 (PSS-4) (Cohen & Williamson, 1988) is a self report measure that is used to assess psychological stress. The original PSS comprises 14 items (PSS-14) with two (negative and positive) subscales. We here used the shorter version with four items (PSS-4) that were rated on a Likert scale, ranging from 0 to 4, with those on the positive subscale scored in reverse and the total score was calculated as a sum of these items. The scores vary from 0 to 16, with a higher score indicating higher perceived stress.

ii. Motivation to quit smoking: Participants were asked to estimate how motivated they were to quit smoking from 0 to 100%.

iii. Adverse events: Participants were asked to daily report the adverse events they may have had experienced.

(For the time points of each measurement, see Table 2).

DATA ANALYSIS

SPSS software version 27.0 was used for the statistical analysis of the data (IBM corporation, Endicott, New York). We calculated the mean score of the 8 VAS scores and 4 CO scores of each day. A one-way ANOVA and Pearson chi-square test were used to test for differences in baseline demographic and smoking-related variables and rMT scores between the three groups. Mixed factorial ANOVAs were conducted to investigate the effect of both the within factor (Time) and the between factor (Group: TMS-N group, TMS-S group, Sham group). The dependent variables used for each model were: cigarette consumption, nicotine dependence, craving and perceived stress. Greenhouse–Geisser and Huynd-Feldt degree of freedom corrections were applied to correct for the non-sphericity the data. Post hoc comparisons using paired samples t-test were used to evaluate the significance of mean change in cigarette consumption, nicotine dependence, craving and perceived stress at different timepoints. Non-parametric tests were used as the variable Motivation to quit smoking was not normally distributed at all time-point assessments. Non-parametric Wilcoxon signed-rank tests were conducted to evaluate the significance of mean change in Motivation to quit smoking scores at different time points for each Group separately and non-parametric Kruskal–Wallis H tests were conducted to compare the mean scores of motivation to quit of the three Groups at different timepoints. Pearson chi-square test was used to test for differences in adverse events between the active TMS and sham TMS. Finally, a Pearson correlation analysis was applied to correlate a subjective measure (self-reported) with an objective measure (CO) of nicotine consumption. A significance level was set at $\alpha = 0.05$ for all analyses.

Results

BASELINE CHARACTERISTICS

Eight-nine participants completed the entire treatment program (60males and 29 females; age 45.62±13.42 years; see Enrollment in SupplementaryMaterial for enrollment information and Figure 1 for study recruitment flow diagram). Participant demographics and smoking-related variables are listed in Table 1. Analysis showed that the three groups did not differ significantly in demographic or smoking-related characteristics (all p > 0.05).

PRIMARY OUTCOME

Self-Reported Nicotine Consumption

A 5 (Time: Baseline, AfterDay1, AfterDay2, After Day3, AfterDay4) × 3 (Group: TMS&N group, TMS&S group, Sham group) mixed factorial ANOVA was conducted for the analysis of the

number of cigarettes smoked per day. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(9) = 167.688, p = 0.00$, therefore degrees of freedom were corrected using Greenhouse-Geisser of sphericity ($\varepsilon = 0.470$). There was a statistically significant main effect of Time, Q $F(1.879,142.840) = 166.548, p < 0.0001, \eta p^2 = 0.687$, suggesting a significant decrease in the number of cigarettes smoked per day over time. However, there was no significant effect of Type of Group, $F(2,76) = 0.363, p = 0.697, \eta p^2 = 0.009$ (Figure 2, see Supplementary Table 1 for means and standard deviations). The interaction effect between Time and Group was not statistically significant, $F(3.759,142.840) = 0.414, p = 0.787, \eta p^2 = 0.011$. Post hoc comparisons using paired-samples t-test were used to evaluate the significance of mean change in the number of cigarettes smoked per day at different time points (Table 3). Results indicate that mean scores were statistically significantly lower over time in all the comparisons, except of the pair AfterDay1 vs. AfterDay2, where no statistically significantly changes were found.

CO-Evaluated Nicotine Consumption

A 6 (Time: Baseline, Day1, Day2, Day3, Day4, Day5) × 3 (Group: TMS&N group, TMS&S group, Sham group) mixed factorial ANOVA was conducted for the analysis of CO scores. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(14) = 340.631, p = 0.00$, therefore degrees of freedom were corrected using Greenhouse-Geisser of sphericity ($\varepsilon = 0.368$). The interaction effect between Time and Group was not statistically significant, $F(3.678,154.484) = 1.964, p = 0.109, \eta p^2 = 0.045.$ There was a statistically significant main effect of Time, $F(1.839,154.484) = 82.421, p < 0.0001, \eta p^2 = 0.495,$ suggesting a significant decrease in CO scores over time. However, there was no significant effect of Group, $F(2,84) = 0.589, p = 0.557, \eta p^2 = 0.014$ (Figure 2, see Supplementary Table 1 for means and standard deviations).

Nicotine Dependence

A 3 (Time: Baseline, End of treatment, 1 week follow up) × 3 (Group: TMS&N group, TMS&S group, Sham group) mixed factorial ANOVA was conducted as measured by the FTND. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(2) = 11.064, p = 0.004,$ therefore degrees of freedom were corrected using Huynh-Feldt of sphericity ($\varepsilon = 0.911$). The interaction effect between Time and Group was not statistically significant, $F(3.642,116.549) = 0.095, p = 0.978, \eta p^2 = 0.003$. There was a statistically significant main effect of Time, $F(1.821,116.549) = 119.672, p < 0.0001, \eta p2 = 0.652,$ suggesting a significant decrease in nicotine dependence over time. However, there was no significant effect of Group, $F(2,64) = 1.784, p = 0.176, \eta p^2 = 0.053$ (Figure 3, see Supplementary Table 1 for means and standard deviations). Post-hoc paired sample t-tests were used to evaluate the significance of mean change in FTND scores at different time points (Table 4). Results indicate that mean scores were statistically significantly lower at the End of treatment and at 1 month follow up compared to

the baseline, however, no statistically significantly changes were found between the scores at the End of treatment compared to the scores at 1 week follow up.

Momentary Craving

A 6 (Time: Baseline, Day 1, Day 2, Day3, Day 4, Day 5) × 3 (Group: TMS&N group, TMS&S group, Sham group) mixed factorial ANOVA was conducted for the analysis of VAS scores. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(14) = 160.748$, $p = 0.00$, therefore degrees of freedom were corrected using Greenhouse- Geisser of sphericity (ε = 0.539). The interaction effect between Time and Group was not statistically significant, $F(5.389, 231.740) = 0.400$, $p = 0.861$, $\eta p^2 = 0.009$. There was a statistically significant main effect of Time, $F(2.695, 231.740) = 25.667$, $p < 0.0001$, $\eta p^2 = 0.230$, suggesting a significant decrease in VAS scores over time. However, there was no significant effect of Group, $F(2,86) = 1.511$, $p = 0.226$, $\eta p^2 = 0.034$ (Figure 2, see Supplementary Table 1 for means and standard deviations).

General Craving

A 3 (Time: Baseline, End of treatment, 1 week follow up) × 3 (Group: TMS&N group, TMS&S group, Sham group) mixed factorial ANOVA was conducted as measured by the TCQSF. Mauchly's test indicated that the assumption of sphericity had been violated in both situations, $\chi^2(2) = 11.572$, $p = 0.003$, therefore degrees of freedom were corrected using Huynh- Feldt of sphericity (ε = 0.905). The interaction effect between Time and Group was not statistically significant, $F(3.620, 115.845) = 1.320$, $p = 0.269$, $\eta p^2 = 0.040$. There was a statistically significant main effect of Time, $F(1.810, 115.845) = 32.881$, $p < 0.0001$, $\eta p^2 = 0.339$, suggesting a difference in tobacco craving over time. However, there was no significant effect of Group, $F(2,64) = 2.289$, $p = 0.110$, $\eta p^2 = 0.067$ (Figure 3, see Supplementary Table 1 for means and standard deviations). Post-hoc paired sample t-tests were used to evaluate the significance of mean change in TCQ-SF scores at different time points (Table 4). Results indicate that mean scores were statistically significantly lower at the End of treatment and at 1 month follow up compared to the baseline, however, no statistically significantly changes were found between the scores at the End of treatment compared to the scores at 1 week follow up.

SECONDARY OUTCOMES

Perceived Stress

A 3 (Time: Baseline, End of treatment, 1 week follow up) × 3 (Group: TMS&N group, TMS&S group, Sham group) mixed factorial ANOVA was conducted as measured by PSS-4. The interaction effect between Time and Group was not statistically significant, $F(4,128) = 1.132$, $p = 0.344$, $\eta p^2 = 0.034$. There was a statistically significant main effect of Time, $F(2,128) = 9.398$, $p <$

0.0001, ηp² = 0.128, suggesting a significant decrease in perceived stress over time. However, there was no significant effect of Group, *F(2,64) = 1.415, p = 0.250, ηp² = 0.042* (Figure 3, see Supplementary Table 1 for means and standard deviations). Post-hoc paired sample t-tests were used to evaluate the significance of mean change in PSS-4 scores at different time points (Table 4). Results indicate that mean scores were statistically significantly lower at the End of treatment and at 1 month follow up compared to the baseline, however, no statistically significantly changes were found between the scores at the End of treatment compared to the scores at 1 week follow up.

Motivation to Quit Smoking

Wilcoxon signed-rank tests yielded no statistically significantly changes, expect of the pair End of treatment vs. 1 week follow up of the TMS& N Group (Z = −2.392, p = 0.017) where scores at 1 week follow up (Mean = 72.37, SD = 23.41) were statistically significantly lower compared to the scores at the End of treatment (Mean = 82.41, SD = 20.59). Also, Kruskal– Wallis H tests showed that there were no statistically significant differences in Motivation scores between the different Groups in the baseline, *χ²(2) = 0.646, p = 0.724*, at the End of treatment, *χ²(2) = 0.202, p = 0.904* and at the 1 week follow up, *χ²(2) = 0.810, p=0.667* (Figure 3, see Supplementary Table 1 for means and standard deviations).

Adverse Events

Eleven participants (37.93%) of the TMS-N Group, five participants (16.67%) of the TMS&S group and seven participants (23.33%) of the Sham group reported mild adverse events. There were no statistically significant differences between Active and Sham TMS in terms of adverse events as determined by Pearson chi-square test (p = 0.574). The most frequent adverse events were mild headache and sleepiness (Table 5). No severe adverse events such as seizure or mania have been reported in the study.

Correlations Between Self-Reported and CO-Measured Nicotine Consumption

A Pearson correlation analysis was applied to correlate self reported and CO-measured nicotine consumption. Results showed a significant positive correlation between the two variables in all timepoints (see Supplementary Table 2).

Assessed for eligibility (n=159)

Excluded (n=55)
- Not meeting inclusion criteria (n=55)

Randomized (n=104)

Allocation

TMS & N Group (n=34)

TMS & S Group (n=33)

Sham Group (n=37)

End of the treatment

TMS & N Group (n=29)
- Completed (n=29)
- Dropouts (n=5)
  Reasons:
  o Had problems with her neck – During the first day (n=1)
  o Sickness of his wife – After of second day (n=1)
  o Had pain because of the rTMS – After the first day (n=1)
  o Had pain because of TMS – During the first day (n=1)
  o Unknown reason – After the first day (n=1)

TMS & S Group
- Completed (n=30)
- Dropouts (n=3)
  Reasons:
  o No improvements -After the fourth day (n=1)
  o Problem with the treatment schedule – After the third day (n=1)
  o Unknown reason – During the second day (n=1)

Sham Group
- Completed (n=30)
- Dropouts (n=7)
  Reasons:
  o Problem with the treatment schedule - After the second day(n=1)
  o Had a family emergency – After the second day (n=1)
  o Was very sick – After the second day (n=1)
  o Could not come to the appointment – After the first day (n=1)
  o Had strong headache – After the first day (n=1)
  o Unknown reason – During the first day (n=1)
  o Unknown reason – After the third day (n=1)

One week follow up

TMS & N Group (n=19)
- Dropouts (n=10)

TMS & S Group (n=23)
- Dropouts (n=7)
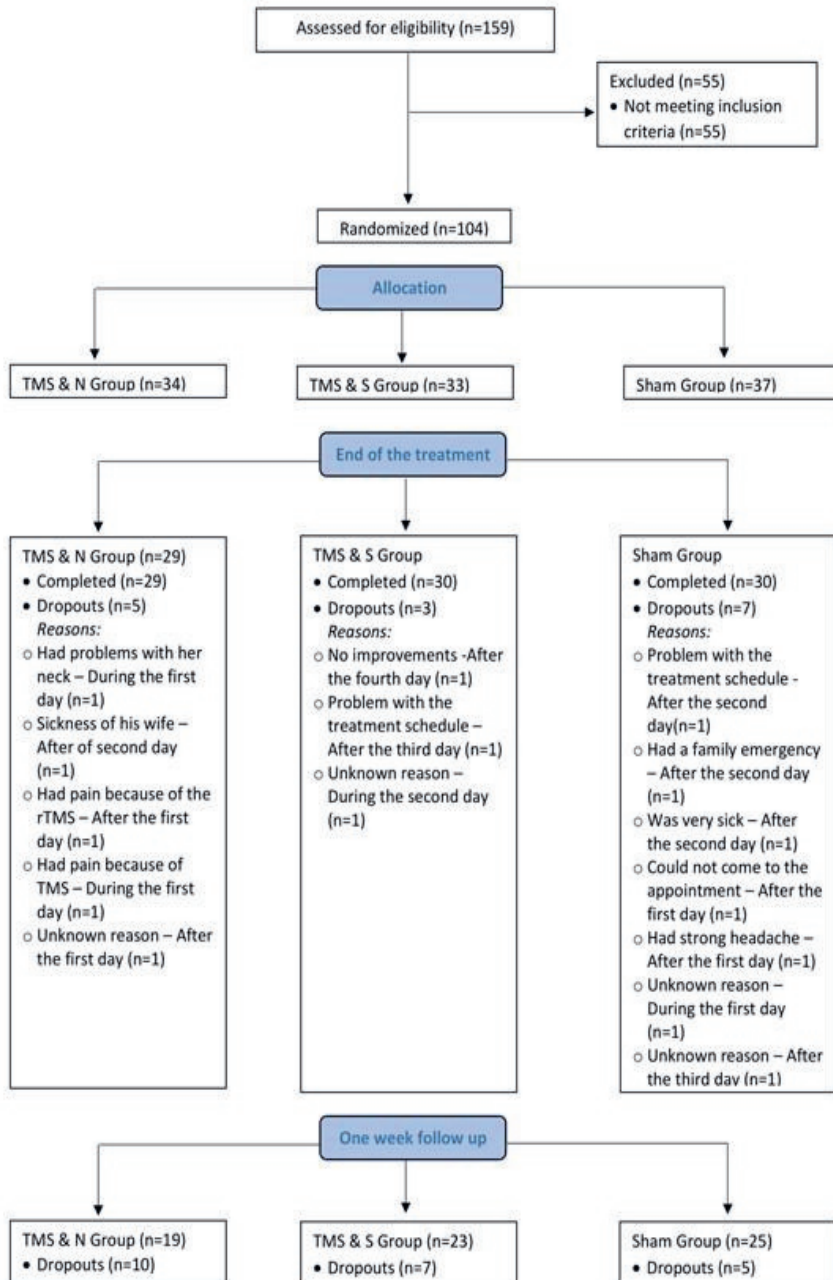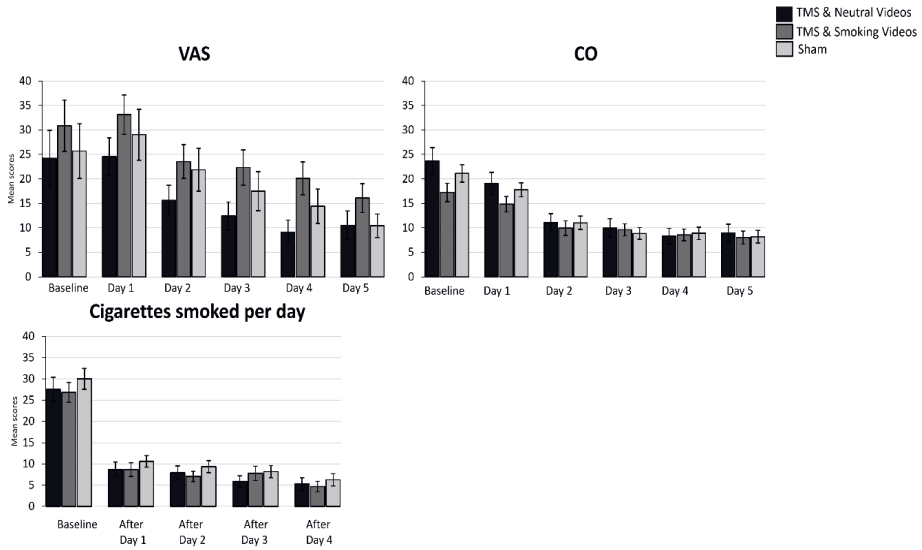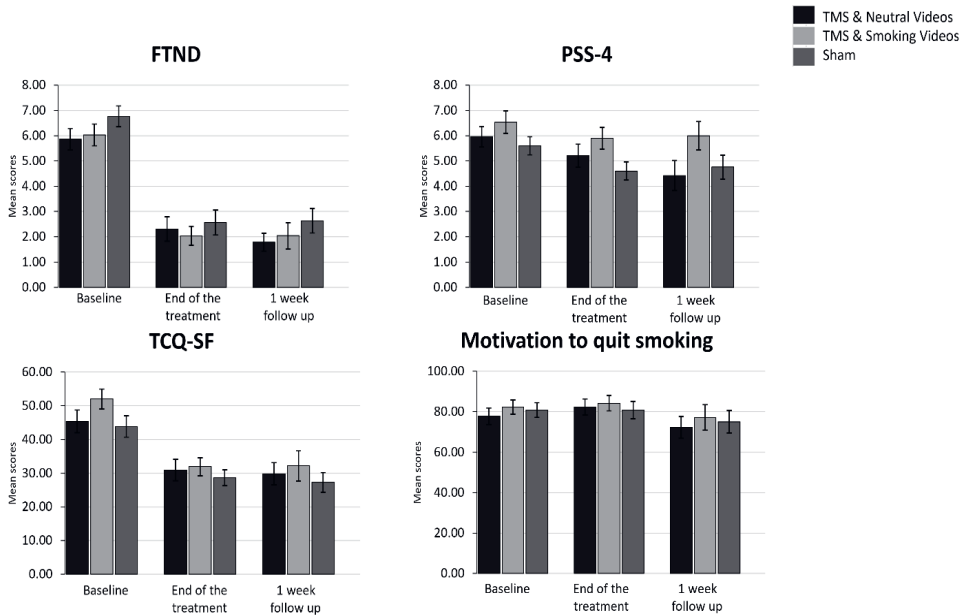
Sham Group (n=25)
- Dropouts (n=5)

Figure 1: Flow chart of the selection procedure.

Figure 2: Bar graphs showing difference in mean scores of VAS, CO, Cigarettes smoked per day over time. Data are presented as mean ± SEM.

Figure 3: Bar graphs showing difference in mean scores of FTND, PSS-4, TCQ-SF and Motivation to quit smoking over time. Data are presented as mean ± SEM.

Discussion

The current study investigated the efficacy of a rapid accelerated iTBS therapy (four sessions per day for five consecutive days) combined with smoking related cues in smoking cessation. We hypothesized that an active TMS group that is exposed to smoking related videos during stimulation (TMS&S group) shows more improvement with regard to reducing their cigarette consumption and smoking craving compared to the group that receives sham stimulation while watching smoking-related videos (sham group), and to the group receiving active TMS while watching neutral videos (TMS&N group).

In contrast to these expectations, we however found that all conditions, including sham stimulation, were equally effective in reducing cigarette consumption, CO levels, smoking craving and nicotine dependence. Contrary to our expectations and to what is reported in the literature, active TMS combined with smoking related cues was not more effective than active TMS combined with neutral cues, not sham stimulation.

Most interestingly was the fact that our TMS intervention was highly effective in facilitating smoking cessation. Our participants in the active TMS conditions showed 80.7 and 82.59% decrease in cigarette consumption in TMS &N Group and TMS&S group respectively, and 56.38 and 47.59% reduction in nicotine craving in TMS &N Group and TMS&S group respectively. The number of cigarettes smoked per day was statistically significantly lower over time, from the baseline to the End of treatment of the fifth day. These results are consistent with previous TMS trials, which show that rTMS can significantly reduce cigarette consumption and nicotine craving (Amiaz et al., 2009; Dinur-Klein et al., 2014; Hauer et al., 2019). Surprisingly, our advanced placebo coil technology condition specifically designed to support true "double blinded" clinical trials showed to be equally effective in treating smoking cessation. Our participants in Sham group showed 79.1% decrease in cigarette consumption and 59.34% reduction in nicotine craving. A similar reduction in cigarette consumption was found in a recent RCT, where the reduction in the active group was 76.19% (Li et al., 2020), although, contrary to our findings, a much smaller reduction in cigarette consumption was found in the sham group (35.29%). Similarly, participants in all conditions showed huge reductions in CO scores (TMS&N group: 62.01%, TMS&S group: 53.42%, Sham group: 61.29%).

We were thus able to show, that, especially when using such an advanced double blind placebo stimulation technology, the placebo effect of TMS in clinical context can be considerably large and even equal to the effect achieved with active TMS stimulation. Placebo effects in TMS are known to be playing a certain role on the clinical results obtained with TMS and have been documented before (Jin et al., 2021; Kaptchuk et al., 2000; Mansur et al., 2011; Razza et al., 2018). There are several factors that contribute to the enhancement of placebo effect in rTMS studies (Granato et al., 2019; Kaptchuk et al., 2000). A systematic review and meta-analysis by

Razza et al. (2018) evaluated the efficacy of rTMS for depression using data from a sham group of 61 RCTs, concluding that placebo effect sizes in depression trials are rather large (g = 0.8). Previous studies also demonstrated that placebo effects may be a component of the therapeutic response to rTMS (Jin et al., 2021; Razza et al., 2018). The placebo effect was also shown to be larger in more intense TMS protocols [HF rTMS (Granato et al., 2019)] and especially accelerated protocols (Baeken, 2018).

We therefore support that several specific factors not directly associated with rTMS treatment have contributed to the enhanced placebo effect found in the present study. First, our participants were highly motivated to quit smoking. Our data clearly indicate that already at day 1 and 2 during the treatment cycle, a strong effect of both, active and placebo TMS, was revealed. The timeline of these effects indicate that this is likely driven more by the motivation and expectation of our participants rather than by actually induced neuroplastic changes. Second, we used an intensive and state-of-the art TMS design, applying accelerated TMS with multiple sessions per day using theta burst stimulation sequences. It has been shown before that placebo effects scale with the intensity and complexity of the used TMS technology (Baeken, 2018; Granato et al., 2019). Finally, we used an advanced placebo coil technology capable of creating a true double blind clinical trial and an undistinguishable experience for each participant whether or not to be in a placebo or active stimulation condition. Unlike previous TMS studies, we did not use a simple coil tilting procedure (Mennemeier et al., 2009), or a standard sham coil (Duecker & Sack, 2015) to achieve our placebo condition. Instead, we used a novel and advanced placebo coil technology capable of mimicking not only the visual and auditory experience of active TMS, but also the somatosensory skin sensation using a low intensity current stimulator built into the A/P coils and a pair of surface electrodes placed just below the hairline on the scalp of each participant. These factors likely contributed to the fact that we do find our accelerated TMS intervention to be highly effective in reducing cigarette consumption and smoking craving, but not significantly more effective than placebo. The actual effect of our active rTMS had to show statistically to be on top of the highly effective placebo condition, which turned out to be not the case in our trial due to the factors mentioned above.

Additionally, our results demonstrated a statistically significant difference in perceived stress over time. However, due to the absence of a significant effects of the Group and the interaction effect between Time and Group, these results are inconclusive regarding the efficacy of active TMS in reducing perceived stress. Nevertheless, previous findings have shown that left DLPFC is a principal target of noninvasive brain stimulation techniques in regulating stress-related cognitive processes (Era et al., 2021). It was reported in the literature that perceived stress may be a barrier to smoking cessation (Stubbes et al., 2017), and thus further investigation on the association of perceived stress and smoking cessation during rTMS treatment is required.

The follow up assessment proved that these positive effect in nicotine dependence and perceived stress, as measured by FTND, TCQ-SF and PSS-4, lasts at least 1 week after the End of treatment. The findings of this study have to be seen in light of some limitations. Firstly, we did not measure self-reported cigarette consumption after the fifth day of treatment and during the 1-week follow up. Another potential limitation is the absence of a fourth group receiving sham stimulation while watching neutral videos. Finally, we did not use any formal assessment of blinding efficacy.

Although future RCTs are necessary to validate these conclusions, the present study highlights the importance of placebo effects and the role of specific placebo coil technologies in evaluating the efficacy of TMS in any psychiatric and psychological contexts. This could be used to further improve the administration of TMS based interventions, both for designing better placebo conditions in clinical trials, as well as for utilizing TMS placebo for enhancing coping and other psychological strategies of patients during rTMS treatment (Granato et al., 2019).

Conclusion

Our findings show that active aiTBS combined with smoking related cues, is as effective as active aiTBS combined with neutral cues as well as placebo aiTBS in smoking cessation. These findings extend the results of previous studies indicating that rTMS therapy is associated with considerably large placebo effects and that these placebo effects may be further increased when using advanced placebo coil technology. These beneficial effects in reducing cigarette consumption and craving for smoking in this and previous studies are likely a combination between the active rTMS effect and the placebo TMS effect. Future RCTs using advanced placebo coil technology are needed to confirm these results. Finally, future studies should emphasize on how to minimize placebo effect on TMS treatment.

Table 1: Demographic and smoking-related characteristics of (N=89) participants.

Characteristics	TMS&N Group n=29	TMS&S Group n=30	Sham Group n=30	p values
Demographic				
Age (yr)	46.52 ±13.05	42.93±14.42	47.43±12.72	.395[a]
Gender (M/F)	22/7	20/10	18/12	.427[b]
Education (yr)	14.07±3.95	14.43±3.77	13.60±3.27	.681[a]
Occupation*				.167[b]
Private employee	13 (14.61%)	19 (21.35%)	22 (24.72%)	
Public employee	7 (7.87%)	4 (4.49%)	1 (1.12%)	
Self-employed/Freelancer	5 (5.62%)	1 (1.12%)	4 (4.49%)	
Unemployed	2 (2.25%)	1 (1.12%)	0 (0%)	
Retired	2 (2.25%)	4 (4.49%)	3 (3.37%)	
Student	0 (0%)	1 (1.12%)	0 (0%)	
Smoking-related				
Cigarettes per day	27.55±15.37	26.83±12.86	30.00±13.38	.654[a]
Types of cigarettes*				.184[b]
Normal	16 (17.98%)	25 (28.09%)	24 (26.97%)	
Hand-rolled	10 (11.24%)	5 (5.62%)	5 (5.62%)	
Cigarillos	1 (1.12%)	0 (0%)	0 (0%)	
Mixed	2 (2.25%)	0 (0%)	1 (1.12%)	
Years of smoking	23.18±9.82	23.13±13.58	28.73±12.21	.125[a]
If ever quitted*				.899[b]
No	9 (10.11%)	10 (11.24%)	11 (12.36%)	
Yes	20 (22.5%)	20 (22.5%)	19 (21.3%)	
How many times quitted	0.90±0.77	1.00±1.11	1.20±1.56	.614[a]

Data are means ± standard deviation. *n(%); [a]One-way ANOVA; [b]Pearson chi-square test. TMS, Transcranial Magnetic Stimulation.

Table 2: Overview of data collection time points

Measurements		Time points
Primary measures	Self-reported cigarette consumption	i.Baseline ii.AfterDay1 iii.AfterDay2 iv.AfterDay3 v.AfterDay4
	Carbon monoxide (CO)- evaluated nicotine consumption	Prior to each rTMS session
	Fagerström test for Nicotine Dependence (FTND)	i.Baseline ii.End of the treatment iii.1 week follow up
	The Visual Analogue Scale (VAS)	Prior to and post each rTMS session
	Tobacco Craving Questionnaire–Short Form (TCQ-SF)	i.Baseline ii.End of treatment iii.1 week follow up
Secondary measures	Perceived Stress Scale-4 (PSS-4)	i.Baseline ii.End of the treatment iii.1 week follow up
	Motivation to quit smoking	i.Baseline ii.End of the treatment iii.1 week follow up
	Adverse events	After each treatment day

Table 3: Results of paired sample t-test for the number of cigarettes smoked per day

	Mean change	SD	*t* value	*p* value
Pair 1: Baseline vs AfterDay1	-19.13	11.89	14.731	**<.0001**
Pair 2: Baseline vs AfterDay2	-20.48	11.73	16.188	**<.0001**
Pair 3: Baseline vs AfterDay3	-21.20	12.83	14.962	**<.0001**
Pair 4: Baseline AfterDay4	-22.93	12.89	16.208	**<.0001**
Pair 5: AfterDay1 vs AfterDay2	-1.14	5.35	1.940	.056
Pair 6: AfterDay1 vs 1 AfterDay3	-2.13	7.44	2.597	.011
Pair 7: AfterDay1 vs AfterDay4	-3.82	6.85	5.051	**<.0001**
Pair 8: AfterDay2 vs AfterDay3	-1.09	4.90	2.006	.048
Pair 9: AfterDay2 vs AfterDay4	-2.84	5.09	5.050	**<.0001**
Pair 10: AfterDay3 vs AfterDay4	-1.74	4.64	3.363	**.001**

Paired sample t-test; p<0.05. Significant after Bonferroni correction in bold.

Table 4: Results of paired sample t-test for the three self-reported measures

	Mean change	SD	*t* value	*p* value
FTND				
Pair 1: Baseline vs End of treatment	-3.92	2.570	14.379	**<.0001**
Pair 2: Baseline vs 1 week follow up	-3.82	2.57	12.170	**<.0001**
Pair 3: End of treatment vs 1 week follow up	.12	1.79	-.544	.588
TCQ-SF				
Pair 1: Baseline vs End of treatment	-16.59	19.60	7.988	**<.0001**
Pair 2: Baseline vs 1 week follow up	-15.13	20.56	6.026	**.010**
Pair 3: End of treatment vs 1 week follow up	1.72	14.09	-.997	.323
PSS-4				
Pair 1: Baseline vs End of treatment	-.79	1.95	3.861	**<.0001**
Pair 2: Baseline vs 1 week follow up	-1.07	2.47	3.561	**.001**
Pair 3: End of treatment vs 1 week follow up	-.18	2.24	.654	.516

Paired sample t-test; p<0.05. Significant after Bonferroni correction in bold.

Table 5: Adverse events of (N=23) participants, n (%)

Adverse events	Active TMS	Sham TMS	Total
Mild headache	6 (26.1%)	1 (4.3%)	7 (30.4%)
Sleepiness	3 (13%)	2 (8.7%)	5 (21.7%)
Insomnia	1 (4.3%)	1 (4.3%)	2 (8.7%)
Tension	1 (4.3%)	1 (4.3%)	2 (8.7%)
Nausea	0 (0%)	1 (4.3%)	1 (4.3%)
Numbness on stimulation site	1 (4.3%)	0 (0%)	1 (4.3%)
Lightheadedness	1 (4.3%)	0 (0%)	1 (4.3%)
Coughiness	1 (4.3%)	0 (0%)	1 (4.3%)
Numbness on stimulation site & Forgetfulness	0 (0%)	1 (4.3%)	1 (4.3%)
Numbness on stimulation site & Sleepiness	1 (4.3%)	0 (0%)	1 (4.3%)
Mild headache & Sleepiness	1 (4.3%)	0 (0%)	1 (4.3%)
Total adverse events	**16 (69.6%)**	**7 (30.4%)**	**23 (100%)**

TMS, Transcranial Magnetic Stimulation.

Supplementary Material

The MagVenture Cool-B65 Active/Placebo (A/P) coil

The Cool-B65 Active/Placebo (A/P) coil is designed to support true "double blinded" clinical trials as it can produce active and placebo stimulation by flipping the coil and can mimic a tapping sensation during placebo condition (MagVenture, 2018). Using a randomization code, the TMS operator obtains information from the MagPro, which shows either "Flip Coil" or "Coil Ready". Thus, the TMS operator is blinded to the treatment condition.

During the placebo condition, the coil produces the same sound and only a very small amount of current is induced in tissue, and thus no skin-sensation is present. To do so, a low intensity current stimulator is built into the A/P coils and a pair of surface electrodes are placed just below the hairline on the scalp of every participant. Using the surface electrodes, the participant has a similar skin-sensation as in the real active condition.

Resting Motor Threshold (rMT)

The rMT is the amount of machine output (intensity) required to elicit a motor-evoked potential (MEP) in 50% of all attempts (Borckardt et al., 2006). There were no statistically significant differences between the three groups in terms of rMT as determined by a one-way ANOVA, $F_{(2,86)}=1.060$, $p=.351$ (TMS-N group: 44.73 ± 55.41; TMS-S group: 44.84 ± 57.62, sham group: 42.69 ± 55.25).

Beam_F3 Locator Software

Beam_F3 Locator software was used to locate the left DLPFC. This locator software is an efficient and accurate method to mark the F3 position according to the 10-20 EEG system (Beam et al., 2009). Three main measurements are required for the determination of the F3 position: nasion to inion, tragus to tragus and head circumference.

Cronbach's alpha

Cronbach's alpha measure was used to assess the internal consistency ("reliability") of the three self-reported questionnaires (FTND, TCQ-SF, PSS-4). Data analysis showed that our version of TCQ-SF had excellent internal consistency (Cronbach's α=.90). Also, results showed that FTND and PSS-4 had internal consistency of Cronbach's α=.65 and α=.62, respectively.

Enrollment

A total of 159 cigarettes smokers, who wanted to quit smoking, were enrolled, out of which 104 (65.41%) were meeting the inclusion criteria and were randomly divided into the three experimental groups. 5 (14.71%) participants in the TMS & N group, 3 (9.09%) participants in the TMS & S group and 7 (18.92%) participants in the Sham group dropped out during the 5-day treatment period. The data of the participants who dropped out during the treatment (n=15) were removed from the final analysis.

Supplementary Tables

sTable 1: Means and standard deviations

Self-reported cigarette consumption					
	Baseline	*After Day 1*	*After Day 2*	*After Day 3*	*After Day 4*
TMS&N group	27.55(15.37)	8.72(8.97)	7.94(8.13)	5.92(6.68)	5.27(7.51)
TMS&S group	26.83(12.86)	8.67(8.56)	7.07(6.43)	7.79(8.61)	4.67(6.50)
Sham group	30.00(13.38)	10.60(7.49)	9.38(7.90)	8.20(7.80)	6.27(7.84)

CO (mean)						
	Baseline	*Day 1*	*Day 2*	*Day 3*	*Day 4*	*Day 5*
TMS&N group	23.64(14.68)	19.09(12.14)	11.09(9.69)	9.98(10.15)	8.35(8.44)	8.98(9.68)
TMS&S group	17.24(10.17)	14.83(8.47)	9.94(8.17)	9.61(6.63)	8.58(6.65)	8.03(7.27)
Sham group	21.13(9.63)	17.77(7.88)	11.03(7.50)	8.85(6.58)	8.89(6.96)	8.18(7.02)

FTND			
	Baseline	*End of treatment*	*1-week follow up*
TMS&N group	5.86(2.26)	2.31(2.62)	1.79(1.55)
TMS&S group	6.03(2.37)	2.03(2.08)	2.04(2.49)
Sham group	6.77(2.27)	2.57(2.69)	2.64(2.41)

VAS (mean)						
	Baseline	*Day 1*	*Day 2*	*Day 3*	*Day 4*	*Day 5*
TMS&N group	24.21(30.64)	24.55(20.66)	15.62(16.69)	12.45(15.33)	9.16(13.12)	10.57(15.74)
TMS&S group	30.87(28.63)	33.13(22.12)	23.54(18.88)	22.32(19.87)	20.14(18.41)	16.08(16.14)
Sham group	25.70(30.42)	29.03(28.59)	21.87(24.12)	17.48(21.78)	14.44(19.18)	10.46(13.13)

TCQ-SF			
	Baseline	*End of treatment*	*1-week follow up*
TMS&N group	45.38(17.95)	30.93(17.05)	29.84(14.18)
TMS&S group	52.03(16.20)	31.97(14.61)	32.17(21.57)
Sham group	43.83(17.25)	28.63(13.10)	27.28(14.82)

PSS-4			
	Baseline	*End of treatment*	*1-week follow up*
TMS&N group	5.97(2.18)	5.21(2.47)	4.42(2.59)
TMS&S group	6.53(2.40)	5.90(2.34)	6.00(2.66)
Sham group	5.60(1.98)	4.60(1.96)	4.76(2.35)

Motivation to quit smoking			
	Baseline	*End of treatment*	*1-week follow up*
TMS&N group	77.78(21.18)	82.41(20.59)	72.37(23.41)
TMS&S group	82.41(18.10)	84.26(19.79)	77.17(30.07)

| Sham group | 80.83(20.43) | 80.83(23.38) | 75.00(27.95) |

Data are means (standard deviation), averaged over all participants per group.

sTable 2: Correlations between CO-measured and self-reported nicotine consumption

		N	*r* value	*p* value
CO Day 1 (mean)	Cigarettes smoked baseline	89	.469	<.0001
CO Day 2 (mean)	Cigarettes smoked after Day 1	89	.756	<.0001
CO Day 3 (mean)	Cigarettes smoked after Day 2	86	.643	<.0001
CO Day 4(mean)	Cigarettes smoked after Day 3	82	.752	<.0001
CO Day 5 (mean)	Cigarettes smoked after Day 4	83	.671	<.0001

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CHAPTER 3

Accelerated Intermittent Theta Burst Stimulation in Smoking Cessation: No Differences Between Active and Placebo Stimulation When Using Advanced Placebo Coil Technology. A double-blind follow-up study.

Abstract

Objective: This study aims to investigate the longer-term effects of accelerated intermittent theta burst stimulation (aiTBS) in smoking cessation and to examine whether there is a difference in outcome between active and placebo stimulation. The present study constitutes an ancillary study from a main Randomized Controlled Trial (RCT) evaluating the acute effects of aiTBS in smoking reduction.

Method: A double-blind randomized control trial was conducted where 89 participants were randomly allocated to three groups (transcranial magnetic stimulation (TMS)&N group: active aiTBS stimulation combined with neutral videos; TMS&S group: active aiTBS stimulation combined with smoking-related videos; Placebo group: placebo stimulation combined with smoking-related videos). Nicotine dependence, tobacco craving, perceived stress and motivation to quit smoking were measured after completion of 20 aiTBS sessions and during various follow ups (post one week, post one month and post six months).

Results: Our results show that the positive effect on nicotine dependence and tobacco craving that occurred at the end of treatment lasts at least one month post treatment. This effect seems to dissipate six months post treatment. No significant differences were found between the three groups.

Conclusion: Both active and placebo stimulation were equally effective in reducing nicotine dependence and tobacco craving up to one month after the end of treatment..

Introduction

Tobacco use is a leading cause of various health problems and premature death (WHO, 2021). Nicotine is a highly addictive chemical in tobacco which makes smoking cessation difficult for many smokers (FDA, 2022). In addition to first line tobacco cessation medication such as nicotine replacement therapy (Silagy et al., 2004), alternative and effective treatment methods are offered to support smoking cessation, including noninvasive brain stimulation technologies. Transcranial magnetic stimulation (TMS) is one of these noninvasive brain stimulation techniques representing a versatile intervention that has shown to be clinically effective in various contexts (Klomjai et al., 2015; Mikellides et al., 2021; Pell et al., 2011). Through electromagnetic induction, time-varying magnetic fields are created via an insulated electromagnetic coil placed over a specific area of the scalp (Koutsomitros et al., 2021). These magnetic fields or pulses then pass transcranially through the intact scalp to induce an electric current in the targeted neural tissue (Klomjai et al., 2015; Schilberg et al., 2021). In repetitive transcranial magnetic stimulation (rTMS) electromagnetic pulses are produced repeatedly and can modulate cortical excitability beyond the stimulation period itself (Pell et al., 2011) with low frequency rTMS generally reducing cortical excitability, whereas high frequency rTMS tends to increase cortical excitability of the stimulated brain region (Pell et al., 2011). The more recently introduced Theta Burst Stimulation (TBS) protocols have been shown to be capable of inducing longer lasting neuroplastic changes with intermittent TBS (iTBS) increasing and continuous TBS (cTBS) reducing cortical excitability (Chung et al., 2015; Huang et al., 2005; Schilberg et al., 2017; Thomson et al., 2020). For clinical purposes, TBS is especially interesting, as it provides a much faster brain stimulation intervention, allowing to modulate neuroplasticity based on much shorter stimulation durations as compared to standard rTMS protocols (Schilberg et al., 2017). The accelerate form of iTBS has gained popularity recently, providing multiple sessions within a day to reduce overall treatment duration. An RCT study by Duprat et al. (2016) found that 20 iTBS sessions spread over 4 days at five sessions per day, lead to clinical response in patients with treatment resistant depression (TRD) (Duprat et al., 2016).

The dorsolateral prefrontal cortex (DLPFC) is a frontal brain region involved in executive functions such as inhibitory control as well as reward processing (Feil et al., 2010). These processes are implicated in smoking craving, making DLPFC a potential target region in non-invasive brain stimulation treatments (Yuan et al., 2017). High frequency (HF) - rTMS over the left DLPFC has shown promising results in reducing nicotine craving and cigarette consumption (Amiaz et al., 2009; Hauer et al., 2019; Li et al., 2020). In 2020, the FDA cleared the BrainsWay deep TMS system for its use as an aid in short-term smoking cessation in adults (BrainsWay, 2020). Exposure to smoking related cues has been shown to activate the DLPFC (Brody et al., 2002). Also, the combination of HF- deep TMS treatment and presentation of smoking cues was

shown to reduce cigarette consumption with high and long lasting abstinence (Dinur-Klein et al., 2014).

We recently conducted a double-blind randomized control trial to evaluate the effect of active and placebo accelerated intermittent theta burst stimulation (aiTBS) (4 sessions per day for 5 consecutive days) over the left DLPFC in smoking cessation and the impact of smoking-related or neutral cues, during the stimulation, in treatment outcome (Mikellides et al., 2022). The study participants were divided into three groups (TMS&N group: active aiTBS stimulation combined with neutral videos; TMS&S group: active aiTBS stimulation combined with smoking-related videos; Placebo group: placebo stimulation combined with smoking-related videos). Simultaneously with the rTMS treatment, participants were instructed to pay attention to videos that were presented on a monitor placed opposite the treatment chair. Two different forms of videos were used (smoking related videos, e.g. a person smoking cigarette in a restaurant, and neutral videos, e.g. a man cleaning his shoes) in order to either or not induce a state of craving at the time of stimulation. Results showed that the main effect of treatment time was statistically significant, indicating a significant reduction of cigarette consumption, nicotine dependence, craving and perceived stress in all treatment groups, which was maintained for at least a week after the end of treatment. Nevertheless, the type of treatment group and/or the interaction effect between treatment time and treatment group were not statistically significant. Thus, the results showed that both, active as well as placebo stimulation, did not affect immediate treatment outcome (Mikellides et al., 2022).

TMS-induced neuroplastic changes take time to develop and differences between active and placebo stimulation may become stronger and more visible when looking at prolonged effects (Cirillo et al., 2017). The current study investigated, in a double-blind randomized control trial using several follow up measurements, the long-term effects of rTMS in smoking cessation. Also, we examined whether there is a difference in outcome between active and placebo stimulation, combined with smoking-related or neutral cues. We hypothesized that a positive prolonged effect would be observed in the Active TMS groups while relapse would be observed in the Placebo TMS group, because the immediate and acute placebo effects should wear off over time, since no neuroplastic changes should have been induced.

Methods

STUDY DESIGN & PARTICIPANTS

Detailed methods of our randomized controlled trial (RCT) have been reported previously (Mikellides et al., 2022). We performed a multi-arm parallel group, double-blinded, randomized, controlled study, where eighty-nine participants were randomly allocated into

three groups: the first group received active aiTBS stimulation combined with neutral videos (TMS&N), the second group received active aiTBS stimulation combined with smoking-related videos (TMS&N) and the last group received placebo stimulation (Placebo) combined with smoking-related videos. Participants were aware that there was a 1/3 chance of receiving placebo stimulation but were otherwise blinded to the treatment condition. All patients were TMS naïve and due to the between-subject design had no means to directly compare different TMS conditions.

Eligibility criteria included participants aged 18-70 who were native or fluent Greek speakers. Exclusion criteria included mental objects or implants in the brain, skull or near head (e.g., pacemakers, metal plates), past or current of diagnosis of neurological or psychiatric disorder, use of psychiatric medication, past or current drug or alcohol abuse (other than nicotine), and use of IQOS ("I Quit Original Smoking") or electronic cigarettes (e-cigarettes).

A total of 89 participants completed the treatment program (60 males; age 45.62 ± 13.42 years). The experiment was carried out at the Cyprus rTMS Center in Larnaca, Cyprus. This study was approved by the Cyprus National Bioethics Committee and written informed consent was obtained from all participants (ΕΕΒΚ/ΕΠ/2019/08) (ClinicalTrials.gov Identifier: NCT05271175).

INTERMITTENT THETA BURST STIMULATION

An accelerated iTBS (aiTBS) treatment comprised 20 sessions in total. Four iTBS sessions were administrated per day, with a 30 minutes break between them, during a 5-day period using a MagPro X100 stimulator (MagVenture, Farum, Denmark). The standardized stimulation localization was over the left DLPFC, determined using the Beam_F3 Locator software (https://www.clinicalresearcher.org/software.htm). A figure-of-eight coil (Coil Cool-B65 A/P) was placed at a 45° angle of the midline over the 10-20 EEG position F3. We applied an iTBS protocol, consisting of triplets of 50Hz that were repeated in a 5Hz rhythm for 2 seconds, followed by an inter train interval of 8 seconds, for a total of 20 trains. A total number of 600 pulses was given per session for 3:08 minutes (Blumberger et al., 2018; Huang et al., 2005). Before the first session, the resting Motor Threshold (rMT) was determined using the Coil C-B60 TMS coil. Stimulation was performed at 100% of rMT.

MEASUREMENTS

Participants were asked to complete three self-reported questionnaires:

(1) The Fagerström test for Nicotine Dependence (FTND) (Heatherton et al., 1991) to assess nicotine dependence. The FTND is a short, self-report measure that contains six questions, and the total score is calculated as a sum of these six questions. The total scores of the questionnaire vary from 0 to 10, with lower scores indicating lower dependence on nicotine.

(2) the Tobacco Craving Questionnaire–Short Form (TCQ-SF) (Heishman et al., 2008) to assess tobacco craving. The TCQ-SF is a self-report measure that assesses tobacco craving in four dimensions: emotionality, expectancy, compulsivity, and purposefulness. Each factor scale contains three items. TCQ-SF items were rated on a Likert scale of 1 (strongly disagree) to 7 (strongly agree). Total scores vary from 12 to 84. A high score indicates high tobacco craving.

(3) the Perceived Stress Scale-4 (PSS-4) (Cohen & Williamson, 1988) to assess perceived stress. The PSS-4 is a self-report measure that contains four items which were rated on a Likert scale, ranging from 0 to 4, with those on the positive subscale scored in reverse and the total score being calculated as a sum of these items. The scores vary from 0 to 16, with a higher score indicating higher perceived stress.

Finally, participants were asked to estimate how motivated they were to quit smoking from 0% to 100% using a Visual Analogue Scale.

These three questionnaires and the Motivation to quit smoking were administered to participants at baseline, at the end of treatment (on the fifth day), one week post treatment, one month post treatment and six months post treatment. Participants completed the questionnaires by hand at baseline and at the end of the treatment, and then via phone during the follow ups (post one week, post one month and post six months, see Figure 1). All participants who completed the study (n=89) were asked to complete the post one-week follow up, post one-month follow-up and post six-months follow up, regardless of whether they completed the previous follow ups. No extra sessions of iTBS were performed in any of the follow-up phases.

DATA ANALYSIS

SPSS software version 27.0 was used for the statistical analysis of the data (IBM corporation, Endicott, New York). One-way ANOVAs and Pearson chi-square tests were used to test for differences in baseline demographic and smoking-related variables between the completers and dropouts in post one week follow up, post one month follow up and post six months follow up. Mixed factorial ANOVAs were conducted to investigate the effect of both the within factor (Time: end of treatment, post one week follow up, post one month follow up, post six months follow up) and the between factor (Group: TMS&N, TMS&S, Placebo). The dependent variables used for each model were: nicotine dependence, tobacco craving, and perceived stress.

Greenhouse–Geisser and Huynh–Feldt degree of freedom corrections were applied to correct for the non-sphericity of the data. Non-parametric tests were used as the variable Motivation to quit smoking was not normally distributed at all time-point assessments. Kruskal-Wallis H tests were conducted to compare the mean scores of motivation to quit of the three groups at different timepoints. Non-parametric Friedman Tests were used to determine whether there is a statistically significant difference between the means of the four timepoints. Post hoc Wilcoxon signed-rank tests were conducted to evaluate the significance of mean change in Motivation to quit smoking scores between different time points. Missing data were excluded from the final analyses. A significance level was set at α=.05 for all analyses.

Results

STUDY FLOW

A total of 89 participants completed the 5-day treatment program (60 male and 29 female; age 45.62 ± 13.42 years), of which 59 received active stimulation and 30 received placebo stimulation. Sixty-seven of the participants (65.5% of the TMS & N group, 76.7% of the TMS & S group and 83.3% of the Placebo group) completed the post one-week follow-up, 61 of the participants (58.6% of the TMS & N group, 76.7% of the TMS & S group and 70.0% of the Placebo group) completed the post one-month follow-up and 77 of the participants (72.5% of the TMS&N group, 93.3% of the TMS&S group and 93.3% of the Placebo group) completed the post six-months follow-up. Figure 1 shows the study flow. Table 1 shows the comparison of the baseline and smoking-related characteristics of dropouts and completers during the follow ups. The data suggests that completers did not differ significantly from dropouts in demographic characteristics across all follow ups (see Table 1). Regarding smoking-related characteristics, completers of post one week follow up were more likely to have quitted smoking in the past compared to dropouts and completers of post six months follow up were more likely to be smokers for more years compared to dropouts. No significant differences were found in the remaining smoking-related variables (Table 1).

PRIMARY OUTCOMES

Nicotine dependence

A 4 (Time: end of treatment, post one week follow up, post one month follow up, post six months follow up) X 3 (Group: TMS&N, TMS&S, Placebo) mixed factorial ANOVA was conducted

as measured by the FTND. Mauchly's test indicated that the assumption of sphericity had been violated, *χ2(5) =24.693, p<0.001*, therefore degrees of freedom were corrected using Greenhouse-Geisser of sphericity (ε=.774). The interaction effect between Time and Group was not statistically significant, *F(4.642,97.473)=.478, p=.778, ηp2=.022*. There was a statistically significant main effect of Time, *F(2.321,97.473)=11.153, p<0.0001, ηp2=.210* but no significant effect of Group, *F(2,42)=.673, p=.516, ηp2=.031* (see Table 2 for means and standard deviations) (Figure 2). Post-hoc pairwise comparisons using the Bonferroni correction revealed that nicotine dependence was significantly increased in post one month follow up (M=2.87, SD=2.67) compared to post one week follow up (M=2.02, SD=2.32) and in post six months follow up (M=3.58, SD=2.78) compared to the end of treatment and post one week follow up (M=2.02, SD=2.32) (Table 3).

Tobacco craving

A 4 (Time: end of treatment, post one week follow up, post one month follow up, post six months follow up) X 3 (Group: TMS&N, TMS&S, Placebo) mixed factorial ANOVA was conducted as measured by the TCQ-SF. Mauchly's test indicated that the assumption of sphericity had been violated in both situations, *χ2(5) =25.824, p<0.001*, therefore degrees of freedom were corrected using Huynh–Feldt of sphericity (ε=.821). The interaction effect between Time and Group was not statistically significant, *F(4.925,103.435)=1.042, p=.397, ηp2=.047.* There was a statistically significant main effect of Time, *F(2.463,103.435)=12.175, p<0.0001, ηp2=.225.* However, there was no significant effect of Group, *F(2,42)=.643, p=.531, ηp2=.030* (see Table 2 for means and standard deviations) (Figure 2). Post-hoc pairwise comparisons using the Bonferroni correction indicated that tobacco craving was significantly increased in the post six months follow up (M=44.11, SD=22.64) compared to the end of the treatment (M=28.33, SD=15.57), post one week follow up (M=29.13, SD=18.45) and post one month follow up (M=32.60, SD=19.62) (Table 3).

SECONDARY OUTCOMES

Perceived stress

A 4 (Time: end of treatment, post one week follow up, post one month follow up, post six months follow up) X 3 (Group: TMS&N, TMS&S, Placebo) mixed factorial ANOVA was conducted as measured by PSS-4. The interaction effect between Time and Group, *F(6,126),=.510, p=.800, ηp2=.024*, as well as the main effect of Time, *F(3,126)=1.187, p=.317, ηp2=.027,* and the effect of Group, *F(2,42)=1.389, p=.260, ηp2=.062*, were not statistically significant (Figure 2).

Motivation to quit smoking

Kruskal-Wallis H tests showed that there were no statistically significant differences in Motivation scores between the three groups during all the time points, except of the post six months follow up where there was a statistically significant difference, *H(2)=6.803, p=.033*, with a mean rank of 30.74 for TMS&N group, 46.88 for TMS&S group and 37.32 for Placebo group. Comparison of the repeated measures was performed using Friedman's test showing a statistically significant difference across the sample, *χ2(3)=18.079, p= p<0.0001* (Figure 2). Post-hoc analysis with Wilcoxon signed-rank tests were conducted, to evaluate the significance of mean change in Motivation to quit smoking scores between different time points. A significant decrease was seen in all the pairs, except of the pair post one month follow up vs post six months follow up where no statistically significant differences were found (Table 4).

Discussion

This study sought to evaluate the long-term effects of aiTBS in smoking cessation. We hypothesized that active TMS leads to a positive prolonged effect compared to placebo TMS. However, the findings of the current study do not support this hypothesis. In fact, the positive effect of the treatment on nicotine dependence and tobacco craving lasted at least up one month post treatment, independent of the treatment condition. After 6 months, this effect was gone in all groups.

The findings of the current study do not support previous findings. Earlier studies using HF-rTMS over the left DLPFC, have found a significant reduction of cigarette consumption in active TMS groups compared to placebo TMS groups at the end of treatment, which lasted three weeks up to one month post treatment (Huang et al., 2016; Li et al., 2020; Prikryl et al., 2014). Also, the outcome of the present study is contrary to that of recent study who found a reduction in nicotine dependence and tobacco craving at the end of treatment in both the HF-rTMS active and placebo groups, but during the 3 months follow up this improvement was persistent only in the active group (Abdelrahman et al., 2021). On the other hand, our post 6 months follow up results are in line with those of Amiaz et al. (2009), where no significant differences were found between active and placebo TMS groups in nicotine dependence and craving six months post treatment. Finally, it is clear from the results that the type of video did not affect the treatment outcome. This result is consistent with a previous study showing that exposure to smoking-related cues had no effect on nicotine consumption and nicotine dependence (Amiaz et al., 2009).

Contrary to the expectations, all treatment conditions lead to significant reduction in nicotine dependence and tobacco craving, which lasted at least one month post treatment. This pattern of results is consistent with previous literature on chronic headaches and post-stroke rehabilitation, which reports that the placebo effect of rTMS treatment persists at least 3 months after treatment (Granato et al., 2019; Jin et al., 2021). Large placebo effects appear in pharmacological as well as in neurostimulation and surgical trials (Brunoni et al., 2009; Vase & Wartolowska, 2019). Placebo effects are a very common phenomenon in TMS practice and can be considerably large and even equal to the effect achieved with active TMS stimulation, which may influence the clinical results obtained with TMS (Kaptchuk et al., 2000; Mansur et al., 2011; Razza et al., 2018). Several factors of a TMS treatment may contribute to enhanced placebo effects such as the interaction with the TMS technician, the TMS device, or realistic placebo coils (Burke et al., 2019).

Different placebo TMS approaches can be used to achieve a placebo condition in TMS , aiming to mimic the auditory and somatosensory experience of active TMS without brain stimulation (Duecker & Sack, 2015). The use of electrical stimulation in combination with a placebo TMS coil has been reported as an effective TMS approach to achieve placebo condition (Duecker & Sack, 2015). In Mikellides and colleagues study (2022), both, active and placebo, stimulation were performed using an advanced double blind placebo stimulation technology, the figure-of-eight coil (Coil Cool-B65 A/P), which is capable to mimic both, the visual and auditory experience of active TMS as well as similar somatosensory skin sensation. Using a low intensity current stimulator built into the coil and a pair of surface electrodes placed just below the hairline on the scalp of each participant, this coil is designed to support true "double blinded" clinical trials as it can produce active and placebo stimulation by flipping it. The use of a novel and advanced placebo coil technology in Mikellides et al (2022) study may contribute to the fact both active and placebo stimulation were highly effective in reducing cigarette consumption and craving.

The placebo effect was also shown to be larger in more intense TMS protocols and especially accelerated protocols (Baeken et al., 2013). The current study confirmed the findings of Baeken (2018), reporting no clinical differences between the placebo and active accelerated treatments (accelerate HF-rTMS and accelerate iTBS) in refractory MDD patients (Baeken, 2018). In a similar vein, no statistically significant effects were found between placebo and active stimulation on depression severity symptoms following aiTBS (Duprat et al., 2016). On the contrary, the Stanford neuromodulation therapy (SNT) protocol, an FDA cleared, accelerated iTBS protocol, was found to be more effective compared to placebo stimulation in treatment resistant depression (TRD) (Cole et al., 2022). It is currently unclear why the SNT protocol showed so small placebo effects as compared to other studies. Maybe the small and selective

sample or the very short treatment duration of 5 days only in the SNT study contributed to this discrepancy.

In the present study, nicotine dependence and tobacco craving increased at post 6 months follow up. The observed increase could be attributed to the outbreak of the COVID-19 pandemic that started in March 2020 and included prolonged periods of lockdown mandates. Almost all data of post 6 months follow up were obtained in the period April-June 2020, a period related to the first lockdown in Cyprus, which was followed by strict guidelines and measures (Stylianou et al., 2020). As mentioned in the literature, the COVID-19 lockdown was associated with an increase in cigarette consumption in European countries as a result of the social isolation (Malta et al., 2021; Vanderbruggen et al., 2020). Nevertheless, the outbreak of COVID-19 may be a possible factor for the increase in nicotine dependence and tobacco craving in the present study, but this cannot be statistically substantiated. Another possible explanation for this increase during the post 6 months follow up may be the absence of maintenance sessions after the completion of the treatment period. Maintenance after a successful response to rTMS treatment can contribute in preventing relapse (Rachid, 2018). However, the optimal stimulus parameters for maintenance rTMS remain unclear (Rachid, 2018).

Some potential limitations of this double-blind follow-up study need to be acknowledged. For instance, participants were not asked to avoid receiving any other form of smoking cessation treatments or interventions during the follow-ups. Therefore, we have no information on whether their clinical condition remained stable throughout the follow-up period and whether our findings are due to the rTMS treatment alone. Secondly, cigarette consumption in numeric values was not measured during the follow up phase. Additionally, all data were collected via phone calls through self-reported questionnaires which may have affected the accuracy and reliability of the assessment. We did not use objective measures of nicotine consumption (e.g., breath carbon monoxide meter device) during the follow ups.

Conclusion

In summary, our results demonstrate that both active and placebo stimulation were equally effective in reducing nicotine dependence and tobacco craving up to one month after the end of treatment. Placebo effect should be considered a major source of bias in the assessment of rTMS efficacy.

Table 1: Demographic and smoking related characteristics of completers and dropouts

Characteristics	POST ONE WEEK FOLLOW UP			POST ONE MONTH FOLLOW UP			POST SIX MONTHS FOLLOW UP		
	Completers n=67	Dropouts n=22	*p* values	Completers n=61	Dropouts n=28	*p* values	Completers n=77	Dropouts n=12	*p* values
Demographic									
Age (yr)	46.10 ±13.81	44.14±12.31	.554[a]	47.39 ±14.02	41.75±11.29	.065[a]	46.45 ±13.58	40.25±11.37	.137[a]
Gender (M/F)	43/24	17/5	.256[b]	41/20	19/9	.952[b]	52/25	8/4	.953[b]
Education (yr)	13.82±3.73	14.68±3.43	.341[a]	13.85±3.62	14.43±3.77	.493[a]	14.00±3.72	14.25±3.36	.827[a]
Occupation*			.264[b]			.683[b]			.828[b]
Private employee	41 (61.2%)	13 (59.1%)		35 (57.4%)	19 (67.9%)		47 (61.0%)	7 (58.3%)	
Public employee	6 (9.0%)	6 (27.3%)		9 (14.8%)	3 (10.7%)		9 (11.7%)	3 (25.0%)	
Self-employed/ Freelancer	8 (11.9%)	2 (9.1%)		6 (9.8%)	4 (14.3%)		9 (11.7%)	1 (8.3%)	
Unemployed	3 (4.5%)	0 (0.0%)		2 (3.3%)	1 (3.6%)		3 (3.9%)	0 (0.0%)	
Retired	8 (11.9%)	1 (4.5%)		8 (13.1%)	1 (3.6%)		8 (10.4%)	1 (8.3%)	
Student	1 (1.5%)	0 (0.0%)		1 (1.6%)	0 (0.0%)		1 (1.3%)	0 (0.0%)	
Smoking-related									
Cigarettes per day	26.73±13.10	32.41±15.29	.094[a]	27.20±13.20	30.18±15.08	.347[a]	28.13±12.83	28.17±19.65	.993[a]
Types of cigarettes*			.353[b]			.349[b]			.699[b]
Normal	50 (74.6%)	15 (68.2%)		47 (77.0%)	18 (64.3%)		57 (74.0%)	8 (66.7%)	
Hand-rolled	15 (22.4%)	5 (22.7%)		12 (19.7%)	8 (28.6%)		16 (20.8%)	4 (33.3%)	
Cigarillos	0 (0.0%)	1 (4.5%)		0 (0.0%)	1 (3.6%)		1 (1.3%)	0 (0.0%)	
Mixed	2 (3.0%)	1 (4.5%)		2 (3.3%)	1 (3.6%)		3 (3.9%)	0 (0.0%)	
Years of smoking	25.62±12.90	23.36±9.72	.454[a]	26.10±13.27	22.82±9.21	.184[a]	25.89±12.66	19.75±6.57	.016[a]
If ever quitted*			.017[b]			.451[b]			.179[b]
No	18 (26.9%)	12 (54.5%)		19 (31.1%)	11 (39.3%)		28 (36.4%)	2 (16.7%)	
Yes	49 (73.1%)	10 (45.5%)		42 (68.9%)	17 (60.7%)		49 (63.6%)	10 (83.3%)	
How many times quitted	1.190±1.28	0.55±0.67	.026[a]	1.05±1.20	1.00±1.19	.858[a]	1.03±1.25	1.08±0.79	.878[a]

Data are means ± standard deviation. *n(%); [a]Independent sample t-test; [b]Pearson chi-square test. TMS, Transcranial Magnetic Stimulation.

Table 2: Means and standard deviations

	End of treatment	Post one week follow up	Post one month follow up	Post six months follow up
FTND				
TMS & N	2.31 (2.62)	1.79 (1.55)	3.35 (1.97)	3.71 (2.43)
TMS & S	2.03 (2.08)	2.04 (2.50)	2.78 (2.80)	3.32 (2.74)
Placebo	2.57 (2.69)	2.64 (2.41)	3.38 (2.84)	3.96 (2.57)
TCQ-SF				
TMS & N	30.93 (17.05)	29.84 (14.18)	37.06 (17.94)	51.52 (19.50)
TMS & S	31.97 (14.61)	32.17 (21.57)	30.61 (19.63)	38.32 (18.22)
Placebo	28.63 (13.10)	27.28 (14.82)	35.24 (20.63)	44.68 (22.34)
Motivation to quit smoking				
TMS & N	82.41 (20.59)	72.37 (23.41)	47.06 (31.72)	41.67 (34.76)
TMS & S	84.26 (19.79)	77.17 (30.07)	70.65 (37.43)	67.86 (32.53)
Placebo	80.83 (23.38)	75.00 (27.95)	52.38 (38.65)	52.68 (34.92)

Data are means (standard deviation), averaged over all participants per group. FTND, Fagerström test for Nicotine Dependence; TCQ-SF, Tobacco Craving Questionnaire–Short Form.

Table 3: Pairwise Comparisons

	FTND			TCQ-SF		
Pairs	**Mean change**	**Standard Error**	**p value**	**Mean change**	**Standard Error**	**p value**
EndOfTreatment - PostOneWeekFollowUp	-.001	.270	1.000	1.466	2.174	1.000
EndOfTreatment - PostOneMonthFollowUp	.882	.361	.113	4.919	2.855	.553
EndOfTreatment - PostSixMonthsFollowUp	1.554	.391	.002	16.402	3.588	<0.0001
PostOneWeekFollowUp - PostOneMonthFollowUp	.882	.222	.002	3.453	2.069	.616
PostOneWeekFollowUp - PostSixMonthsFollowUp	1.555	.343	<0.0001	14.936	3.629	.001
PostOneMonthFollowUp - PostSixMonthsFollowUp	.673	.300	.183	11.483	3.345	.008

FTND, Fagerström test for Nicotine Dependence; TCQ-SF, Tobacco Craving Questionnaire–Short Form. p<0.05. Adjustment for multiple comparisons: Bonferroni

Table 4: Results of Wilcoxon signed-rank tests for Motivation to quit smoking scores

Pairs	Mean change	Z value	p value
EndOfTreatment - PostOneWeekFollowUp	-8.33	-3.136	.002
EndOfTreatment - PostOneMonthFollowUp	-25.86	-4.461	<.0001
EndOfTreatment - PostSixMonthsFollowUp	-28.38	-5.058	<.0001
PostOneWeekFollowUp - PostOneMonthFollowUp	-13.02	-2.633	.008
PostOneWeekFollowUp - PostSixMonthsFollowUp	-18.10	-3.149	.002
PostOneMonthFollowUp - PostSixMonthsFollowUp	-2.59	-.460	.646
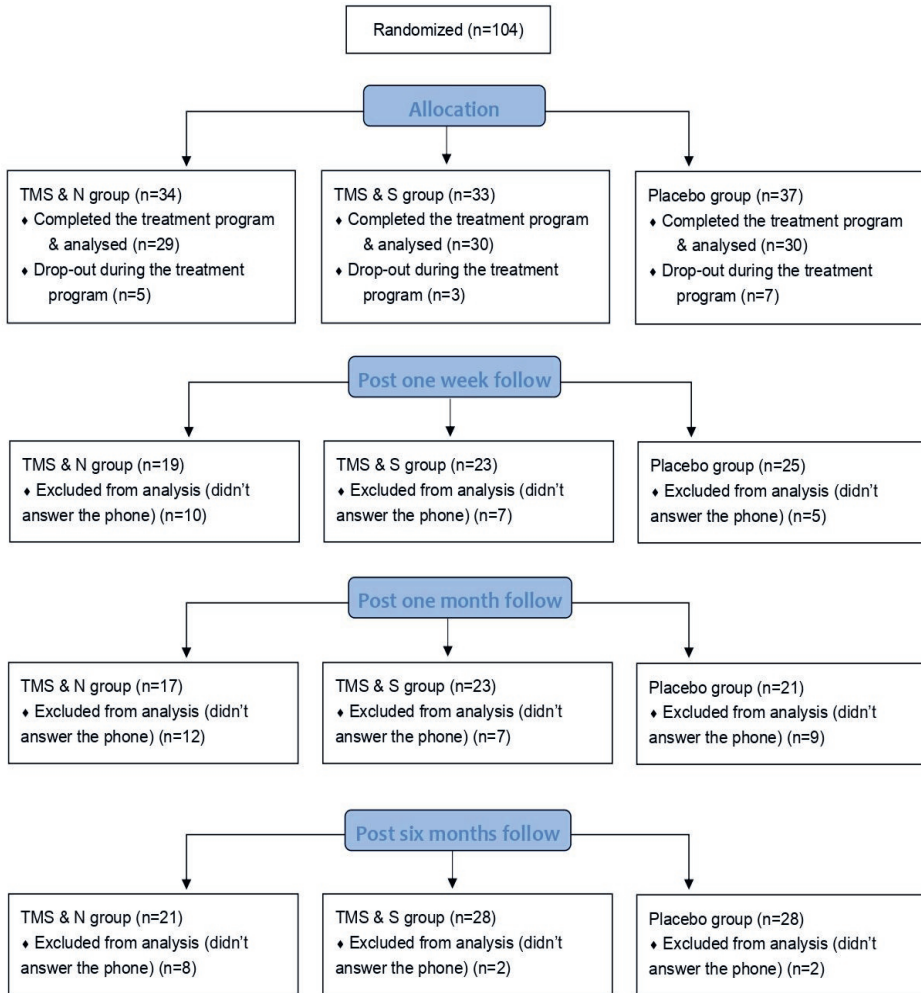
Figure 1: Study flow
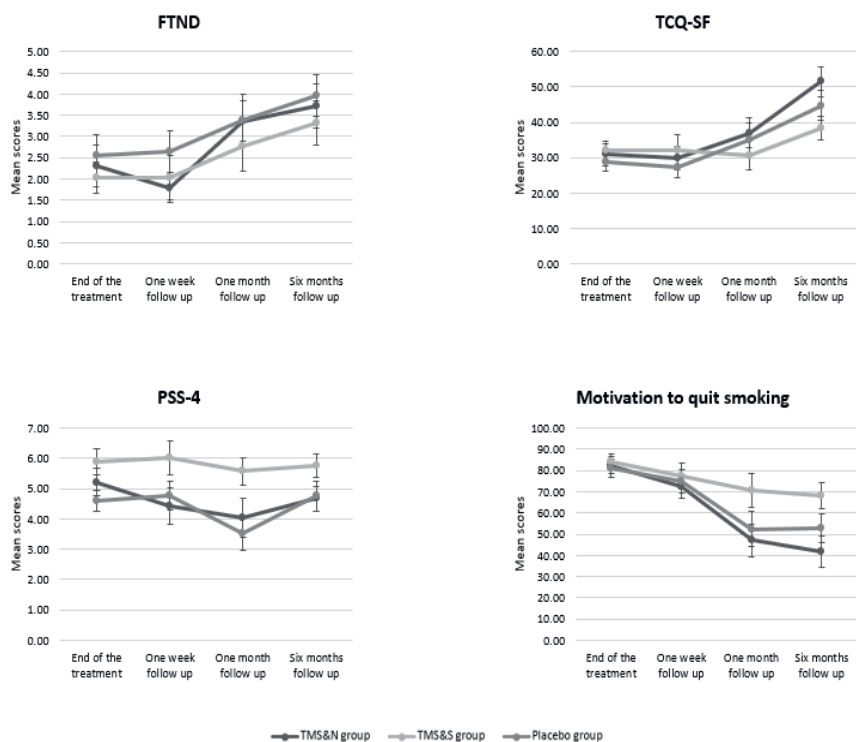
Figure 2: Line graphs showing FTND, PSS-4, TCQ-SF and Motivation to quit smoking scores over time. Data are presented as mean ± SEM

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CHAPTER 4

A retrospective naturalistic study comparing the efficacy of ketamine and repetitive transcranial magnetic stimulation in the acute treatment of depression

Abstract

Depression is a common mental disorder that affects many people worldwide, while a significant proportion of patients remain non-responsive to antidepressant medications. Alternative treatment options such as ketamine therapy and repetitive transcranial magnetic stimulation (rTMS) therapy are offered nowadays. This study aims to describe and compare the acute antidepressive efficacy of both, intramuscular ketamine and rTMS in depression patients seeking help in a naturalistic clinical mental health setting. The clinical records of 24 patients with treatment resistant depression were collected from the clinical base of a real life clinic. Twelve patients were treated with intramuscular ketamine, twice weekly for 8 sessions, and twelve patients were treated with 30 sessions of left dorsolateral prefrontal cortex – intermittent theta-burst stimulation (DLPFC-iTBS). Using three clinical assessments (HDRS, HAM-A, BDI-II), our data reveal that both therapies led to significant improvement in symptoms from pre- to post- treatment, as well as that the two experimental groups did not differ significantly with respect to pre- to post- depressive and anxiety symptoms, indicating that the effect of both experimental groups in our sample was equally effective. Furthermore, our results showed high remission and response rates in both groups, with no statistical differences between the patients of ketamine group and rTMS group in remission and response rates. We show a significant pre- to post- treatment reduction in depressive and anxiety symptoms, with no significant differences between the two experimental groups, indicating that the effect of both therapies was equally effective in our limited sample.

Introduction

Depression is a common mental disorder that affects more than 264 million people worldwide, irrespective of age (WHO, 2020). Clinically effective first-line treatments include pharmacotherapy and psychotherapy. However, ~30% of depression patients remain non-responsive to antidepressant medications and are suffering from treatment resistant depression (TRD) (Conway et al., 2017; Souery et al., 2006). Conventionally, TRD is diagnosed when a patient is not experiencing any significant clinical improvement from at least two different methods of antidepressants (Little, 2009). TRD patients are therefore in need of new (non)pharmacological treatment alternatives.

In recent years, there has been a considerable interest in the use of ketamine as an antidepressant in humans. Ketamine is a racemic mixture of two enantiomers, S-ketamine (esketamine) and R-ketamine and the antidepressant properties of N-methyl d-aspartate (NMDA) receptor antagonists have received much attention in experimental animal studies several years ago (Marcantoni et al., 2020; Papp & Moryl, 1994). In patients suffering from TRD, the antidepressant effect of ketamine can be observed within a few hours following a single subanesthetic intravenous infusion (Murrough et al., 2013a). As reported by a two-site randomized controlled trial, a single infusion of ketamine was associated with greater improvement in the Montgomery Åsberg Depression Rating Scale (MADRS) score, compared to an active placebo control condition (anesthetic midazolam), 24 h after treatment (Murrough et al., 2013a). The administration of ketamine was not only found to be effective for treating depression, but also in bipolar disorder, as well as in suicidal ideation (Corriger & Pickering, 2019; Fond et al., 2014). Furthermore, repeated administration of ketamine may be associated with rapid, longer-term and sustained antidepressant effects (Kim et al., 2021; Murrough et al., 2013b). According to a recent article by Kim and colleagues (2021), methyl-CpG-binding protein 2 (MeCP2) phosphorylation at Ser421 (pMeCP2) plays a crucial role in the sustained antidepressant effects of ketamine in mice. The authors also found that repeated ketamine administration induces processes of metaplasticity through post-synaptic functional changes. This may explain why repeated intake of ketamine doses produce sustained effects (Kim et al., 2021).

As a drug with brief euphoric effects that may last from 1 to 2 h, ketamine must be administrated under controlled settings (Lee et al., 2015). The most common adverse effects of ketamine
administration are dizziness, drowsiness, poor coordination, blurring of vision, feeling strange, light-headedness, headache and nausea (Iqbal & Mathew, 2020).

Ketamine is associated with a robust increase in glutamate and dopamine release in the prefrontal cortex as well as with improvement in neuroplasticity within the hippocampus. Both

these brain regions play a crucial role in the pathophysiology of depression (Lacerda, 2020). The first randomized clinical trial (RCT) that aimed to assess the effectiveness of a single dose of an NMDA receptor antagonist in depressed patients showed a robust significant improvement in depressive symptoms within 3 days post ketamine (Berman et al., 2000). A recent review and meta-analysis highlighted the effectiveness of a single ketamine (0.5 mg/kg) infusion in reducing depression scores in TRD participants (Marcantoni et al., 2020). The impact of ketamine was found to be rapid, as the antidepressant effect was observed 4 h post-infusion. However, a subsequent reduction of this antidepressant effect of ketamine appeared 7 days post-infusion, so its effectiveness seems to be short-term (Marcantoni et al., 2020). In line with this, also other studies documented that the antidepressant effect of a single dose of ketamine typically vanishes after ca 7 days (Lee at al., 2015; Murrough et al., 2013a).

Ketamine can be delivered in several manners such as via intravenous (IV), intranasal, oral, sublingual, subcutaneous and intramuscular (IM) routes (Iqbal & Mathew, 2020). Only very few studies are available that investigated the potential use of IM ketamine delivery in the treatment of depression (Cusin et al., 2012; Harihar et al., 2013; Zanicotti et al., 2012). A recent study aimed to compare the safety, tolerability, and efficacy of IM and IV ketamine delivery in treatingmajor depression, showing that a small dose of IMketamine (0.25 mg/kg) is as effective and safe as a larger dose (0.5 mg/kg). No statistically significant differences were found between IM and IV groups. Reduction of HAM-A scores have been reported 2 h post ketamine in all groups and sustained for the following 3 days. The adverse effects were mild and subsided within an hour post ketamine (Chilukuri et al., 2014). Furthermore, 6 IV ketamine infusions over a 12-day period were associated with a large, sustained effect as the median time to relapse was 18 days (Murrough et al., 2013b).

The United States Food and Drug Administration (FDA) approved ketamine (ketalar) for human use for the first time in 1970 and more recently, in 2019, approved esketamine as an intranasal spray for the treatment of TRD in adults who have failed to receive sufficient improvements from other antidepressant medicines (FDA, 2019). However, the intranasal application of ketamine might not be the best treatment for TRD patients. According to a recent systematic review and metaanalysis, esketamine was found to be less effective, compared to racemic IV ketamine, in treating depression (Bahji et al., 2021). IV and IM administrations of ketamine were also found to be 100 and 93% bioavailable, respectively, in contrast to other routes of administration such as intranasal, which is only 8–45% bioavailable (Li & Vlisides, 2016). Medications with higher bioavailability could potentially be more effective. Furthermore, treatment using intranasal esketamine spray is more expensive compared to treatment using IV or IMketamine. Ketamine can be safely given through the IM route and has an easier access of administration than then IV route. In the present study, we therefor applied IM ketamine.

Another, fundamentally different treatment alternative for TRD that has received much attention in the literature is transcranial magnetic stimulation (TMS). TMS is a non-invasive brain stimulation method using the repetitive administration of electromagnetic pulses to targeted regions in the brain to modulate neural activity (Thomson et al., 2020). Repetitive TMS (rTMS) has been shown to lead to longer lasting neuroplastic changes with beneficial clinical effects across various neuropsychiatric disorders (Mikellides et al., 2021; Paes et al., 2011). rTMS is by now a clinically proven effective, widely recognized, approved and well-tolerated depression therapy in TRD patients (Carpenter et al., 2012; Daskalakis et al., 2008; George et al., 2013). The dorsolateral prefrontal cortex (DLPFC) is the most prominent and commonly used target area in rTMS treatment of depression (Baeken et al., 2019; Chou et al., 2021; Donse et al., 2018; Janical & Dokucu, 2015). TMS over the left DLPFC for several weeks been shown to be a safe and effective treatment for TRD (George et al., 2013), including often reported beneficial effects on psychomotor speed and cognitive control (Corlier et al., 2020). Furthermore, TMS over the left DLPFC is associated with improvements of suicidal ideation in adolescents with depression (Croarkin et al., 2018). One of the largest studies testing the effectiveness of rTMS in depression, the THREED study, documented clinically meaningful improvements in patient-reported outcomes (PROs), including quality-of-life (QOL), and disability post rTMS treatment (Giacobbe et al., 2020).

When targeting the DLPFC with TMS, different repetitive or patterned stimulation protocols can be applied. In addition to the standard high frequency 10Hz rTMS protocol administering 3,000 pulses in one of the in total 20–30 treatment sessions each lasting for ca 38min (O'Reardon et al., 2007), theta-burst stimulation (TBS) has more recently gained in popularity due to its much shorter treatment session duration. TBS mimics endogenous theta rhythms and has the ability to induce long-lasting effects on cortical excitability (Li et al., 2014; Trevizol et al., 2019). Intermittent TBS (iTBS) is one of the main patterns of TBS that have been developed, which increases cortical excitability (Chung et al., 2015), similar to high frequency 10Hz rTMS but in a much shorter time frame. According to a recent systematic review and meta-analysis, TBS over DLPFC is well-tolerated and has significant antidepressant effects (Chu et al., 2021). A double-blind sham-controlled study of Li and colleagues among 60 treatment refractory patients showed that iTBS is a safe, well-tolerated, and effective treatment for TRD (Li et al., 2014). A large non-inferiority trial further indicated that iTBS has the same level of clinical efficacy as standard high frequency 10Hz rTMS, thus offering a potentially much shorter and therefore cost-effective rTMS protocol alternative for TRD (Blumberger et al., 2018). In 2018, based on this study, FDA cleared the iTBS protocol for the treatment of MDD, in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication.

A few case reports and a long-term retrospective review reported that the combination of ketamine and rTMS may be an effective long-term therapy for patients with depression (Best,

2014; Best & Griffin, 2015; Best et al., 2019). To the best of our knowledge, there is no study comparing the effectiveness of ketamine and rTMS in patients with depression in a naturalistic setting. Only a limited number of alternative non-pharmacological treatments for TRD are available today and more research is needed to directly compare a non-pharmacological treatment with a pharmacological treatment in terms of their efficacy and tolerability. In this study, we exploratively describe and compare the acute antidepressive efficacy of both, 8 sessions of intramuscular ketamine administered twice weekly for 4 weeks, as well as 30 sessions of left DLPFC-iTBS (over a period of 6 weeks) in depression patients seeking help in a naturalistic clinical mental health setting. While the iTBS protocol is FDA approved and by now a widely used method for the treatment of TRD in clinical practice, the potential use of IM ketamine in TRD has not been extensively researched and therefore is not widely used. This comparative study is important in order to point out that more research need to be done in this area and in order IM ketamine to be considered for FDA approval for TRD. Thus, the present study aimed to indicate for first time the potential of IM ketamine to reach similar effects in TRD as rTMS in shorter duration (less visits).

Materials & Methods

DESIGN

A retrospective comparative study was conducted which included clinical records of TRD patients, as collected from the clinical database of Cyprus rTMS Center. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by Cyprus National Bioethics Committee (EEBK E 5 2021.01.149) and written informed consent was obtained from all patients.

PATIENTS

Clinical records of twenty-four patients with treatment resistant depression who were referred to the Cyprus rTMS Center in the period of January 2018 to August 2021 and received either IM ketamine or rTMS as treatment for depression were included in this retrospective comparative study. During the clinical evaluation for treatment purposes, all patients were assessed using the ICD- 10 Classification of Mental and Behavioral Disorders and met the criteria for either moderate depressive episode or severe depressive episode without psychotic symptoms. All patients were on psychotropic medication (such as Sertraline and Venlafaxine) before, during

and after the study. The Cyprus rTMS Center commonly offers both treatment options, IM ketamine and rTMS, to the patients. Treatment options were discussed with patients and literature findings were explained to them. Then, patients chose the treatment option (IM ketamine or rTMS) based on their preference. Twelve patients were treated with IM ketamine and twelve patients were treated with rTMS therapy using the iTBS protocol. An experienced psychiatrist and a TMS technician performed the rTMS treatment. Patients were reviewed regularly by the treating psychiatrist, every few weeks. The psychiatrist had regular contact with patients, weekly during the sessions of rTMS or ketamine, as well as a formal monthly review.

Depression and anxiety severity were measured prior and after the completion of each treatment using clinician-rated and self-rated assessments (HDRS, HAM-A, BDI-II). The time between the two assessments (pre and post treatment) was not the same for both groups, as IM ketamine treatment was completed after 4 weeks and rTMS treatment was completed after 6 weeks. Patients thereafter followed an individual treatment plan, which may or may not, include maintenance and there was no relapse in their mental state for the following 4 months based on psychiatric reviews, no formal questionnaires were given. The criteria for inclusion of patients' clinical records in the study were: (1) patients aged 18 years and older, (2) patients meeting the criteria for either moderate depressive episode or severe depressive episode without psychotic symptoms, (3) patients not experiencing any significant clinical improvement from at least two different methods of antidepressants and (4) the existence of completed clinical evaluations prior and post treatment. The exclusion criteria were: (1) patients aged younger than 18 years and (2) mental objects or implants in the brain, skull or near head (e.g., pacemakers, metal plates). Demographic (age and gender) and depression severity (duration of current episode, number of episodes, duration of depression, number of unsuccessful antidepressants tried in current episode) data were collected.

CLINICAL ASSESSMENTS

Hamilton Depression Rating Scale (HDRS) and Hamilton Anxiety Rating Scale (HAM-A): HDRS (Hamilton, 1960) and HAM-A (Hamilton, 1959) are the most widely used depression and anxiety assessment scales to be administered by clinicians in order to assess the severity of depressive and anxiety symptoms, respectively. HDRS consists of seventeen items whereas HAM-A consists of fourteen items and a total score in both instruments is calculated by summing the individual scores from each item. In HDRS, the total score range of 0–52, where 0–7 is generally accepted to be within the normal range and represent the absence or remission of depression, while a score of 20 or higher indicated at least moderate severity. In HAM-A, the total score range of 0–56, where scores <17 indicated mild severity, scores 18-24 mild to moderate severity and scores 25–30 moderate to severe anxiety.

Beck Depression Inventory II (BDI-II): BDI-II is a one of the most widely used multiple-choice self-reported instruments that designed to assess depression severity (Beck et al., 1996). It consists of 21 items and the score of each item range from 0 to 3. The total score range of 0–63 with higher total scores indicating more severe depressive symptoms. Specifically, scores 0–13 indicated minimal range, scores 14–19 mild severity, scores 20–28 moderate severity, and scores 29–63 indicated severe depression.

TREATMENT PROCEDURE

As mentioned above, data of both experimental samples were retrospectively obtained from a real-life clinic. The patients had chosen the treatment method based on their preference; hence they were not randomly placed to these two experimental groups. However, both groups were being compared for relevant parameters (age, gender, depression severity) to ensure that they are not fundamentally different. Essentially, the only difference between the two experimental groups was the treatment method that they had received.

In the *rTMS treatment condition*, stimulation was performed using a MagPro X100 stimulator (MagVenture, Farum, Denmark) and a figure-of-eight coil (Cool-B65). Prior to stimulation, the individual resting Motor Threshold (rMT) was estimated over the left primary motor cortex (Mean = 50.25, SD = 4.03). The rMT is the amount of machine output (intensity) required to elicit a motor-evoked potential (MEP) in at least 50% of all attempts (Borckardt et al., 2006). Five iTBS sessions were administrated per week for 6 weeks, over the left DLPFC. To localize left DLPF, the software Beam_F3 Locator, an efficient and accurate method to mark the F3 position according to the 10-20 EEG system was used (Beam et al., 2009). Stimulation intensity was set at 120% of the rMT. The stimulation coil was placed at a 45° angle off the midline. iTBS was administrated at 5 Hz and each session included 20 trains with 8 s inter train interval (triplets of 50 Hz). A total number of 600 pulses was given per session for 3:08 min (Blumberger et al., 2018).

In the *ketamine treatment condition*, intramuscular ketamine was administrated twice weekly for 8 sessions. In the first session, patients received a dose of 0.25 mg/kg, and then the dosage was titrated upwards, to a maximum of 1 mg/kg by session 4, depending on patient effect and safe vital sign assessments in order to achieve the maximal antidepressant effect. All the necessary requirements were followed: ketamine was administrated by an experienced physician, the patient was monitored for 2 h after the administration under control settings and

any side effects were recorded. The administration took place in a private room specially designed for the purposes of the treatment.

DATA ANALYSIS

SPSS software version 27.0 was used for statistical analysis of data (IBM corporation, Endicott, New York). Independent sample *t*-tests and chi-square tests were used to compare the demographic and clinical characteristics between ketamine group and rTMS group. Due to the small sample size, Wilcoxon Signed-Ranks tests were used to evaluate changes in HDRS, HAM-A, BDI-II scores from pre treatment to post treatment for each experimental group individually and for the overall sample. The χ^2 test was used to compare responders and remitters between the two groups. Responders were defined as patients with a 50% or greater decrease on the post treatment scores from the pre-treatment scores and remitters were defined as patients with HDRS post score ≤7, HAM-A ≤7 and BDI-II ≤13 (Griffiths et al., 2019; Matza et al., 2010; Wang et al., 2017). Mixed factorial ANOVAs were conducted to investigate the effect of both the within factor (Time) and the between factor (Experimental group). The within factor evaluated time depended effects (baseline vs. end of the treatment) on depressive and anxiety symptoms (HDRS, HAM-A, BDI-II). The between factor determined whether the patients who received ketamine had a different response compared with patients who received rTMS. The significance level was set at $p < 0.05$.

Results

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

The clinical records of twenty-four TRD patients (11 male, mean age 47.9 ± SD 12.7) were collected. From these reports two groups were created, one group which received ketamine therapy and one group which received iTBS therapy. Analysis showed that both groups did not differ in demographic (age, gender) as well as clinical (duration of current episode, number of episodes, duration of depression, number of unsuccessful antidepressants tried in current episode, HDRS, HAM-A, BDI-II) characteristics. Accordingly, no significant differences were observed between the TRD patients who underwent the intramuscular ketamine therapy and those patients receiving rTMS (all *p > 0.05*; Table 1).

TREATMENT OUTCOME

In the Ketamine group, a Wilcoxon Signed-Ranks test indicated that the post HDRSscores were significantly reduced compared to pre-treatment scores (Mean change = 26.08, SD = 7.33)

(Z=−3.06, $p < 0.005$). Alike, post HAM-A scores were significantly reduced compared to baseline scores (Mean change = 29.08, SD = 6.93) (Z = −3.06, $p < 0.005$). Finally, significant reductions were observed also in BDI-II scores (Mean change = 32.50, SD = 15.40) (Z = −2.98, $p < 0.005$).

In the rTMS group, a Wilcoxon Signed-Ranks test indicated that post HDRS scores were significantly reduced compared to pre-treatment scores (Mean change = 23.18, SD = 3.97) (Z=−2.94, $p < 0.005$). Similarly, post HAM-A scores were significantly reduced compared to baseline scores (Mean change = 27.42, SD = 8.99) (Z = −3.06, $p < 0.005$). Finally, significant reductions were observed also in BDI-II scores (Mean change = 30.00, SD = 17.01) (Z=−2.93, $p < 0.005$).

RESPONSE AND REMISSION

Responders were defined as patients with a 50% or greater decrease from the baseline scores to the post treatment scores and remitters were defined as patients with HDRS post score ≤ 7, HAM-A ≤ 7, and BDI-II ≤ 13.

Out of a total of 12 patients in the Ketamine group, based on HDRS, 4 patients were responders (33.30%) and 8 patients were remitters (66.7%). Based on the HAM-A, the Ketamine group consisted of 3 responders (25%) and 9 remitters (75%). Finally, based on the BDI-II, 3 patients were responders (25%), 7 patients achieved remission (58.30%), whereas 2 patients were non-responders (16.70%) (Table 2).

Out of a total of 12 patients in rTMS group, based on HDRS, 3 were responders (25%), 8 achieved remission (66.70%), whereas 1 was a non-responder (8.30%). Based on the HAM-A, 3 patients were responders (25%) and 9 patients were remitters (75%). Finally, based on the BDI-II, 1 patient was a responder (8.30%), 9 patients achieved remission (75%), and 2 patients were non-responders (16.70%) (Table 2).

Overall, using χ^2 tests, no significant differences were observed between the MDD patients of ketamine group and rTMS group in terms of responders, remitters and no-responders (all $p > 0.05$).

KETAMINE VS rTMS

2 (Time: pre-treatment, post-treatment) * 2 (Experimental Group: Ketamine Group, rTMS group) mixed factorial ANOVAs were conducted as measured by the three clinical assessments

(HDRS, HAM-A, BDI-II). Results were consistent in all three clinical assessments. The interaction effect between Time and Experimental Group was not statistically significant [HDRS: $F_{(1,21)}$= 1.355, $p > 0.05$, η2p = 0.061; HAM-A: $F_{(1,22)}$ = 0.258, $p > 0.05$, η2p = 0.012; BDI-II: $F_{(1,22)}$ = 0.142, $p > 0.05$, η2p = 0.006]. There was a statistically significant main effect of Time [HDRS: $F_{(1,21)}$ = 390.771, $p < 0.05$, η2p = 0.949; HAM-A: $F_{(1,22)}$ = 295.945, $p < 0.05$, η2p = 0.931; BDI-II: $F_{(1,22)}$ = 89.008, $p < 0.05$, η2p = 0.802], suggesting a difference in the pre-treatment compared to post treatment. However, there was no significant effect of Experimental Group [HDRS: $F_{(1,21)}$ = 0.273, $p > 0.05$, η2p = 0.013; HAM-A: $F_{(1,22)}$ = 0.013, $p > 0.05$, η2p = 0.001; BDI-II: $F_{(1,22)}$ = 2.934, $p > 0.05$, η2p = 0.118]. Wilcoxon Signed-Ranks tests indicated that post HDRS (Z = −4.20, $p < 0.005$), HAM-A (Z = −4.29, $p < 0.005$) and BDI-II (Z = −4.17, $p < 0.005$) scores were significantly reduced compared to pre-treatment scores (Figure 1).

Post-hoc power analysis was conducted using the Superpower's Power Shiny App. Results showed that with 12 participants per group, we have 100% power for the main effect of Time. Also, the observed power of the main effect of Time was 1.s00.
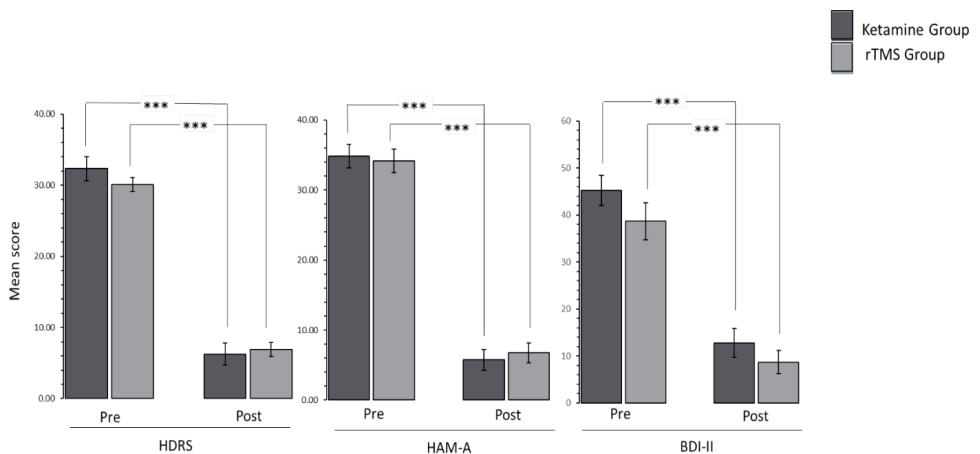
Figure 1: Bar graphs showing difference in pre-treatment and post-treatment scores of patients in Ketamine and rTMS groups. *** *P*=0.00.

Discussion

To our knowledge, this is the first study describing the effectiveness of both, ketamine treatment and rTMS treatment, in depressive and anxiety symptoms of MDD patients in a naturalistic real-life setting. Patients in the rTMS treatment group received 30 iTBS sessions over a period of 6 weeks, whereas patients in the Ketamine treatment group received 8 IM injections over a period of 4 weeks. Using three clinical assessments (HDRS, HAM-A, BDI-II), our data reveals that both therapies led to significant improvement in symptoms from pre- to post-treatment. Based on the HDRS, in the Ketamine group, 33.3% were responders and 66.7% were remitters and in rTMS group, 25% were responders and 66.7% were remitters. Based on HAM-A, in both experimental groups, 25% were responders and 75% were remitters. Finally, based on BDI-II, in Ketamine group, 25% were responders and 58.3% were remitters and in rTMS group 8.3% were responders and 75% were remitters. An explorative *post-hoc* direct statistical comparison indicated that ketamine therapy did not differ significantly from rTMS therapy with respect to pre- to post- depressive and anxiety symptoms, indicating that the effect of both experimental groups in our sample was equally effective. In line with this notion, statistical χ^2 tests showed that there were no statistical differences between the patients of ketamine group and rTMS group in remission and response rates. These results indicated that IM ketamine therapy has the potential to reach similar effects in patients with TRD as rTMS therapy in a shorter treatment period as less visits are needed to complete the treatment. No significant side effects were reported from either the rTMS group or the ketamine group.

The results support the preliminary effectiveness of the treatments and adds to the existing literature regarding the efficacy of both treatment options in depression. Regarding TMS, a prior study by O'Reardon et al. (2007), found that TMS was effective in treating MDD with minimal side effects. Furthermore, iTBS protocol, has proven to be an effective, safe and well-tolerated treatment for depression (Blumberger et al., 2018; Chu et al., 2021; Li et al., 2014). Although there are many studies regarding the efficacy of ketamine in depression (Marcantoni et al., 2020; Murrough et al., 2013a; Murrough et al., 2013b), the research in IM ketamine remains limited. There are only a few case reports that demonstrated the potential effectiveness of IM ketamine in depression, therefore the optimal use of IM ketamine warrants further investigation. A report on two cases with acute depression has shown that IM ketamine injection bring rapid relief from depressive symptoms and especially in the suicidal ideation (Harihar et al., 2013). Another case report demonstrated that IM ketamine is a potential treatment for treatment-resistant bipolar depression (Cusin et al., 2012). IM ketamine injection was also used in a female patient with metastatic ovarian cancer. The treatment was well-tolerated and after 6 sessions the patient achieved remission of her depressive symptoms (Zanicotti et al., 2012).

Previous studies investigated the potential efficacy of combining ketamine and rTMS therapy in depression and bipolar disorder. However, to our knowledge, only a few case reports and a long-term retrospective review were reported so far. It is important to note that, a case report by Best and Grifflin, indicated that the combination therapy of ketamine and rTMS may be a more effective treatment for refractory depression, than either ketamine or rTMS alone (Best & Griffin, 2015). Furthermore, a recent long-term retrospective review demonstrated statistically significant reduction of depressive symptoms, after the combination therapy showing clear indication of the effectiveness of the treatment for refractory depression (Best et al., 2019). Their review also found that this reduction in depressive symptoms could be sustained for a period of 2 years (Best et al., 2019). Finally, according to some case reports, the combination therapy can be effective in treating severe depression in bipolar I disorder (Best, 2014) and in bipolar II disorder (Best et al., 2015).

Whereas previous research suggests that a combined treatment by ketamine and rTMS is an effective and long-term treatment for depression, the present comparative study represents a first attempt to describe and exploratively compare both treatment options as standalone therapies in a naturalistic setting. It is important to consider the limitations of our conclusions here. The current study is a retrospective comparative study with no a priori randomization and a very limited number of patients. Small sample sizes usually undermine the internal and external validity of a study and affect the generalizability of the results (Faber & Fonseca, 2014; Tipton et al., 2017). Especially for statistically comparing the effectiveness of two treatment options (clinical inferiority trial), a much larger same size would be needed. Another main limitation is the retrospective design of the study. Specifically, this study was based on data of patients with MDD, who were referred to the Cyprus rTMS Center in the past and received either intramuscular ketamine or rTMS as treatment for depression. Therefore, the patients were not randomly divided into these two experimental groups and no sham control groups were used. Finally, this study suffers from sample selection bias. A larger number of patients was treated with either IM ketamine or rTMS in the Cyprus rTMS center during that period, but we chose to include only patients who completed the total number of sessions required (rTMS: 30 sessions; Ketamine: 8 sessions) and patients with completed clinical evaluations prior and post treatment in our analysis. Unfortunately, we did not collect information about the number of patients with incomplete clinical evaluations prior or post treatment and the number of patients who terminated treatment prematurely. Thus, we selected only completers from a larger sample of patients of unknown size. Despite these limitations, this study could serve as a starting point for identifying and comparing the efficacy of these two depression treatments in a real life clinical setting.

Future research should further develop and confirm these initial findings by comparing the efficacy of ketamine treatment, rTMS treatment and the combination treatment in depression

using a randomized, double-blind, sham-controlled clinical trial sufficiently powered to also reveal potential non-inferiority. Furthermore, clinical assessments should be collected weekly in order to investigate whether there are differences in response time between the treatment groups. In a future study, a follow up measurement is needed to examine and compare the long-term efficacy of these treatments. To the best of our knowledge, this comparative study was the first that directly compare the efficacy of rTMS and IM ketamine, a non-pharmacological treatment, and a pharmacological treatment for TRD. Finally, our results showed that the iTBS protocol, which has received FDA approval for MDD, and IM ketamine, which is not an FDA approved treatment for MDD, are equally effective treatments. This is an important finding as IM ketamine treatment is not widely used in clinical practice and can be administrated in a shorter duration compared to rTMS. Further research with more focus on the use of IM ketamine treatment in depression is therefore suggested, which may allow this treatment to gain a formal approval and a wider acceptance in daily practice.

Conclusion

This retrospective study compared the efficiency of IM ketamine administered twice weekly for 8 sessions and 30 sessions of iTBS applied to the left DLPFC in MDD patients. Our results indicated significant pre- to post-treatment reduction in depressive and anxiety symptoms, with no significant differences between the two experimental groups, indicating that the effect of both therapies was equally effective in our limited sample. In line with this notion, response and remission rates were not statistically different between the two treatment groups. This study can be seen as a first step toward enhancing our knowledge regarding the therapeutic efficacy of two alternative depression treatment options such as ketamine therapy and rTMS therapy in a naturalistic real-life setting.

Table 1: Baseline characteristics of (N=24) participants.

Factors	Ketamine Group n=12	rTMS Group n=12	*df* values	*p* values
Demographic characteristics				
Age (years)	44.08(13.18)	51.67 (11.39)	22	0.146[a]
Gender (male/female)	5/7	6/6	22	0.682[b]
Clinical characteristics				
Duration of current episode (months)	5.50 (0.52)	5.67 (0.49)	22	0.430[a]
Number of episodes	3.08 (0.90)	3.58 (0.67)	22	0.137[a]
Duration of depression (years)	7.25 (3.70)	6.83 (3.01)	22	0.765[a]
Number of unsuccessful antidepressants tried				
in current episode	2.67 (0.78)	2.50 (0.80)	22	0.610[a]
HDRS Pre	32.33 (6.00)	30.25 (3.14)	22	0.298[a]
HAM-A Pre	34.83 (5.78)	34.17 (5.80)	22	0.781[a]
BDI-II Pre	45.25 (10.98)	38.67 (13.65)	22	0.206[a]

Data are presented as the mean (with standard deviation, SD). [a]Independent sample *t*-tests. [b]χ^2 test, rTMS, repetitive Transcranial Magnetic Stimulation; HDRS Pre, Hamilton depression rating scale before treatment; HAM-A Pre, Hamilton anxiety rating scale before treatment; BDI-II Pre, Beck depression inventory – II before treatment

Table 2: Responders and remitters, n (%).

		Ketamine Group	rTMS group	*p* values
HDRS				0.565[a]
	Responders	4 (33.30%)	3 (25%)	
	Remitters	8 (66.70%)	8 (66.70%)	
	No responders	0 (0%)	1 (8.30%)	
HAM-A				1.00[a]
	Responders	3 (25%)	3 (25%)	
	Remitters	9 (75%)	9 (75%)	
	No responders	0 (0%)	0 (0%)	
BDI-II				0.535[a]
	Responders	3 (25%)	1 (8.30%)	
	Remitters	7 (58.30%)	9 (75%)	
	No responders	2 (16.70%)	2 (16.70%)	

[a] χ^2 test. rTMS, repetitive Transcranial Magnetic Stimulation; HDRS, Hamilton depression rating scale; HAM-A, Hamilton anxiety rating scale; BDI-II, Beck depression inventory – II

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PART 2

TRANSCRANIAL MAGNETIC
STIMULATION IN NEUROLOGY

CHAPTER 5

Bilateral Orbitofrontal Repetitive Transcranial Magnetic Stimulation in Frontal Lobe Epilepsy: A Case Report

Abstract

Epilepsy is a common and severe neurological disorder affecting millions of people worldwide. Nowadays, antiseizure medications (ASMs) are the main treatment for most epilepsy patients, although many of them do not respond to ASMs and suffer from drug-resistant epilepsy (DRE). Alternative and novel treatment methods have been offered nowadays, showing promising results for the treatment of DRE. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive method that has become increasingly popular in the last decades. This article reports a patient with frontal lobe epilepsy. We aimed to investigate whether bilateral orbitofrontal (OFC) low-frequency rTMS (LF-rTMS) is feasible and tolerable, safe, and potentially clinically effective in treating epileptic seizures. The patient's satisfaction with rTMS therapy was self-reported to be high, as rTMS helped in reducing the frequency of the focal attacks and completely abolished the preceding feeling of fear and panic. Therefore, bilateral OFC rTMS treatment can be well tolerated in patients with frontal epilepsy although the findings of the present case report with regard to clinical efficacy warrant further investigation.

Introduction

Epilepsy is a common and severe neurological disorder affecting approximately 50 million people worldwide (WHO, 2019). According to the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE), epilepsy can be defined as "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures," with at least a history of one seizure, and by the "neurobiological, cognitive, psychological, and social consequences of this condition" (Fisher et al., 2005). Antiseizure medications (ASMs) are the main and often effective treatments for most epilepsy patients. Nonetheless, approximately 25% of epilepsy patients suffer from drug-resistant epilepsy (DRE), not adequately responding to any available combination of ASMs (Lopez et al., 2015). A recent systematic review and meta-analysis revealed that the cumulative incidence of DRE was 14.6% in adult/mixed-age studies as well as that the prevalence of DRE was 13.7% in community-based populations and 36.3% in clinic-based populations (Sultana et al., 2021).

Nonpharmacological treatment options are actively explored to address the need for treatment alternatives in DRE patients. Recently, immunomodulatory therapies in epilepsy have been introduced, such as corticosteroids, intravenous immunoglobulins, plasmapheresis, and steroid-sparing drugs such as azathioprine (Melvin & Hardison, 2014). Other treatment options include dietary changes (Sampaio, 2016), brain surgery (Tellez-Zenteno et al., 2005), and also brain stimulation, including deep brain stimulation (Salanova et al., 2015) and neuromodulation techniques (Krishna et al., 2016). Regarding neuromodulation techniques, several noninvasive stimulation therapies are currently available for patients with epilepsy such as transcranial electric stimulation (Berenyi et al., 2012), transcranial direct current stimulation (Yang et al., 2020), and transcranial magnetic stimulation (TMS) (Fregni et al., 2006). Repetitive TMS (rTMS) uses time-varying electromagnetic pulses applied transcranially, through the intact scalp, via an insulated electromagnetic coil placed over a specific area of the brain in order to modulate the underlying cortical excitability (Klomjai et al., 2015). In the past 20 years, rTMS has shown to be clinically effective in treating various neurological and psychiatric disorders such as neuropathic pain or major depressive disorder (Lefaucheur et al., 2020). At the same time, rTMS has shown to be very well tolerated with very few to no side effects (Rossi et al., 2021). The ability of rTMS to modulate cortical excitability also for longer periods outlasting the stimulation itself has shown to depend on specific stimulation parameters such as intensity, frequency, number of sessions, and duration of stimulation (Klomjai et al., 2015). Regarding stimulation frequency, low-frequency rTMS (LF-rTMS) (<1 Hz) generally decreases cortical excitability, whereas high-frequency rTMS (>5 Hz) generally increases cortical excitability, triggering longer-lasting neuroplasticity processes resembling long-term depression or long-term potentiation, respectively (Klomjai et al., 2015). The most serious adverse event of rTMS is the potential induction of seizures. However, seizure induction occurs very rarely (Lerner et al., 2019; Rossi et

al., 2009). A recently published article regarding safety recommendations for the use of TMS in healthy volunteers and patient populations highlighted factors that are increasing the risk for TMS-provoked seizures. These include the presence of neuropsychiatric diseases associated with structural cerebral damage (e.g., stroke), some medical conditions (e.g., metabolic abnormalities), and general factors like sleep deprivation and increased alcohol consumption (Rossi et al., 2021). In 2019, Lerner et al. presented the results of a survey among TMS laboratories and clinics, conducted between 2012 and 2016, and reported that the statistical likelihood of inducing a seizure with rTMS is extremely low for participants without such risk factors (<1 seizure per 60,000 sessions).

A small but growing number of studies also investigated the potential of LF-rTMS in treating epileptic patients (Mishra et al., 2020; Sun et al., 2012). Here, we describe a case report of a patient suffering from frontal lobe epilepsy who underwent LF-rTMS over both orbitofrontal cortices. The patient was followed over a course of 30 sessions to investigate whether bilateral prefrontal LF-rTMS is feasible and tolerable, safe, and potentially clinically effective in treating epileptic seizures.

Case Report/Case Presentation

PARTICIPANT

In this case report, a 28-year-old female patient presented suffering from frontal lobe epilepsy. She first experienced a focal to bilateral tonic-clonic seizure at the age of 14 followed by a similar event at the age of 18. MRI was performed after the first seizure revealing bilateral subependymal periventricular heterotopia, a neuronal migration disorder notoriously resulting in DRE in the majority of cases (Fig.1). There was also an impression of mild degree of cortical dysplasia in the insular cortex on both sides, slightly more prominent in the left side. At the age of 19, she experienced 4–5 focal to bilateral tonic-clonic seizures per week. After being treated with various combinations of ASMs, the frequency of generalized seizures was reduced to 1 per year for the following 3 years (the focal events continued). By the age of 23, the generalized seizures were well controlled by medication, but she continued to experience daily focal seizures (1–3 times per day) characterized by episodes of a sudden onset of fear of impending doom associated with tachycardia and sweating, followed by a "strange" sensation in the right face spreading to the right hemitongue, occasionally accompanied by right hand numbness, lasting for less maximally 30 s without any loss of consciousness. We assume that these episodes involved several structures including the amygdala and the insula (as part of the central autonomic network), spreading to involve also the postcentral gyrus and somatosensory cortex causing the sensory disturbances.
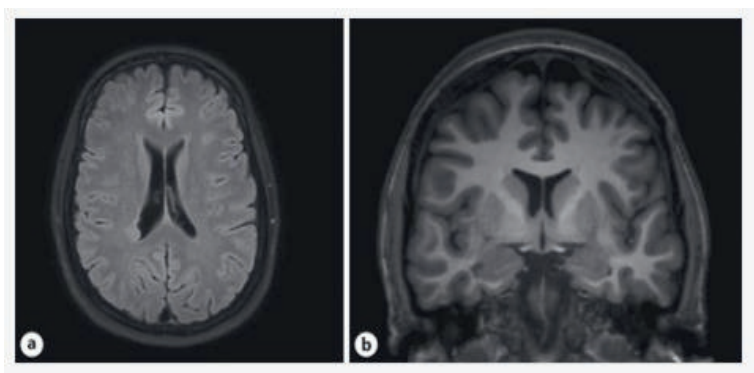
Figure 1: MRI scans: bilateral subependymal periventricular heterotopia.

rTMS TREATMENT

The patient has been on treatment with different ASMs starting at the onset of the first seizures. Some of the medications used were topiramate, levetiracetam, clobazam, lamotrigine, and gabapentin. The doses of her medications were not standard, as dosing had been changed frequently in an attempt to better control the attacks. Prior to rTMS treatment, the patient was on lamotrigine 375 mg/day. Whilst undergoing rTMS treatment, the patient continued taking levetiracetam 2,500 mg/day and started reducing the dose of lamotrigine by 25 mg every fortnight in an attempt to achieve monotherapy as she aimed to become pregnant in the near future. She also started taking vitamin D 50,000 IU once every month and a daily dose of folic acid 5 mg, B complex, and iron supplements.

Written informed consent for the rTMS treatment was obtained from the patient. In the first session, the patient's resting motor threshold (rMT) was determined over the left primary motor cortex. rMT is the amount of machine output (intensity) required to elicit a motor-evoked potential in at least 50% of all attempts (Borckardt et al., 2006). The patient underwent rTMS using the MagPro X100 stimulator (MagVenture, Farum, Denmark), with a figure-eight coil (MC-B70). The TMS coil was placed over the left and right orbitofrontal cortex sequentially (left side for 8, 23 min and right side for 8, 23 min), positioned over the Fp1 and Fp2 EEG sites according to the 10–20 EEG system (Fig. (Fig.2).2). Each rTMS session consisted of 12 trains of 42 pulses administered at 1 Hz with an intertrain interval of 1 s (42 s per train, 504 pulses in total within 8, 23 min). Stimulation intensity was set at 100% of the rMT for the first day of

treatment, 110% of rMT for the second day, and then at 120% of rMT for the remaining treatment days.
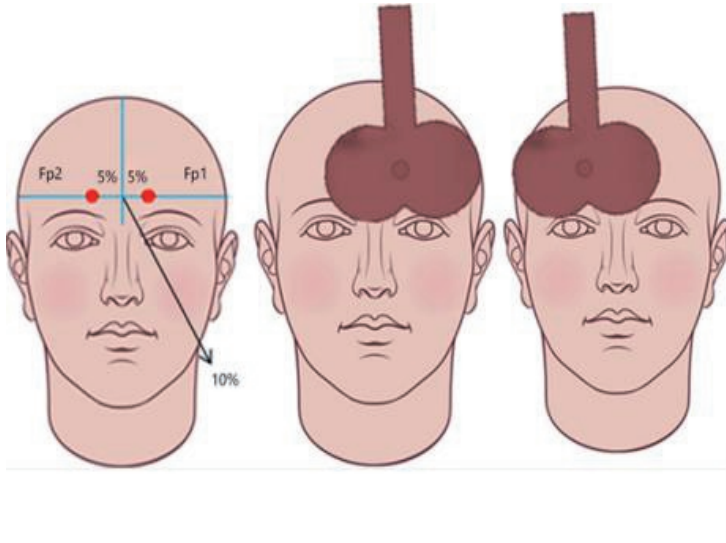
Figure 2: Coil placement: a stimulation areas: to localize Fp1 and Fp2 within the 10–20 EEG system, we measured 10% of the nasion to inion distance along the midline (site FPz in the 10–20 EEG), followed by measuring 5% of the head circumference on the left and right of Fpz (Fp1 and Fp2). b Coil orientation at the left side. c Coil orientation at the right side.

The patient received a total of 30 rTMS sessions during the first 5-week period (the patient came to the clinic 3 days per week, and on each visit, she received 2 rTMS sessions, left and right OFC, with a 30-min break between sessions). After the completion of the 30 sessions, the patient continued with 10 maintenance sessions (once weekly for 1 month, once fortnightly for 1 month, and once monthly for the following 4 months as maintenance). To the best of our knowledge, this is the first time that this form of sequential bilateral OFC rTMS was used in a patient with epilepsy and was personalized to the patient's specific epileptic seizures as she received low-frequency inhibition of both orbitofrontal cortices. The orbitofrontal cortex was chosen as a target due to its accessibility as well as due to its significant connectivity with the amygdala and the rest of the central epileptic network (Liang et al., 2009; Liu et al., 2020). Bilateral stimulation was chosen due to the bilateral nature of the patient's neuronal migration disorder despite the unilaterality of the patient's symptoms during most seizures.

Results

The patient reported a quick reduction in seizure frequency after the first 2 weeks of treatment (seizure frequency dropped from 1–3 per day to 2–3 per week). After 30 sessions, the patient reported further frequency reduction (seizures appeared only 1–2 per week), and also reported that while she was still feeling an aura of fear on a daily basis, this was now not automatically followed by the above-reported sequence of semiology anymore. During the maintenance period, seizures remained on low frequency with 1–2 seizures per week, including a further reduction in duration and intensity and with the absence of any feeling of fear or panic.

Toward the end of the maintenance period, she started increasing the dose of levetiracetam to 3,000 mg/day and reducing lamotrigine to 100 mg/day in an attempt to achieve monotherapy as mentioned above. Unfortunately, after this reduction of lamotrigine, she experienced 3 focal to bilateral tonic-clonic seizures within 1 month resembling the seizures she had experienced at younger age. Consequently, the dose of lamotrigine was reinstated at 200 mg/day with a return to a better control of seizures.

Overall, the patient's satisfaction with rTMS therapy was self-reported to be high (70% satisfied with treatment outcome), as rTMS helped in reducing the frequency of the focal attacks and completely abolished the preceding feeling of fear and panic. It also allowed her to reduce the dose of her ASMs, which resulted in reduction in at least some of the side effects caused by ASMs. No adverse events of rTMS were reported during the whole treatment period.

Discussion

In this case report, we demonstrated that sequentially applied bilateral OFC rTMS is a safe and well-tolerated treatment for DRE resulting from bilateral subependymal heterotopia. We also showed that rTMS did reduce the frequency, duration, and intensity of the patient's seizures.

Although the induction of seizures is reported as the most serious side effect of rTMS, the actual occurrence of seizures as a consequence of rTMS can be considered as extremely rare with a probability of <1 in 60,000 sessions [Lerner et al., 2019; Rossi et al., 2009; Rossi et al., 2021]. Several studies aimed to investigate the effectiveness of TMS in epilepsy using different stimulation parameters and positions (Table (Table1).1). The present patient underwent LF-rTMS, as LF-rTMS could help inhibit the brain overactivity, which potentially will cause a new neuroadaptation to the brain circuits, preventing them from overfiring and causing epileptic seizures. This case report adds to the existing literature regarding the safety and effectiveness

of LF-rTMS in the reduction of seizure frequency in patients with medically refractory epilepsies (Menkes & Gruenthal, 2000; Tergau et al., 1999). A recent meta-analysis suggested that LF-rTMS may indeed be an effective therapy for patients with DRE based on its ability to reduce cortical excitability and consequently reduce seizure frequency and interictal epileptiform discharges (Mishra et al., 2020). Similarly, according to a randomized controlled trial, LF-rTMS can produce antiepileptic effects in patients with refractory focal seizures (Sun et al., 2012). rTMS has here and in other studies indicated to be potentially effective without causing rTMS-triggered seizures. It may therefore be considered as an additional therapeutic tool in the treatment of DRE. In addition, our results showed that panic attacks prior to the onset of an episode may be strongly reduced during rTMS treatment. It has been clearly shown in the past that LF-rTMS to the right dorsolateral prefrontal cortex may result in clinical improvement of panic disorder and reduce the ipsilateral motor cortex excitability (Mantovani et al., 2007). Of course, it must be clearly stated here that this case report is not suited to draw any scientifically strong conclusion with regard to the clinical efficacy of OFC rTMS in treating frontal lobe epilepsy due to the complete absence of a control or placebo condition as well as to the unique case reported here mainly in descriptive and qualitative terms.

Nonetheless, this case report may be the first to mention the safe and feasible application of sequential rTMS to the bilateral orbitofrontal cortex in a patient with epilepsy. Some authors had previously reported on the effectiveness of LF-rTMS over the orbitofrontal cortex in treating neuropsychiatric disorders such as major depression (Feffer et al., 2018) or OCD (Nauczyciel et al., 2014). Several lines of evidence have shown that the OFC has connections with multiple neural areas such as the hypothalamus, the amygdala, and the somatosensory cortex that are involved in emotional function (Rempel-Clower, 2007). The amygdala, for example, receives inputs from the OFC and has been shown to have a functional relationship with the OFC according to some rat studies (Rempel-Clower, 2007). As was already mentioned before, the bilateral OFC was chosen as a target due to its accessibility as well as due to its significant connectivity with these neural areas and finally because of the bilateral nature of the patient's neuronal migration disorder. These results take us a step further in personalizing and adapting rTMS targets to patients' individual symptoms rather than categorical diagnoses in the years to come.

Table 1: Characteristics of TMS studies

Reference	Study Design	No. of patients	Stimulation site	rTMS protocol	Notes/remarks
Tergau et al., 1999	Open pilot study	9	Over the vertex	0.33Hz, two trains of 500 pulses, 5 consecutive days	Low-frequency rTMS may temporarily improve drug-resistant ~~seizures~~
Theodore et al., 2002	A randomized, sham- controlled study	24	At seizure focus	1Hz, 120% of MT, twice daily for 1 week	No significant effect of TMS on focal or focal to bilateral tonic-clonic seizures
Fregni et al., 2005	Open study	8	The malformations of cortical development	0.5 Hz, 600 pulses, 65% of maximum stimulator output intensity, 1 session	Significant antiepileptic effect of rTMS
Fregni et al., 2006	Randomized, double-blind, sham-controlled trial	21	The malformations of cortical development	1Hz, 1200 pulses, 70% of maximum stimulator output intensity, five consecutive sessions	rTMS significantly decreased the number of seizures
Santiago-Rodriguez et al., 2008	Open-label study	12	The epileptogenic zone of each patient	0.5 Hz, 900 pulses, 120% rMT, one daily session for 2 weeks	rTMS decreases the number of seizures, without reduction in IEDs
Sun et al., 2012	A randomized, single-blind, controlled parallel group study.	60	The epileptogenic focus	0.5 Hz, 500 pulses, 90% (group 1) or 20% (group 2) of resting motor threshold (rMT), daily with three sessions for 2 weeks	Low-frequency high intensity rTMS had a significant antiepileptic effect

Conclusion

We believe that bilateral OFC rTMS treatment can be well tolerated in patients with frontal epilepsy although the findings of the present case report with regard to clinical efficacy warrant further investigation. Future placebo-controlled, double-blinded randomized controlled trials with sufficiently powered sample sizes are needed to conclusively determine the clinical value of target-specific rTMS in the treatment of epilepsy.

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CHAPTER 6

High-frequency rTMS improves quality of
life and depressive symptoms in
Parkinson's disease: A case report

Abstract

Introduction: Parkinson's disease (PD) is a common neurodegenerative disorder, characterised by both motor and nonmotor symptoms. There is currently no cure for PD, although there are several treatment options for relieving PD symptoms. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation therapy that shows promising results for the treatment of PD.

Methods: Here, we present a patient with PD. We investigated whether an accelerate form of high-frequency (HF) rTMS on the contralateral side to the patient's main difficulties is clinically effective in treating health-related quality of life (QoL) symptomatology and depressive symptoms in PD as well as the long-term effects of rTMS in PD during the maintenance phase.

Results: Results showed that HF-rTMS administered over the right primary motor cortex (M1) is a safe and well-tolerated treatment that improved the patient's health related QoL and depressive symptoms. These positive effects lasted at least five months post treatment.

Conclusion: Therefore, HF-rTMS over the right M1 can be a possible treatment option for patients with PD, although further investigations are necessary to validate the findings of the present case report.

Introduction

Parkinson's disease (PD) is the most common movement disorder and second most common neurodegenerative disorder (Tysnes & Storstein, 2017), characterised by both motor and nonmotor symptoms (NMS). It is prevalent in approximately 1% of the population over 60 and 3–4% of the population over 80 years old (Ayton et al., 2018; Tysnes & Storstein, 2017). The term parkinsonism is used to describe the motor symptoms of PD: tremors, muscle rigidity, and depressed movement (Bologna et al., 2022; DeMaagd & Philip, 2015a). The most prevalent NMS include, among others, depression, anxiety, psychosis, sleep disturbances, autonomic dysfunction, and dementia (Chen et al., 2015; DeMaagd & Philip, 2015a; Sung & Nicholas, 2013; Truong et al., 2008). The impact of NMS on quality of life (QoL) is evident through the international study by Martinez-Martin et al. (2007) who identified an average of 9–12 NMS per patient in their sample of 545 individuals. Also, the high comorbidity of anxiety and depression in PD has even led researchers to suggest that both are regarded as preliminary symptoms for PD (Burke et al., 2005; Fernandez & Simuni, 2005; Hemmerle et al., 2005; Ishihara & Brayne, 2006).

Pharmacological treatments for NMS include the use of antidepressants, antipsychotics, and anxiolytics for comorbid mood disorders (Burke et al., 2005; Fernandez & Simuni, 2005). However, medications used for treating motor and NMS of PD can interact and often exacerbate symptomology. Deep-brain stimulation (DBS) is an approved nonpharmacological treatment that stimulates brain regions via electrical impulses (DeMaagd & Philip, 2015b) and has been beneficial in treating PD symptomology (Georgiev et al., 2021). Although the exact mechanisms of DBS are unknown (Li et al., 2016), there is compelling evidence for its effective alleviation of rigidity, dyskinesia, and tremors (Ashkan et al., 2012). However, evidence for the effectiveness of DBS in treating NMS is dubious (Ebenezer, 2015; Kawaguchi et al., 2020; Li et al., 2013).

Over the past two decades, interest increased on the less invasive procedure of repetitive transcranial magnetic stimulation (rTMS) for treating PD (Li et al., 2016). With rTMS, high currents of single, repeated magnetic pulses are delivered to the targeted brain region at high or low frequencies, lowering motor cortex and cortical activity respectively (Mishra et al., 2011; Wagle Shukla et al., 2016). Low frequency rTMS (LF-rTMS) administers magnetic pulses of ≤1Hz that have inhibitory effects on cortical excitation, while high frequency rTMS (HF-rTMS) (≥5Hz) increases cortical excitation (Mishra et al., 2011; Kamble et al., 2014). Several studies investigated the effects of rTMS on PD motor and nonmotor symptoms. HF-rTMS has been found to positively influence voice and speech (Dias et al., 2006) and depression (Shin et al., 2016) in PD, while LF-rTMS has been shown to alleviate parkinsonism (Chou et al., 2015; Shimamoto et al., 2001). Such findings are crucial, given that alleviating motor and mood

symptoms in PD could improve patients' QoL. However, while rTMS shows promising results in treating motor and nonmotor PD symptoms, research findings are inconclusive, lack uniformity in their methods of conducting rTMS, and placebo effects cannot be ruled out (Kamble et al., 2014; Helmich et al., 2006). In this single casereport, we describe the effects of HF-rTMS over the right primary motor cortex in a patient suffering from PD. We wanted to investigate whether an accelerate form of HF-rTMS, on the contralateral side to the patient's main difficulties, is clinically effective in treating health-related QoL symptomatology and depressive symptoms in PD. Furthermore, we investigated the long-term effects of rTMS in PD during the maintenance phase.

Case report/ case presentation

PARTICIPANT

This case study presents a 70-year-old married male (L.P.034) diagnosed with PD. Symptoms were first present in 2013, when the patient reported leg pain. A Magnetic resonance imaging (MRI) scan showed brain aging and partially empty sella turcica with a fine imaging pituitary gland (Figure 1a). Following the MRI scan in 2013, he was diagnosed with PD. During 2020 the patient experienced worsening of his symptoms and had a second MRI scan. The MRI scan showed mild cerebral atrophy/aging more pronounced in the curvatures of the cerebral hemispheres. Also, few, micro-ischemic focal lesions occurred in the periventricular and deep white matter of the cerebral hemispheres (Figure 1b). He initially attended physiotherapy on a daily basis which was subsequently reduced to two or three sessions per week. Following his PD diagnosis, he was prescribed levodopa, entacapone, pramipexole, and rasagiline. Along with PD, the patient experienced comorbid symptoms of depression and anxiety. To treat psychological symptoms, the patient was prescribed escitalopram, amitriptyline hydrochloride, and bromazepam. Solpadine was used to treat pain. Written informed consent for the rTMS treatment and the publication of this paper were obtained from the patient.
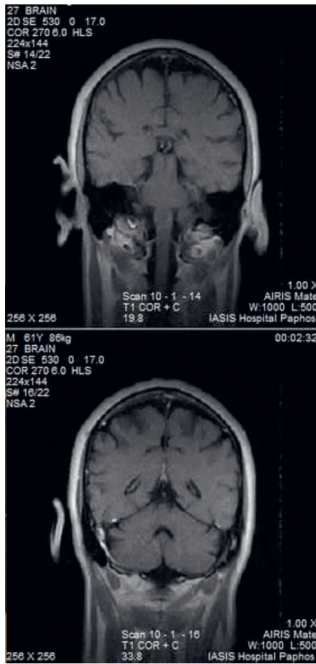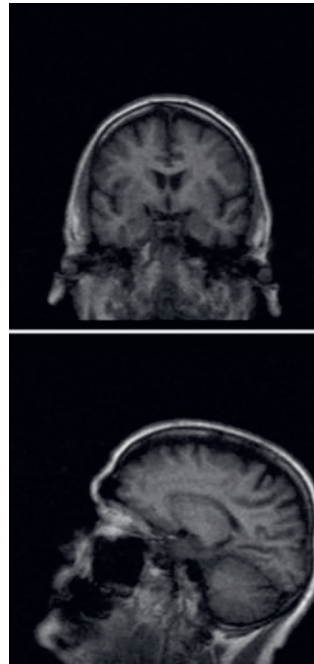
Figure 1. (a) Coronal sections of magnetic resonance imaging (MRI) performed in 2013, showing brain aging and partially empty sella turcica, (b) Coronal and sagittal sections of MRI performed in 2020, showing mild cerebral atrophy / aging more pronounced in the curvatures of the cerebral hemispheres.

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS)

The patient underwent rTMS using the MagPro X100 stimulator (MagVenture, Farum, Denmark). Before the first session, the patient's resting motor threshold (rMT) in the left primary motor cortex (M1) was measured using the Coil C–B60. This determined the intensity required to elicit a motor-evoked potential (MEP) in at least 50% of attempts. The stimulation intensity was set at 100% of the rMT. The rTMS protocol was administrated over the right M1 of the hand using a figure-eight coil (Coil Cool-B65). For locating the targeting area, the 10–20 EEG system was used (Silva et al., 2021). The patient received a total of 30 rTMS sessions over a five-week period, where six sessions were administrated per week. Two rTMS sessions were administered per visit with a 40-minute break between sessions. Upon completion of 30 sessions, the patient continued with nine maintenance rTMS sessions. These were scheduled weekly for the first four sessions, biweekly for the fifth and sixth sessions, and once a month for

the last three sessions. Each rTMS session was administered according to the following protocol: 10Hz, 25 trains with 40 pulses per train, and 20-second inter-train intervals. This choice follows the bulk of literature which favours HF-rTMS to the M1 for treating motor, and to a lesser extent, depressive symptoms (Shirota et al., 2015). Due to moderate effect sizes reported in other studies, we have used an accelerated form with more trains and pulses per session, with two administrations of the protocol per session. A total of 2000 pulses were given per session for approximately 20 min.

CLINICAL ASSESSMENTS

Two self-reported scales were used to assess the health-related QoL in PD (Parkinson's Disease Quality of Life Questionnaire; PCQ-39) and depression severity (Beck Depression Inventory–II; BDI-II). The PCQ-39 (Jenkinson et al., 1997) assesses eight factors (Bodily Discomfort, Communication, Cognition, Social Support, Stigma, Emotional well-being, Activities of daily living, Mobility) pertaining to the health-related QoL which can be found in Table 1. PDQ-39 items were rated on a 5-point Likert scale ranging from 0 – 4. The total score and sub-factor scores range between 0 – 100, with 0 indicating the best and 100 the worst QoL (Souza et al., 2007). The BDI-II is one of the most widely used multiple-choice self-report instruments, designed to assess depression severity (Beck et al., 1996). It consists of 21 items, where each item has a possible score between 0-3. The possible range of the total score is 0–63, with a higher total score indicating more severe depressive symptoms. Specifically, the total scores determine the following classifications: 0–13 are minimal, 14–19 are mild, 20–28 are moderate, and 29–63 are severe depression. For the purposes of the present case, we used the Greek version of PCQ-39 (Katsarou et al., 2001) and BDI-II (Giannakou et al., 2013). The patient was assessed on both scales (BDI-II and PCQ-39) at 15 different time points: immediately before the first rTMS session (T0), after six sessions (T1), after 12 sessions (T2), after 18 sessions (T3), after 24 sessions (T4), and after 30 sessions/end of treatment (T5), and then after each maintenance session: one week post treatment (T6), two weeks post treatment (T7), three weeks post treatment (T8), four weeks post treatment (T9), six weeks post treatment (T10), eight weeks post treatment (T11), three months post treatment (T12), four months post treatment (T13), and five months post treatment (T14).

Additionally, the Mini Mental State Examination (MMSE) was used immediately before the first session (T0) and after the completion of 30 sessions/end of treatment (T5). The MMSE is a 30-point test that is widely used by health-care providers to assess cognitive impairment (Folstein et al., 1975)]. Scores of 26 and above indicate normal cognitive functioning, scores between 21-25 indicate mild cognitive impairment, scores between 13-20 indicate moderate cognitive impairment, and scores 12 and below indicates severe cognitive impairment.

Results

No adverse effects of the rTMS were reported throughout the treatment and maintenance periods. The patient completed the treatment and maintenance with observable improvements on both self-reported scales (PDQ-39 and BDI-II). Figure 2 illustrates the changes in parkinsonism scores as measured by the PDQ-39. During the treatment phase, levels range from 48.72 to 19.87 and the trendline indicates that there has been a steady decrease in parkinsonism scores. A slight variation was observed between T4 and T5, where the level increased from 19.87 to 23.08. The level decreased further from the end of treatment (T5) to one week post treatment (T6). During the maintenance phase, levels range from 17.31 to 14.10 and the trend remains approximately stable indicating that there is no change. However, there is a slight variation between T8 and T12. Furthermore, Figure 3 indicates the patient's reports of depressive symptoms on the BDI-II. During the treatment phase, levels range from 17 to 11. According to the graph, there is a downward trend, which shows that the severity of patients' depression has decreased from mild to minimal. Nevertheless, the scores fluctuated slightly throughout the treatment period. There is a gently drop from the end of treatment (T5) to one week post treatment (T6). During the maintenance phase, levels range from 11 to 8 and the trendline remains approximately stable with some strong fluctuations between T7 and T11. Specifically, a major variation was observed between T9 and T10, where the level increased from 10 to 13, and then again decreased in T11. After the questionnaire was administered in T10, a discussion followed with the patient, who stated that he was experiencing some temporary personal problems, which may explain this increase. The MMSE score increased to 27/30 after completing 30 sessions (T5) which is indicated as normal compared to 24/30 at the baseline (T0), which indicate mild cognitive impairment.

The patient additionally reported a greater ease in communication. Particularly, he feels more sociable, has less difficulties in conversing, and assists himself more easily. Finally, the patient has reduced his intake of anxiolytics and has terminated physiotherapy subsequent to the rTMS treatment. After completing 30 sessions, the patient underwent physiotherapy again, simultaneously with maintenance. The physiotherapist reported that his left side (the side of the patient's main difficulties) was significantly stronger than before treatment.
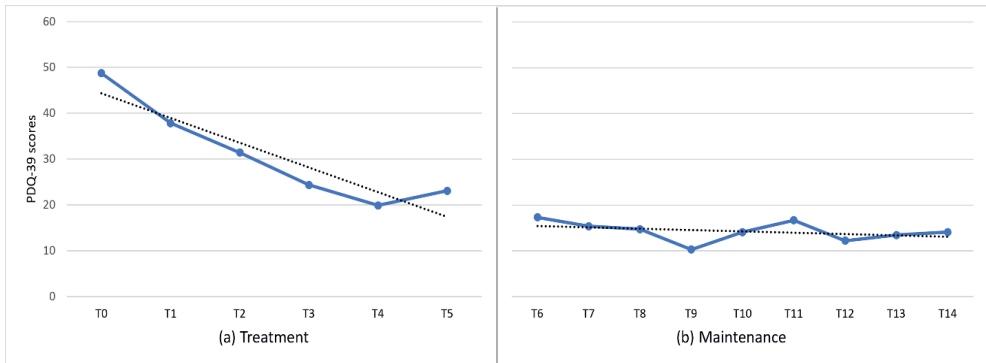
Fig. 2. Changes in parkinsonism scores during the (a) treatment and (b) maintenance phases | This line graph shows the difference in PDQ-39 scores at the 15 time points.
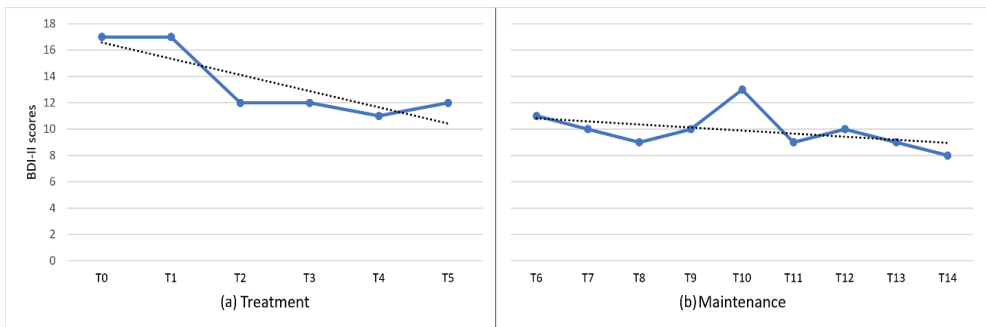
Figure 3. Changes in depression scores during the (a) treatment and (b) maintenance phases | This line graph shows the difference in BDI-II scores at the 15 time points.

Discussion

In this case study we have found that two administrations of a HF-rTMS protocol per session over the right primary motor cortex is a safe and well-tolerated treatment for PD. These administrations were done on the contralateral side to the patient's main difficulties. Overall, we have been able to demonstrate that HF-rTMS administered over M1 improved the patient's

health status and QoL, as measured by the PDQ-39. Additionally, the patient showed marked improvements in their depressive symptoms. These results were maintained or further improved during the maintenance phase that lasted up to five months post-treatment. Nevertheless, some fluctuations and slight increases in parkinsonism scores were observed during both phases.

This study's findings are in accordance with previous research. In the study of Yang et al. (2018), it was demonstrated that multi-session HF-rTMS (but not LF-rTMS) over the M1 with a total of 18.000–20.000 pulses was the most efficacious protocol in treating PD. Furthermore, in the review of Lefaucheur et al. (2020) advocate for HF-rTMS in the M1 contralateral to the pain side for patients with neuropathic pain and also reported that HF-rTMS of the left dorsolateral prefrontal cortex (DLPFC) can be used to reduce depressive symptoms in PD. Additionally, HF-rTMS of bilateral M1 stimulation (Aftanas et al., 2020; Lefaucheur et al., 2020) and left DLPFC stimulation (Aftanas et al., 2020) is likely efficacious in improving parkinsonism symptoms. Another study (Brys et al., 2016) found support for the effectiveness of bilateral M1 HF-rTMS in treating PD motor symptoms. However, they found no effect of HF-rTMS in the DLPFC on mood, and no added benefit of combined M1 and DLPFC HF-rTMS for improving mood or motor symptoms. In agreement with our study's findings, a randomised, double-blind, placebo-controlled study by Makkos et al. (2016) demonstrated the beneficial effects of bilateral M1 HF-rTMS on depressive symptoms and health related QoL in PD patients with mild or moderate depression. Notably, the antidepressant effects of 10-day HF-rTMS had a lasting effect for up to 30 days.

The importance of post-treatment maintenance should be emphasised. Maintenance of rTMS treatment could prolong and strengthen its antidepressant effects. This, in turn, can delay or even prevent symptom recovery. Studies including patients with treatment resistant depression, have shown that maintenance rTMS can potentially delay relapse after successful treatment (Fitzgerald et al., 2013; Richieri et al., 2013). In a more recent randomised, sham-controlled study of maintenance HF-rTMS over the left DLPFC for treatment resistant depression, results indicated that the antidepressant effect of HF-rTMS arose three months post-treatment (Benadhira et al., 2017). Most importantly, maintenance rTMS was well-tolerated and had no side-effects. Finally, a review of rTMS for treatment resistant depression suggested a proposed a treatment protocol of HF-rTMS (10Hz) to the left DLPFC using 3000 pulses per session for a duration of 20–30 sessions (van Belkum et al., 2018).

This case study highlights some significant implications. Firstly, HF-rTMS has demonstrated its efficacy in treating motor and affective symptoms of PD. This is particularly important to consider in the case of treatment resistant patients, or patients who experience side effects from medication (Korczyn, 2004). RTMS has demonstrated comparable efficacy to

pharmacological interventions, bypassing the complications that can arise from medical treatment (Korczyn, 2004).

Being limited to a single case study, our findings cannot be used to draw scientifically strong and generalisable conclusions. In addition, this study did not include a control or placebo condition. Therefore, future placebo-controlled, double-blinded, randomised trials with powered sample sizes are needed to substantiate the efficacy of HF-rTMS as an alternative for treating motor and mood symptoms of PD. A second limitation to this study is that rTMS was only administered in the M1. Current research consistently shows the benefits of M1 HF-rTMS in treating motor symptoms. However, findings on the effect of HF-rTMS in the M1 and DLPFC in treating PD mood symptoms are conflicting. An interesting line for future research would be to investigate the effect of M1 and DLPFC HF-rTMS on mood symptoms through placebo-controlled, randomised trials.

Table 1: Sub-factors of PDQ-39 scale

	Mobility	Activities of daily living	Emotional well-being	Stigma	Social Support	Cognition	Communication	Bodily Discomfort
Treatment								
T0	62.50	37.50	54.17	31.25	16.67	68.75	33.33	58.33
T1	47.50	33.33	37.50	25.00	.00	56.25	33.33	50.00
T2	27.50	37.50	50.00	12.50	.00	43.75	25.00	41.67
T3	25.00	25.00	41.67	12.50	.00	43.75	.00	25.00
T4	27.50	12.50	25.00	12.50	.00	31.25	8.33	25.00
T5	17.50	33.33	50.00	.00	.00	25.00	16.67	25.00
Maintenance								
T6	17.50	20.83	25.00	.00	.00	25.00	16.67	25.00
T7	15.00	16.67	20.83	.00	.00	25.00	16.67	25.00
T8	17.50	12.50	25.00	.00	.00	18.75	8.33	25.00
T9	7.50	12.50	20.83	6.25	.00	12.50	.00	16.67
T10	12.50	16.67	20.83	6.25	.00	25.00	.00	25.00
T11	20.00	16.67	25.00	12.50	.00	25.00	.00	16.67
T12	12.50	20.83	12.50	.00	.00	18.75	.00	25.00
T13	12.50	20.83	16.67	.00	.00	25.00	.00	25.00
T14	15.00	16.67	16.67	.00	.00	18.75	16.67	25.00

Clinical results at the 15 time points: immediately before the first rTMS session (T0), after six sessions (T1), after 12 sessions (T2), after 18 sessions (T3), after 24 sessions (T4), and after 30 sessions/end of treatment (T5), one week post treatment (T6), two weeks post treatment (T7), three weeks post treatment (T8), four weeks post treatment (T9), six weeks post treatment (T10), eight weeks post treatment (T11), three months post treatment (T12), four months post treatment (T13) and five months post treatment (T14).

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Conclusion

rTMS can be a promising alternative treatment for people with Parkinson's disease, taking into account its effectiveness in the motor and NMS of the disease, the lower risk of side effects compared to medication, the improvement in the depressive symptoms, as well as its strengthening effect in medication-treatment-resistance symptomatology.

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PART 3

SAFETY

CHAPTER 7

TMS- Induced Seizure during FDA-Approved Bilateral DMPFC Protocol for Treating OCD: A Case Report

Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation therapy that has become a method of choice for the treatment of several neuropsychiatric disorders such as depression and OCD. It is considered to be a safe and well-tolerated treatment, with only few side effects. The most serious adverse event during any rTMS treatment is the potential induction of a seizure. rTMS has shown very encouraging results for treatment-resistant OCD, although the optimal target area and the stimulation frequency are still matters of controversy. Here, we present a 19-year-old female patient with OCD who experienced seizure during the 7th session of her rTMS treatment using the FDA-approved 20-Hz protocol for OCD applied bilaterally over the left and right DMPFC using a double-cone coil. Nonetheless, it still unknown whether the seizure occurred as a consequence of rTMS, as the patient was also in a specific seizure risk group. Future reviews are needed to further clarify the mechanisms that may trigger seizures during rTMS treatments in order to reduce the likelihood of rTMS-induced seizures.

Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation method that has shown to be clinically effective in treating various neuropsychiatric disorders, in particular depression (Berlim et al., 2014) and obsessive-compulsive disorder (OCD) (Haghighi et al., 2015). rTMS delivers electromagnetic pulses to selective areas of the cerebral cortex using an insulated electromagnetic coil (Klomjai et al., 2015). Depending on the stimulation frequency, rTMS may increase or decrease cortical excitability (Klomjai et al., 2015). The clinical efficacy of TMS in treating depression is by now undisputed, and the FDA-approved depression protocol targeting the dorsolateral prefrontal cortex (DLPFC) is widely recognized and established, with costs for TMS depression treatment being reimbursed by health insurances in a growing number of countries. In a similar vein, also for the treatment of OCD, rTMS has shown encouraging results (Haghighi et al., 2015; Berlim et al., 2013). However, unlike in the case of depression, the optimal target region in the brain for treating OCD with rTMS remains a question of uncertainty. A series of recent studies focused on the effects of stimulating the supplementary motor area (SMA) (Hawken et al., 2016), orbitofrontal cortex (OFC) (Ruffini et al., 2009), and DLPFC (Elbeh et al., 2016) in treating OCD symptoms. In 2018, the US Food and Drug Administration (FDA) approved the Brainsway Deep Transcranial Magnetic Stimulation System for treatment of OCD (FDA, 2018). More recently, in 2020, the FDA cleared MagVenture TMS Therapy for adjunct treatment of OCD. This clearance was based on a prospective multicenter randomized double-blind placebo-controlled trial (Carmi et al., 2019). In this FDA-approved OCD protocol, TMS is applied bilaterally over the left and right dorsomedial prefrontal cortex (DMPFC) using a double-cone coil (specifically designed to achieve deeper stimulation penetration) and applying a high-frequency 20-Hz rTMS sequence. This is different from the other OCD protocols described in the literature, where standard TMS coils are used to stimulate either SMA (Hawken et a., 2016) or DLPFC (Elbeh et al., 2016) with a low-frequency rTMS protocol.

Despite its clinical efficacy, also the tolerability of rTMS is of utmost importance in evaluating its clinical usability. Fortunately, rTMS has been shown to be very well tolerated with very few to no side effects in most patients. The most serious adverse event during any rTMS treatment is the potential induction of a seizure. However, the occurrence of seizures cases is extremely low (<1 in 60,000 sessions) in patients without specific risk factors such as congenital epilepsies or anatomical/brain damages (Lerner et al., 2019). A recent review of the literature on this topic highlights that the presence of neuropsychiatric diseases associated with structural cerebral damage (e.g., traumatic brain injury and stroke), general factors (e.g., stress, sleep deprivation, and increased alcohol consumption), and

some medical conditions (e.g., metabolic abnormalities and alcohol withdrawal) may increase the risk for seizures (Rossi et al., 2021). Until early 2020, a total number of 41 seizures were reported: 13 were healthy individuals and 28 were patients with clinical conditions (like psychiatric disorders and stroke). Regarding the stimulation frequency, 51% of these seizures occurred during HF-rTMS (Chou et al., 2020).

In addition to the frequency, also the location or deeper penetrating nature of some OCD protocols may affect the likelihood of seizure induction by TMS. OCD, in this sense, represents a good opportunity to document the occurrence of seizures across the various available and used treatment protocols (across regions from pre-SMA, DLPFC, and orbitofrontal cortex to bilateral DMPFC), protocols (from 1 to 20 Hz), and coils (from standard figure-8 coils to double-cone coils to H coils). This documentation will be informative in not only assessing the clinical efficacy of these various OCD rTMS protocols but also with regard to their tolerability and risk profile. This explicitly should include single case reports from naturalistic clinical settings. In this spirit, we here present the case of a 19-year-old female patient with OCD who experienced seizure during the 7th session of her rTMS treatment using the FDA-approved bilateral DMPFC 20-Hz protocol applied with a double-cone TMS coil.

Case Report/Case Presentation

A 19-year-old female patient presented with OCD. This patient has also been diagnosed with depression, Pierre Robin sequence, and mild mental retardation. First, the patient received rTMS for her depressive and anxiety symptoms. Prior to the TMS therapy, the treating psychiatrist followed a pre-rTMS treatment evaluation of the patient, indicating no seizure risk factors. Written informed consent for the rTMS treatment was obtained from the patient. She underwent rTMS treatment targeting the bilateral DLPFC, with the TMS coil being placed over the left and right DLPFC for iTBS and cTBS protocols, respectively. These theta burst protocols were applied using a figure-8 coil and consisted of the following parameters: iTBS: 5 Hz, 20 trains with 8-s intertrain interval, 10 pulses per train, 200 pulses per session, and total duration 3:08 min; cTBS: 20 trains with 0.2-s intertrain interval, 10 pulses per train, 200 pulses per session, and total duration 40 s. The stimulation intensity was set at 120% of the resting motor threshold. The patient received a total of 30 rTMS sessions. In addition to the rTMS treatment, she was taking at intervals some of the following medications: escitalopram, risperidone, lorazepam, promethazine, and olanzapine. After the completion of the treatment period, the mother of the patient reported the following changes: better attitude toward her family members, more kindness, gentle reactions, rule-following, improvement in self-care, restoration of empathy, and better appetite. The patient continued with

approximately 20 maintenance rTMS sessions once a week or once a month depending on her availability.

For a period of 18 months, the patient was free of medications, but then she started having more severe OCD symptoms. Following this, the patient underwent rTMS treatment for OCD using the FDA-approved protocol for OCD (Carmi et al., 2019) with a double-cone coil (Cool D-B80 coil). The rTMS protocol was administered at 20 Hz and contained 50 trains (40 pulses per train) and 20-s intertrain interval. A total of 2,000 pulses were given per session for 17:58 min. The double-cone coil was placed over the bilateral DMPFC situated 4 cm in front of the leg motor threshold spot, and the stimulation intensity was set at 100% of the leg motor threshold. The patient was on treatment with clonazepam (0.5 mg/day), quetiapine (600 mg/day), and sertraline (100 mg/day) during the new rTMS treatment for OCD. No adverse events were reported during the first 6 sessions.

During the 7th session, the patient experienced a seizure lasting approximately 2–3 min which was accompanied by a fast and tonic fall, facial grimacing, lateral eye deviation, tongue biting, body shaking, and generalized tonic-clonic movements. The TMS technician stopped the treatment immediately and informed the treating psychiatrist. Until the seizure ended, the TMS technician and the psychiatrist were on the patient's side and put the patient in a lateral decubitus position. Subsequently, the psychiatrist performed a normal neurological examination and checked the patient's breathing and heart rate. An increased heart rate (120 beats per min) was presented immediately after the seizure ended. Her respiration and heart (90 beats per min) rate returned to normal levels after approximately 10 min, and no other adverse events like sweating or vomiting were presented. Her postictal symptoms were confusion and headache. The patient was able to respond to verbal instructions and was discharged home. No risk factors for TMS-provoked seizures were observed on that day (Lerner et al., 2019; Rossi et al., 2021).

An MRI measurement was performed 18 months prior to the seizure episode and 2 weeks after the seizure episode (shown in Fig. 1). No visual differences were presented between them. Specifically, both of these MRIs showed several focal lesions of a few millimeters in diameter in the periventricular and subcortical white matter of the frontal and parietal lobes and in the corpus callosum. The patient continued the rTMS treatments 8 days after the seizure induction. The intensity of the treatment was reduced to 70% of the leg motor threshold. No adverse events were presented during the first 5 days with the new reduced intensity. The patient continued with the rTMS treatment to treat the severe OCD and behavioral symptoms which affected her functionality and her interactions with family and others to a great extent. These severe symptoms put herself at risk (such as cutting her hair by herself) in an OCD manner for no reason, with temper tantrums. The outweighed risk from rTMS was lower and was managed by a further reduction of the intensity of the treatment.

Following the first seizure, the patient was diagnosed with unspecified encephalopathy by a neurologist. Regarding her medication, she reduced the clonazepam dose and started taking sodium valproate. A new seizure episode occurred 10 days after her last TMS session with this new reduced intensity and the abovementioned changes in her medication. This second seizure episode happened at her school area. The situation of the patient resolved without medication or hospitalization. The characteristics of the second seizure as well as its duration were the same as the first one. However, the second seizure episode seemed to be unrelated to the rTMS therapy because it occurred 10 days after her last rTMS session and after a change of her medication.
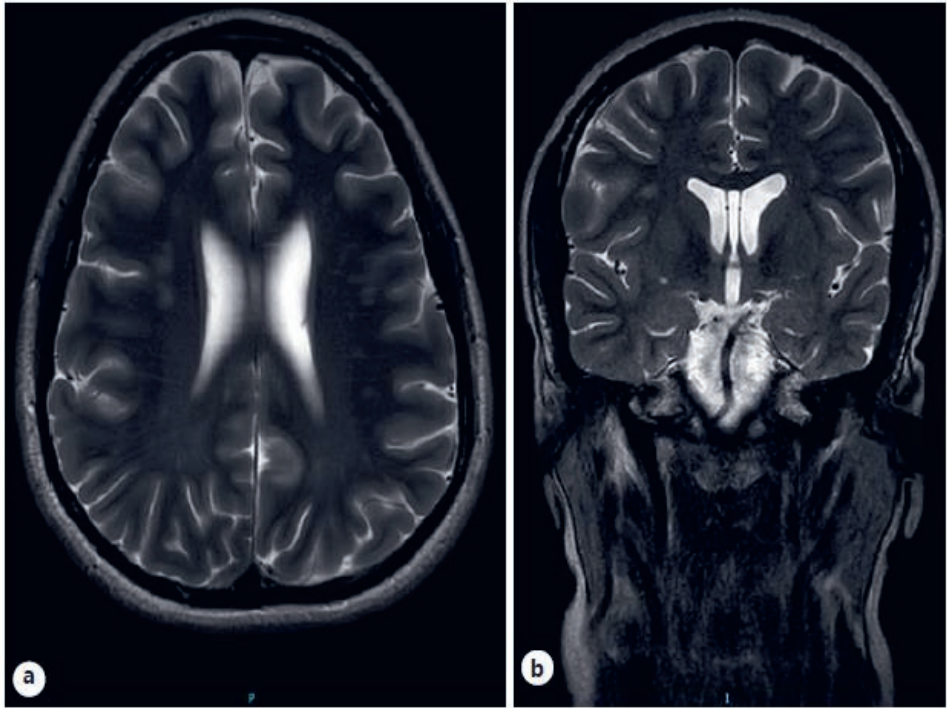
Figure 1. Brain MRI scans 2 weeks after the first seizure episode. The exam showed several focal lesions of a few millimeters in diameter in the periventricular and subcortical white matter of the frontal and parietal lobes and in the corpus callosum.

Discussion

In this case report, we present a patient who experienced a seizure while she was receiving HF-rTMS to the DMPFC using a double-cone TMS coil for treating her OCD symptoms. This patient had been treated already in the past using rTMS for her depressive and anxiety symptoms using a standard figure-8 TMS coil targeting the more superficial DLPFC. This depression rTMS treatment was well tolerated, and no serious adverse events were reported.

Syncope is a condition often misdiagnosed as epileptic seizure. Syncope is "a transient loss of consciousness caused by transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery" (Sheldon, 2015). The most possible reasons for this misdiagnosis are the following: syncope affects a large percentage of the
population (around 40%), syncope may mimic the clinical presentation of epileptic seizures, and finally, epileptic seizures and syncope may coexist in a patient (Ungar et al., 2017). Differentiating epileptic seizure from syncope can be difficult; however, there are several clinical tips to find the correct diagnosis. In the present case report, we discriminate epileptic seizure from syncope using the following clinical information. First of all, the duration of both episodes
lasted around 2–3 min. Regarding seizures, generalized tonic-clonic seizure lasts 30 s–5 min, and secondarily, generalized tonic-clonic seizure lasts 62 s (16 s–108 s), whereas syncope has fewer duration, around ~15 s (3 s–30 s) (15). In epileptic seizures, falls are characterized as fast and tonic, in contrast to syncope where falls are slow and flaccid (Kowacs et al., 2005). The patient experienced tongue-biting, a symptom that is presented rarely in syncope, while is a common symptom in epileptic seizure (Rossi et al., 2021; Sheldon, 2015). Another point that differs between epileptic seizure and syncope is the eye deviation. Lateral eye deviation is more common in epileptic seizures, whereas fixed or upward eye deviation in syncope. As for heart rate, syncope is associated with bradycardia (Rossi et al., 2021), contrastingly the patient in the present case report experienced tachycardia following both episodes. Finally, her postictal phases lasted around 10 min, which is a typical period of time between the end of a seizure and the return to baseline situation. Her postictal phases characterized with symptoms like confusion and headache. Confusion is the most common symptom of the postictal phase of epileptic seizure in contrast to syncope where the most frequent symptoms are brief haziness, fatigue, diaphoresis, and nausea (Sheldon, 2015). During her OCD treatment, however, the first seizure episode occurred during the 7th session using the recently FDA-approved protocol for OCD targeting the DMPFC using a double-cone coil with high-frequency rTMS (Carmi et al., 2019). In a study by Carmi et al. (2019), 89 patients were treated with this protocol, and no seizure cases were reported. To our knowledge, until today, there have been no reported

seizures using this FDA-approved protocol for OCD. As regards the stimulation frequency, Chou et al. (2020) suggested that around half of the reported seizure cases until February 2020 occurred during HF-rTMS. Contrarily, Lerner et al. (2019) noted that HF-rTMS was no more likely to cause seizures than LF-rTMS and single/paired-pulse TMS when applied in patients without risk factors. Taking into account those previous studies, it thus remains unclear whether HF-rTMS is the main or only driving factor for an increased risk for seizure induction compared with other TMS protocol parameters. However, according to the safety and recommendations for TMS use in healthy subjects and patient populations (Rossi et al., 2021), "any type of person with any pattern of stimulation might have a seizure."

During the last decades, different types of TMS coils have been developed with different geometries and stimulation properties. The main types of TMS coils are figure-of-8 coil, circular coil, double-cone coil, and H coil. The figure-of-8 coil is the most commonly used coil in TMS treatment. It is characterized by 2 adjacent wings, and it was designed to provide more focal stimulation of cortical regions, below the central part of the coil. The double-cone coil is characterized by 2 large adjacent circular wings at an angle of 95° (Rossi et al., 2021). Double-cone coils have the ability to stimulate deeper brain areas and produce a higher magnetic field with higher depth of penetration in contrast to standard TMS coils such as figure-of-8 coils (Schecklmann et al., 2020). According to a recent survey, double-cone coils are associated with only 1 seizure case (Lerner et al., 2019). In 2021, a review on safety of use of rTMS in clinical practice and research has been published reporting no serious adverse events using the double-cone coil (Rossi et al., 2021). The risk for seizure induction using the double-cone coil is 0.12/1,000, while using the figure-of-8 coil is 0.08/1,000 (Lerner et al., 2019). Double-cone coils are less frequently used in rTMS practice compared with the figure-of-8 coil. This may be a reason why TMS-induced seizures are less frequent while using the double-cone coil. Our patient, in contrast, did experience a seizure during the first sessions of this novel OCD TMS protocol using a double-cone coil over DMPFC. Interestingly, this patient was experienced with rTMS, undergoing 30 sessions of theta burst rTMS to the DLPFC using a figure-8 coil without any adverse effects. This suggests that the rTMS-induced seizure in her case is related to the change in target region or coil type. Nevertheless, there are several other predisposing factors for the occurrence of seizure in psychiatric patients such as pharmacotherapy that may affect seizure thresholds, substance consumption such as alcohol, caffeine, and some instable behavioral patterns such as agitation and sleep deprivation (Rossi et al., 2021). However, as in all naturalistic settings and most patients, this conclusion may not be the only possible interpretation. It is noteworthy that this patient also experienced a second seizure episode, a few days after the last rTMS session was applied. Therefore, the second seizure episode appears to be unrelated to the rTMS therapy and possibly related to this change of her medication. Also, during and following this rTMS treatment, an unspecific brain anomaly was

detected in her MRI scan, potentially putting her a posteriori in a certain risk group of patients for rTMS. This of course does not explain the well-tolerated depression TMS treatment she received prior to the OCD TMS protocol.

Conclusion

This seizure induction may be the first reported seizure using the recently FDA-approved protocol for OCD targeting the DMPFC with a double-cone TMS coil. This seizure was most likely triggered by rTMS. At this point, we want to nonetheless report this case in order to increase awareness that with new protocols and new coil types, also the evaluation of tolerability needs to be updated and closely monitored. Despite its acceptability and increasing popularity, TMS should still be administered by clinicians or TMS technicians who are aware of such cases and prepared to follow all the appropriate recommendations and seizure management protocols during the rTMS treatment. Future reviews are needed to clarify further the mechanisms that may trigger seizure episodes during rTMS treatment (patient characteristics, TMS parameters, target region, and TMS coil) in order to reduce the likelihood of rTMS-induced seizures.

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CHAPTER 8

General Discussion

The primary objective of this thesis is to delve into the use of rTMS in the field of neuropsychiatry. In pursuit of this objective, various studies were undertaken with distinct methodologies, including a review of existing literature, randomized controlled trials, single-case studies, and a retrospective naturalistic study. These studies aimed to explore diverse facets of rTMS, such as its effectiveness, safety, tolerability, and potential applications in neuropsychiatry. RCTs are widely regarded as the most reliable method for assessing the effectiveness and safety of interventions, such as rTMS. Through randomization, potential sources of bias and confounding factors can be minimized, thereby ensuring that any observed differences between the treatment and control groups are solely attributed to the intervention. The significance of RCTs in the context of this thesis lies in their ability to provide high-quality evidence on the efficacy and safety of rTMS in neuropsychiatry. Such evidence is essential for guiding clinical practice and empowering healthcare professionals to make informed, evidence-based decisions regarding the use of rTMS in their patients. Furthermore, the retrospective study featured in the thesis is a valuable addition, as it offers a distinct perspective on the application of rTMS in neuropsychiatry. In a retrospective study, data is gathered from medical records or databases and analyzed retrospectively. This research design can be instrumental in exploring the practical outcomes of rTMS treatment, such as its long-term effects and tolerability in real-world scenarios. Within the context of the thesis, the retrospective study likely aimed to assess the efficacy of rTMS in treating treatment-resistant depression compared to ketamine, a frequently used alternative treatment. By scrutinizing medical records, the study provided valuable insights into the actual effectiveness of rTMS, facilitating comparisons with other treatments. Additionally, the thesis included unique case reports, which are detailed accounts of individual patients who underwent rTMS treatment for neurological conditions. Case reports can provide valuable insights into the use of rTMS in clinical practice, highlighting both positive and negative outcomes, as well as potential challenges and limitations. In essence, we sought to augment the current literature on rTMS in neuropsychiatry by presenting a comprehensive synopsis of its application, limitations, and potential advantages. By employing various research designs and distinctive case reports, the thesis offers a multifarious outlook on rTMS that could have implications for clinical practice and guide future research endeavors in this domain.

Summary

In *Chapter 2 and 3*, the efficacy of accelerated intermittent theta burst stimulation (aiTBS) was assessed for smoking cessation through a randomized, double-blind, controlled study involving

89 participants. The treatment was administered over five consecutive days to the left DLPFC, and the impact of exposure to smoking-related cues during TMS was also examined in comparison to neutral cues. According to the findings of the study presented in Chapter 2, aiTBS is a tolerable treatment, and all treatment groups demonstrated comparable reductions in cigarette consumption, nicotine dependence, craving, and perceived stress. The effect on nicotine dependence, general craving, and perceived stress persisted for at least one week following treatment. Chapter 3's follow-up study revealed that the beneficial impact of the treatment on reducing nicotine dependence and tobacco craving persists for at least a month after the completion of the therapy. However, it appears to diminish after six months following the treatment. Furthermore, findings suggest that active aiTBS applied over the left DLPFC, in conjunction with smoking-related cues, is as effective in promoting smoking cessation as active aiTBS combined with neutral cues, as well as placebo aiTBS. The study's findings add to the growing body of evidence on the potential use of TMS as a non-pharmacological approach to treating addiction. Additionally, results also indicate that the placebo effect could have a significant impact on the efficacy of aiTBS for smoking cessation. Therefore, when assessing the effectiveness of brain stimulation treatments, it is crucial to consider the role of placebo treatment.

In general, the results of this research could aid in creating better and more focused therapies for quitting smoking. This study emphasizes the significance of comprehending the mechanisms responsible for the therapeutic benefits of brain stimulation methods and controlling for placebo effects during clinical investigations. Moreover, the use of innovative placebo coil technology in this study is a notable advantage as it enabled researchers to differentiate the effects of the actual treatment from the placebo treatment.

Chapter 4 aimed at comparing and demonstrating the immediate antidepressant effectiveness of intramuscular ketamine and rTMS in patients with depression seeking treatment in a naturalistic clinical mental health environment. Clinical data from 24 patients with depression resistant to treatment were collected from a real-life clinic. Twelve of these patients received intramuscular ketamine treatment twice a week for eight sessions, while the remaining twelve were treated with 30 sessions of left DLPFC-iTBS. The study was conducted retrospectively, analyzing medical records of patients who had undergone either ketamine infusions or rTMS treatment, and evaluated their symptom severity before and after treatment. Results showed that both ketamine and rTMS were effective in reducing depressive and anxiety symptoms in patients with TRD, with no significant difference in efficacy between the two treatments, indicating that both treatments were equally effective. Finally, findings revealed high remission and response rates in both groups, with no statistical differences between the ketamine and rTMS groups in terms of remission and response rates.

This study addresses a critical issue in mental health treatment, specifically treatment-resistant depression, which presents a significant challenge for both clinicians and patients. It contributes to the existing knowledge on the effectiveness of ketamine and rTMS in treating depression and provides insights into their use in real-world clinical settings and research. The study emphasizes the importance of personalized treatment plans for patients with treatment-resistant depression and suggests that both ketamine and rTMS could be viable treatment options. However, further research is necessary to identify the factors that influence the efficacy of each treatment and determine which patients would benefit most from each approach. Overall, this study is significant and adds to our understanding of how to better treat patients with treatment-resistant depression.

Chapter 5 and 6 includes two case reports that aimed to evaluate the effectiveness of rTMS in treating two common and persistent neurological conditions: epilepsy and Parkinson's Disease. Chapter 5 presents a case of a patient with frontal lobe epilepsy, and the aim was to examine the feasibility, safety, and potential clinical effectiveness of bilateral orbitofrontal (OFC) LF-rTMS for treating epileptic seizures. Frontal lobe epilepsy is challenging to manage with medication alone, necessitating the exploration of alternative treatments like rTMS. According to the patient's self-reported satisfaction with rTMS therapy, it helped to decrease the frequency of focal attacks and eliminate the preceding feelings of fear and panic. This case study provides valuable insights into the potential use of rTMS as a treatment option for patients with refractory frontal lobe epilepsy. Nevertheless, the study's design limitations warrant cautious interpretation of the findings. Future studies with larger sample sizes and controlled designs are required to investigate further the potential of rTMS in the management of refractory frontal lobe epilepsy. In Chapter 6, a patient with PD is presented who underwent an accelerated form of HF-rTMS on the contralateral side of their main difficulties. The aim was to determine the clinical effectiveness of rTMS in treating health-related quality of life (QoL) symptomatology and depressive symptoms in PD, as well as the long-term effects of rTMS during the maintenance phase. The study is also important, as PD is a debilitating neurodegenerative disorder, and depression is a common comorbidity that further worsens the quality of life of patients. The results indicate that HF-rTMS over the right primary motor cortex (M1) is a safe and well-tolerated treatment that improved the patient's health-related QoL and depressive symptoms. These positive effects persisted for at least five months after treatment. Hence, HF-rTMS over the right M1 may be a viable treatment option for patients with PD. However, it is important to note that this is a single case study, and therefore, the findings warrant further research to better understand the effectiveness of rTMS as a treatment for PD.

Overall, although both reports focus on the outcomes of a single patient, they show that rTMS treatment can successfully suppress seizures in frontal lobe epilepsy and improve depressive symptoms and overall quality of life in PD. These findings suggest that rTMS may be a viable

therapeutic option for certain cases of neurological disorders. However, further research is necessary to establish the safety and effectiveness of rTMS in larger patient populations. In addition, the results may have implications for the development of new treatment strategies for other neurological conditions.

Finally, *Chapter 7* of the thesis addresses the safety concerns related to TMS, which have gained importance due to the emergence of new TMS coil technology. Despite being generally considered safe and well-tolerated with few side effects, the safety of these new coil geometries is not yet fully established. Inducing a seizure is a potential serious adverse event that can occur during any rTMS treatment. Although rTMS has shown promising results in treating treatment-resistant OCD, the optimal target area and stimulation frequency are still controversial. The case report presented in this chapter involves a patient with OCD who experienced a seizure during her 7th session of rTMS treatment using the FDA-approved 20-Hz protocol for OCD, applied bilaterally over the left and right DMPFC with a double-cone coil. Nonetheless, it is unclear whether the seizure was a direct result of the rTMS treatment or if the patient had preexisting risk factors for seizures. Therefore, it is crucial to take into account individual patient characteristics and considerations when selecting treatment protocols, and to make appropriate arrangements to ensure patient safety. The chapter highlights the importance of caution and careful consideration during rTMS administration. However, the study's findings are limited by the use of a single case report, which may restrict the generalizability of the results.

Overall, this study provides valuable insights into the potential risks and benefits of TMS treatment and highlights the need for careful patient selection, monitoring, and management of adverse effects to ensure the safety of patients. The study provides a foundation for further research on the safety and efficacy of TMS treatment and the development of effective protocols to minimize the risk of adverse effects. However, further research is needed to fully understand the potential risk factors and mechanisms underlying TMS-induced seizures and to develop effective strategies to prevent or manage such adverse effects.

TMS & Smoking Cessation

Studies have indicated that rTMS shows potential as a therapy for addiction disorders, including drug and alcohol dependence (Belgers et al., 2022; Terraneo et al., 2016). Additionally, research has explored the use of rTMS as a possible treatment for smoking cessation, with several studies suggesting that it may be an effective tool for this purpose. For example, Zangen et al. (2021) conducted a multicenter double-blind randomized controlled trial, which revealed that active rTMS significantly reduced cigarette consumption and cravings compared to sham

stimulation, as early as two weeks into the treatment. Furthermore, a systematic review by Hauer et al. (2019) reported that HF-rTMS over the left DLPFC is potentially an effective and safe treatment for smoking cessation. Li et al. (2013) found that applying HF-rTMS to the left DLPFC resulted in a significant reduction of subjective cravings elicited by smoking cues in nicotine-dependent participants. Similarly, Amiaz et al. (2009) reported a decrease in cigarette consumption and nicotine dependence after ten daily sessions of rTMS applied to the DLPFC. However, the effects of the treatment appeared to diminish over time. These studies suggest that rTMS may be a promising strategy for smoking cessation, but more research is necessary to determine optimal stimulation targets, treatment protocols, and long-term effectiveness.

The iTBS protocol, a form of rTMS, has gained significant interest and importance in the rTMS community. It has been shown to be effective and safe in clinical trials, and is approved for clinical use in many countries worldwide. It is a valuable tool for clinicians and researchers seeking to improve the efficacy of rTMS treatments and better understand the mechanisms underlying brain function. Additionally, the aiTBS protocol is a variation of the iTBS protocol that has potential to reduce the time and cost of rTMS treatment while maintaining effectiveness. It has been studied for efficacy in treating major depressive disorder and has shown positive results, making it a promising option for patients with limited access to longer-term rTMS treatment. Therefore, the aiTBS protocol represents a valuable tool for improving patient access to effective and timely treatment options in the rTMS community.

This thesis includes a randomized controlled trial that examines the efficacy of aiTBS over the left DLPFC in smoking cessation using advanced placebo coil technology. Additionally, the study explores the effects of exposure to smoking-related cues during TMS. This research contributes to the expanding literature on NIBS techniques, such as TMS, for smoking cessation. Previous studies have already reported promising results in the effectiveness of TMS for smoking cessation, with significant improvements observed in smoking cessation.

The study findings revealed that active aiTBS with smoking-related cues was found to be equally effective as active aiTBS with neutral cues and placebo aiTBS in reducing cigarette consumption, nicotine dependence, craving, and perceived stress for at least one week after the treatment. This study's findings are consistent with previous TMS trials, which have shown that rTMS can significantly reduce cigarette consumption and nicotine craving (Amiaz et al., 2009; Dinur-Klein et al., 2014; Hauer et al., 2019). Therefore, the results of this study further support the potential use of TMS for smoking cessation and indicate that exposure to smoking-related cues during TMS may not affect the efficacy of the treatment.

The follow-up study revealed that the positive effects of aiTBS treatment in reducing nicotine dependence and tobacco craving persisted for at least one month after therapy completion, but gradually diminished after six months. These findings are in line with previous studies

investigating the long-term efficacy of TMS for smoking cessation. For instance, Amiaz et al. (2009) found no significant differences between active and sham TMS groups in terms of nicotine dependence and craving six months post-treatment, and that exposure to smoking-related cues had no effect on nicotine consumption and dependence. However, the study by Abdelrahman et al. (2021) reported a reduction in nicotine dependence and tobacco craving at the end of treatment in both the HF-rTMS active and sham groups, but during the three months of follow-up, this improvement was persistent only in the active group.

These results suggest that while TMS may have short-term benefits in reducing smoking-related behaviors, it may not have a sustained effect over a longer period. Nonetheless, the beneficial impact of active aiTBS on reducing nicotine dependence and tobacco craving is still promising and highlights the potential of NIBS techniques in smoking cessation treatment.

TMS & Depression

rTMS is a promising neurostimulation technique that has rapidly emerged as a potential treatment for various psychiatric disorders, including depression. Depression is a prevalent and debilitating condition affecting millions of people worldwide, with TRD presenting a significant challenge for clinicians. Although traditional treatments like psychotherapy and antidepressant medication are available for depression, they may not be effective for everyone. Hence, alternative treatments like rTMS and ketamine are increasingly in demand.

Among psychiatric disorders, depression has received extensive research attention in the context of rTMS treatment. There is a growing body of randomized controlled trials that demonstrate the efficacy of rTMS in depression treatment (Blumberger et al., 2018; O'Reardon et al., 2007), even in patients who are unresponsive to conventional antidepressants. rTMS is a safe and effective therapy for depression, and it is widely recognized and approved for clinical use in patients with TRD. Multiple studies have shown that applying TMS to the left DLPFC is a well-tolerated and effective treatment for TRD (George et al., 2013). Recently, the iTBS protocol has gained popularity in depression treatment due to its shorter session duration (Blumberger et al., 2018).

In this thesis, a retrospective study was conducted to compare the effectiveness of IM ketamine and iTBS protocol in treating treatment-resistant depression. The study revealed that both ketamine and rTMS were successful in treating this type of depression, with no significant difference in efficacy between the two treatments. These findings are in line with previous literature that has demonstrated rTMS to be a safe and well-tolerated treatment option for depression (Blumberger et al., 2018; Chu et al., 2021; Li et al., 2014; O'Reardon et al., 2007) and

with previous research indicating that ketamine is an effective treatment for depression (Marcanton et al., 2020; Murrough et al., 2013a; Murrough et al., 2013b). Ketamine, a powerful anesthetic with dissociative properties, has been used for treating various psychiatric conditions, including depression. Despite numerous studies on the efficacy of ketamine in depression, research on IM ketamine remains limited. Only a few case reports have illustrated the potential effectiveness of IM ketamine in treating depression, thus necessitating further investigation to determine its optimal use (Cusin et al., 2012; Harihar et al., 2013; Zanicotti et al., 2012).

This retrospective study represented an initial attempt to investigate and compare the effectiveness of ketamine and rTMS treatments in mitigating depression and anxiety symptoms among patients with TRD in a real-life naturalistic setting. Chen et al. (2022) recently published a post hoc pooled analysis of two randomized, double-blind, placebo-controlled studies, which sought to compare the antidepressant and antisuicidal effects of low-dose ketamine infusion and rTMS on TRD. The study revealed that both low-dose ketamine infusion and rTMS protocols (iTBS/10-Hz rTMS) displayed superior antidepressant effects on overall depressive symptoms and specific depressive symptoms, with similar antidepressant effects compared to controls. In addition, the study reported that both iTBS and ketamine infusion exhibited a stronger antisuicidal effect than did 10-Hz rTMS and control. Hence, both rTMS and ketamine should be included in the treatment of TRD, although they may be employed in different clinical contexts.

One approach that has gained attention in recent years is the combination of ketamine and rTMS. Although both treatments have demonstrated efficacy in treating depression, some studies suggest that combining the two may lead to an enhancement in their antidepressant effects. Various case reports have indicated that a combination rTMS and ketamine protocol is effective for treating TRD, treatment-resistant bipolar depression, bipolar II disorder, and severe depression in bipolar I disorder (Best, 2014; Best & Griffin, 2015; Best et al., 2015; Elkrief et al., 2022). Significantly, a long-term retrospective review showed that a combination of TMS with ketamine is an effective and durable therapy for TRD (Best et al., 2019). While earlier research indicates that the combination of ketamine and rTMS is an effective and durable treatment for depression, the current retrospective comparative study represents the first effort to describe and compare both treatment alternatives as independent therapies in a real-life naturalistic setting.

In conclusion, rTMS and ketamine are emerging as promising alternatives to traditional depression treatments, particularly in the context of TRD. Depression is a widespread condition with a significant impact on the lives of millions of people globally, making the need for effective treatments paramount. While rTMS has been extensively studied and demonstrated to be a safe and well-tolerated treatment for depression, ketamine has shown rapid and long-lasting antidepressant effects in patients with TRD. Furthermore, combining these two

treatments may enhance their efficacy, as suggested by some studies. The findings of this thesis add to the growing body of evidence supporting the use of rTMS and ketamine as effective treatments for depression, providing hope for patients who do not respond to conventional therapies.

TMS & Neurological Disorders

As a potential therapeutic intervention for various neurological disorders, rTMS has attracted attention as a non-invasive neuromodulatory technique in recent years. Several studies have investigated the effectiveness of rTMS in the treatment of various neurological disorders, including Parkinson's disease, epilepsy, multiple sclerosis, and stroke.

This thesis presents a case study of a patient diagnosed with frontal lobe epilepsy who received LF-rTMS over the bilateral orbitofrontal cortex. The results demonstrated that the rTMS protocol was effective in reducing the frequency and severity of seizures in the patient, indicating the potential of this treatment approach for other epilepsy patients. These findings are consistent with previous research on rTMS as a possible treatment option for epilepsy, which has shown promising results. Studies have reported a reduction in seizure frequency in patients with medically refractory epilepsy following LF-rTMS (Mishra et al., 2020; Sun et al., 2012). Despite the promising results, safety concerns have been raised regarding the use of rTMS in patients with epilepsy. Seizure induction is a potential risk associated with rTMS, and patients with epilepsy may be at a higher risk for seizure induction during rTMS due to their underlying condition (Lerner et al., 2019; Rossi et al., 2021). To address this concern, several safety guidelines have been established for the use of rTMS in patients with epilepsy (Rossi et al., 2021). Finally, this case report emphasizes the significance of tailoring rTMS treatment to individual patients. The bilateral orbitofrontal cortex was chosen as a target due to its accessibility, significant connectivity with relevant neural areas, and the patient's bilateral neuronal migration disorder. These findings signify a move towards personalizing rTMS targets to patients' specific symptoms, rather than relying on categorical diagnoses alone. Personalized rTMS treatment has demonstrated promising results in improving outcomes for a range of neuropsychiatric disorders. Personalization to a patient's specific characteristics, such as brain location, age, and cognitive state, has been shown to enhance the efficacy of rTMS and symptom reduction. Further investigation is necessary to understand the mechanisms underlying personalized rTMS treatment and to develop effective methods for customizing treatment to individual patients. This case report contributes to the expanding body of research exploring the potential of rTMS as a therapeutic approach for epilepsy. Although further studies involving larger patient groups are required to fully comprehend the effects of rTMS on

epilepsy, the results suggest that this approach may be a promising alternative or supplementary treatment for individuals with medically refractory epilepsy. Nonetheless, safety concerns related to the induction of seizures during rTMS necessitate cautious patient selection and monitoring.

This thesis also presented a case study of a patient with Parkinson's Disease (PD), who underwent an accelerate form of HF-rTMS on the right primary motor cortex, contralateral to his main difficulties. The results showed that the treatment led to improvements in the patient's quality of life and depressive symptoms, and these positive effects were sustained for at least five months post-treatment. The findings align with earlier research indicating that HF-rTMS applied to the primary motor cortex can effectively address PD symptomatology (Aftanas et al., 2020; Brys et al., 2016; Lefaucheur et al., 2020). Additionally, studies have revealed that rTMS can ameliorate cognitive and emotional symptoms, including depression, in this population (Lefaucheur et al., 2020). Furthermore, this case report highlights the significance of post-treatment maintenance, which refers to the continued use of rTMS after an initial treatment course to sustain therapeutic benefits. Various studies have shown that maintenance rTMS can effectively prolong the benefits of treatment and delay relapse, particularly in treating depression (Fitzgerald et al., 2013; Richieri et al., 2013). However, the ideal frequency and duration of maintenance treatment remain under investigation, and further research is required to establish the long-term safety and efficacy of this strategy. This case report presents some initial indications of the potential advantages of utilizing HF-rTMS for enhancing both quality of life and depressive symptoms in PD patients. Nonetheless, larger and more rigorous investigations are essential to verify the efficacy of this treatment approach and to further investigate its possible advantages for individuals with Parkinson's disease.

To sum up, this thesis explores the potential of rTMS as a therapeutic intervention for neurological disorders, including Parkinson's disease and epilepsy, with an emphasis on personalizing treatment to individual patients' symptoms and utilizing post-treatment maintenance to improve outcomes.

Placebo Effect in TMS

Placebo effect refers to the positive outcomes that result from receiving an inactive treatment or intervention, such as a sugar pill or a sham procedure, due to the expectations and beliefs of the patient. Although placebo effect is often considered a nuisance in clinical trials, it is increasingly recognized as an important factor in evaluating the efficacy of treatments, including rTMS. The smoking cessation RCT outlined in this thesis revealed that all conditions, including the placebo stimulation, were equally successful in reducing cigarette usage, CO

levels, smoking cravings, and nicotine dependence. This study contributes to the existing literature by suggesting that placebo effects may be a significant factor in the effectiveness of aiTBS for smoking cessation.

This study's results are in line with previous research, which has also found no significant differences between active and placebo stimulation in rTMS treatment for various conditions. For instance, according to Mansur et al. (2011), a randomized controlled trial conducted on OCD patients showed that applying HF-rTMS over the DLPFC did not result in a significant difference in relieving OC symptoms compared to sham rTMS. In a meta-analysis conducted by Jin et al. (2021), the placebo effect of rTMS on post-stroke motor rehabilitation was examined. The findings indicate that the placebo effect of rTMS stroke trials is moderate in magnitude, with the number of stimulation sessions having an influence on the effect. This suggests that the placebo response may play a role in the therapeutic response to rTMS in stroke rehabilitation. Finally, a systematic-review and meta-analysis of Razza et al. (2018) showed that the depression trials involving rTMS showed a substantial placebo response, which was linked to the improvement of depression in the group receiving active treatment. Additionally, placebo response may contribute to the therapeutic effect of rTMS in MDD. These findings suggest that the placebo effect may play a significant role in the effectiveness of rTMS treatment, and future studies may need to take this into consideration when evaluating its therapeutic effects.

According to Granato et al. (2019) and Kaptchuk et al. (2000), there are various factors that can boost the placebo effect in TMS. High motivation and positive expectations and beliefs can increase the likelihood of experiencing a placebo response. Additionally, the hospital environment, use of a medical device, and positive interaction with healthcare providers can contribute to a stronger placebo response in patients. Furthermore, cognitive conditioning, which refers to the association between the medical setting and the cure, may also play a role in enhancing the placebo effect. In summary, comprehending the factors that can enhance the placebo response is crucial for developing effective clinical trials and maximizing the therapeutic benefits of TMS.

The enhanced placebo effect observed in the RCT in smoking cessation was influenced by several specific factors that were not directly related to rTMS treatment. One of these factors was the high level of motivation among participants to quit smoking, which likely contributed to the initial effects seen in both active and placebo TMS groups. Additionally, a novel and advanced placebo coil technology was used in the study, which mimicked the experience of active TMS and provided an undistinguishable experience for participants in both groups. These factors likely played a significant role in the highly effective placebo condition observed in the study, making it challenging to differentiate the actual effect of active rTMS from the placebo effect.

In summary, the placebo effect is a significant factor in evaluating the efficacy of treatments, including rTMS. This phenomenon has been observed in various studies, including the RCT of the present thesis in smoking cessation, which showed that the placebo effect may contribute to the effectiveness of aiTBS for smoking cessation. The placebo response may play a significant role in the therapeutic response to rTMS, and future studies may need to consider this factor when evaluating its therapeutic effects. Understanding the factors that can enhance the placebo response is crucial for developing effective clinical trials and maximizing the therapeutic benefits of rTMS. Further research is needed to better understand the underlying mechanisms of placebo response in rTMS and to develop more effective ways to control for placebo response in clinical trials.

Safety

This thesis presents a case study of a patient who had a seizure during her rTMS treatment for OCD. The patient received the FDA-approved 20-Hz protocol using a double-cone coil bilaterally over the left and right DMPFC. The case underscores the significance of diligent monitoring and informed consent during rTMS treatment to avert adverse events such as seizures.

rTMS is generally considered a safe treatment option for various neurological and psychiatric disorders, including depression, anxiety, and schizophrenia. However, like any medical intervention, rTMS is not without its potential adverse effects. While the incidence of adverse events associated with rTMS is low, it is important to be aware of them. One of the most commonly reported adverse events of rTMS is scalp discomfort, which can range from mild to severe (Rossi et al., 2021). This discomfort is typically localized to the area where the stimulation coil is placed on the scalp, and it usually subsides shortly after the stimulation session ends. Other common adverse events associated with rTMS include headaches and fatigue, which can also be mild to moderate in intensity and typically resolve on their own within a few hours or days. Less common adverse events of rTMS include seizures and hearing loss (Rossi et al., 2009; Rossi et al., 2021). Nevertheless, the likelihood of seizures is remarkably rare (less than 1 in 60,000 sessions) among patients who do not have specific risk factors such as congenital epilepsies or anatomical/brain damages (Lerner et al., 2019). According to a recent literature review, the likelihood of experiencing seizures may be heightened by the presence of neuropsychiatric disorders associated with structural cerebral damage, as well as general factors such as stress, sleep deprivation, and increased alcohol consumption, and certain medical conditions like metabolic abnormalities and alcohol withdrawal (Rossi et al., 2021).

To minimize potential risks associated with rTMS, several safety protocols and guidelines have been established by researchers (Rossi et al., 2009; Rossi et al., 2021). One of the most critical safety parameters during rTMS treatment is ensuring that the stimulation remains within safe limits, including the maximum intensity of the stimulation, the frequency of pulses, and the length of the stimulation session. The stimulation intensity should not exceed the individual's motor threshold, which is the minimum level of intensity required to elicit a visible muscle twitch. Another critical concern during rTMS is the potential risk of seizures. Although the risk of seizure induction during rTMS is generally low, it can be increased in individuals with pre-existing neurological disorders, such as epilepsy. To mitigate this risk, it is recommended to assess patients for potential seizure risk factors before starting rTMS treatment. Moreover, it is advisable to have a qualified healthcare professional present throughout the entire rTMS session to monitor for any signs of seizure activity and respond appropriately if needed. Additionally, it is crucial to monitor the patient's medical history, medication use, and any potential contraindications to the use of rTMS to ensure their safety during treatment. Patients should also be informed of any potential side effects or risks associated with rTMS, such as mild headaches, scalp discomfort, or changes in mood or behavior.

To conclude, rTMS is a safe and well-tolerated treatment for various neuropsychiatric disorders when applied within safe limits and with appropriate safety parameters and recommendations. It is important for healthcare professionals to carefully monitor and assess the individual risks and benefits of rTMS treatment for each patient to ensure the best possible outcomes while minimizing potential risks and adverse effects.

Limitations

The studies presented in this thesis offer valuable insights into the application of rTMS in the field of neuropsychiatry. However, it is essential to consider the limitations of these studies while interpreting their findings.

The RCTs assessing rTMS as a smoking cessation intervention have several limitations to consider. The use of advanced placebo coil technology in the study can be considered a strength, but it may also restrict the generalizability of the findings to settings where this technology is not available. In addition, some participants may have been able to distinguish between active and placebo stimulation, leading to potential unblinding and impacting the results. The study's lack of diversity, being limited to a specific population of smokers in Cyprus, also limits the generalizability of the results. Furthermore, the study did not compare accelerated intermittent theta burst stimulation to other smoking cessation treatments, which restricts its ability to evaluate its relative efficacy. Regarding the follow-up study, the lack of

objective measures of smoking cessation beyond self-reported rates may be a limitation. The study also did not assess treatment adherence beyond self-reported attendance at treatment sessions, which could affect the interpretation of the results. Finally, the study only followed participants for a short period after the intervention (up to 6 months post-treatment), making it challenging to draw conclusions about the long-term effectiveness of the treatment.

Furthermore, the retrospective naturalistic study that compared the effectiveness of rTMS and ketamine in treating depression was hindered by its retrospective design, which may introduce bias and confounding variables that could impact the results. Additionally, the small sample size may limit the generalizability of the findings, and the lack of randomization may introduce bias and confounding variables that can influence the results of the study. The heterogeneity of the sample also presents difficulties in drawing firm conclusions about the efficacy of ketamine and rTMS for treatment-resistant depression. The lack of blinding also presents the potential for bias to influence the results of the study.

There two case studies examining the effectiveness of rTMS in treating neurological disorders are limited by their reliance on single cases. Specifically, the results are based on single cases, which limits their statistical power and applicability to a wider population. The findings need to be replicated in larger, controlled studies with more participants to confirm their validity. Secondly, the absence of a comparison group or control condition makes it difficult to ascertain whether the observed results are solely due to the rTMS treatment or other factors such as the natural course of the disease or the placebo effect. Lastly, the studies did not provide any long-term follow-up data, so it remains unclear whether the observed improvements persist over time, and long-term follow-up is essential to assess the intervention's lasting effects.

Finally, the case report on TMS-induced seizure is subject to the same limitations as mentioned earlier regarding the single design of the study. Furthermore, since the study only involved one patient, it is challenging to draw definitive conclusions about the safety and efficacy of the DMPFC protocol for treating OCD in a broader population. Additionally, there could be other potential confounding factors that contributed to the seizure event, such as the patient's underlying medical conditions or concurrent medications, which were not adequately examined in the study.

Overall, while these articles provide important insights, future research with larger sample sizes, longer follow-up periods, and more rigorous designs will be necessary to confirm these findings.

Future Directions

Although the current thesis has its limitations, rTMS has shown great potential as a non-invasive treatment option for various neurological and psychiatric disorders. This thesis presents investigations into the effectiveness of rTMS for conditions including depression, smoking cessation, epilepsy, and PD. While the findings of these studies are encouraging, further research is required to advance our understanding of this treatment modality.

The RCT study yields valuable insights for investigating the role of placebo effects in rTMS treatments and informing future research on the use of aiTBS for smoking cessation. While the study specifically focused on advanced placebo coil technology, the results suggest that advancements in placebo technology may play a role in future rTMS research. As the field continues to evolve, it will be important to develop more effective methods for delivering rTMS treatments, including the use of advanced placebo technology to better control for the placebo effect. Additionally, future research may explore the use of personalized rTMS treatments for smoking cessation. By tailoring treatments to the individual, it may be possible to improve the effectiveness of rTMS for smoking cessation and other conditions. The study also highlights the potential of iTBS for smoking cessation. While the results were not significantly different between the active and placebo groups, the use of iTBS is a relatively new area of research, and future studies may further explore its effectiveness for smoking cessation and other conditions. Future research may also explore the use of rTMS for other aspects of smoking cessation beyond the initial quitting phase, such as preventing relapse. Additionally, the potential of rTMS for addressing comorbid conditions in smokers, such as depression and anxiety, may be an important area for future research. Further research could explore the potential benefits of combining aiTBS with other interventions, such as cognitive-behavioral therapy and pharmacotherapy, to enhance the effectiveness of smoking cessation treatments. Additionally, future studies could investigate the long-term effects of aiTBS and explore the potential benefits of maintenance treatment in smoking cessation. Moreover, the use of neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), could help to identify neural biomarkers of addiction and personalize rTMS treatment protocols based on individual brain connectivity patterns.

The retrospective study demonstrated that rTMS is a promising treatment option for treatment-resistant depression, with efficacy rates comparable to those of ketamine. Although the study was retrospective and naturalistic in design, future research could expand upon these findings through the use of larger randomized controlled trials with long-term follow-up periods. Additionally, further research could explore potential differences in efficacy rates based on the specific rTMS protocol used or the location of stimulation. Another important direction for future research could involve the identification of biomarkers that predict an

individual's response to rTMS. This could potentially allow for more personalized treatment approaches, as well as the optimization of stimulation parameters for each individual. In addition, research could explore the potential for combining rTMS with other therapeutic interventions, such as cognitive behavioral therapy or pharmacotherapy, to enhance treatment outcomes. Furthermore, future research could examine the mechanisms underlying the therapeutic effects of rTMS for treatment-resistant depression. By elucidating these mechanisms, researchers could identify potential targets for the development of new treatments and optimize existing rTMS protocols. One promising direction could involve the investigation of the role of neuroplasticity in the antidepressant effects of rTMS, as well as the potential modulation of plasticity through other interventions such as exercise or cognitive training. Finally, future research could focus on the potential use of rTMS as a preventive or maintenance treatment for depression. While the study focused on treatment-resistant depression, research has also demonstrated the efficacy of rTMS for acute depression. Maintenance rTMS could potentially prevent relapse in individuals with a history of depression, which could have significant clinical and economic implications. Additionally, future research could examine the potential use of rTMS for the prevention of depression in at-risk populations, such as individuals with a history of trauma or stress.

The case reports of patients with neurological disorders revealed encouraging outcomes, including the reduction of seizure frequency in epilepsy, and the improvement of quality of life and depressive symptomatology in PD. This finding could lead to further investigations into the effectiveness of rTMS in treating epilepsy and PD. Regarding epilepsy, one area of future research could be to investigate the potential of rTMS in combination with other treatments, such as antiepileptic drugs, to achieve better seizure control. Another potential future direction is to explore the use of rTMS in other types of epilepsy. While the case report focused on frontal lobe epilepsy, it is possible that rTMS could also be effective in treating other types of epilepsy, such as temporal lobe epilepsy. Research in this area could help to determine which patients are most likely to benefit from rTMS treatment, as well as identifying the optimal parameters for magnetic stimulation. There is also a need for research to investigate the long-term effects of rTMS in epilepsy. The case report presented promising short-term results, but it is unclear whether the effects are sustained over a longer period of time. Future studies could include follow-up assessments over several months or years to investigate the durability of the treatment effects, and to determine whether maintenance treatments may be necessary to sustain the benefits. Finally, as with all medical interventions, there is a need for research to establish the safety of rTMS in epilepsy. While rTMS has a good safety profile in general, it is important to determine whether there are any specific risks associated with its use in epilepsy patients, and to identify ways to minimize these risks. Future studies could investigate the safety of rTMS in epilepsy patients, including the risk of seizure induction, and develop guidelines for safe and effective use of this treatment modality. In PD, future directions may

involve conducting larger controlled studies to further explore the efficacy of rTMS in improving outcomes in PD, and potentially investigating its effects on other comorbidities, such as anxiety or cognitive decline. As the case report only presented data from a single case, future research should investigate the effectiveness of HF-rTMS in PD with larger sample sizes and controlled designs. Additionally, further exploration of the optimal stimulation parameters for rTMS in PD may be warranted, such as the number of pulses per session, the frequency and duration of the stimulation, and the optimal placement of the coil. By further understanding the most effective stimulation protocols for rTMS in PD, clinicians may be able to tailor treatment plans to each individual patient for optimal outcomes. While the case report focused on the use of rTMS as an adjunctive treatment for depression and quality of life in PD, future studies may also investigate its potential effects on other symptoms, such as tremors, rigidity, and bradykinesia. Such studies could investigate the effectiveness of rTMS in combination with traditional pharmacological interventions, or as a standalone treatment. Lastly, the study highlights the need for continued research into the potential long-term effects of rTMS in PD. While the study reported short-term improvements, the long-term effects of rTMS on symptoms of PD, as well as potential side effects, remain unknown. Longitudinal studies could provide important information about the lasting effects of rTMS on PD, potentially guiding the development of personalized treatment plans for individual patients.

Lastly, the case report on TMS-induced seizure implies the importance of clinicians' vigilance in monitoring patients for potential adverse events, especially those with a history of epilepsy or other neurological disorders. Future studies may focus on developing more refined safety protocols and risk assessment tools to reduce the likelihood of seizure induction during rTMS. Additionally, further research may be needed to investigate the efficacy of rTMS for treating OCD. While some studies have shown promising results, others have reported inconclusive or weak evidence for the effectiveness of rTMS in this population. Future studies may explore the use of alternative brain stimulation techniques or novel rTMS protocols to improve treatment outcomes for patients with OCD. Finally, as rTMS continues to gain popularity as a treatment option for a range of psychiatric and neurological conditions, there is a growing need for standardized protocols and treatment guidelines. Future research may focus on developing standardized treatment protocols and guidelines for rTMS, particularly for high-risk patient populations such as those with a history of epilepsy or other neurological conditions.

Overall, future research should continue to explore the potential of rTMS in each of these areas, including investigations into personalized treatments, advanced placebo technology, and potential biomarkers for predicting response to treatment. In addition, future research could explore the mechanisms underlying the therapeutic effects of rTMS and identify targets for the development of new treatments. The safety and long-term effects of rTMS should also be investigated to optimize its use as a therapeutic modality.

Conclusions

The studies conducted for the present thesis contribute significantly to the body of knowledge concerning the effectiveness and potential uses of rTMS in neuropsychiatry. The results of these studies provide important insights into the potential of rTMS in the treatment of mental health conditions, including depression, nicotine addiction, and Parkinson's disease, among others. Moreover, these studies suggest the need for further research to better understand the full range of applications and limitations of rTMS. However, it is essential to exercise caution and careful monitoring to prevent any adverse effects associated with rTMS treatment. Additionally, the research presented in this thesis underscores the significance of the placebo effect in rTMS studies, as evidenced by the use of advanced placebo coil technology in the smoking cessation study. It also highlights alternative treatment options such as ketamine, which was compared to rTMS in a retrospective naturalistic study for treatment-resistant depression. By investigating both rTMS and alternative treatments, this thesis provides valuable insights into the complexities of neuropsychiatric treatment and the importance of exploring a range of options to find the best treatment for each individual. Overall, the current thesis highlights the potential of rTMS as a valuable tool for neuropsychiatric treatment, emphasizing the need for further research to fully exploit its therapeutic potential while ensuring safety and minimizing risks.

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APPENDIX

SUMMARY

This thesis offers a valuable contribution to the field of neuropsychiatry by exploring the potential applications of repetitive Transcranial Magnetic Stimulation (rTMS) in treating several neuropsychiatric disorders, including depression, nicotine addiction, epilepsy, and Parkinson's disease (PD). In addition, the presented reserach highlights the importance of taking into account the placebo effect in rTMS studies, as well as exploring alternative treatment options, such as ketamine, for these disorders. Overall, this thesis sheds light on the potential benefits of rTMS in treating various neuropsychiatric conditions and suggests avenues for further research in this promising field.

In Chapters 2 and 3 we conducted a randomized, double-blind study to evaluate the effectiveness of accelerated intermittent theta burst stimulation (aiTBS) for smoking cessation. Our study also aimed to investigate the impact of smoking-related cues versus neutral cues during rTMS treatment on cigarette consumption. TMS was delivered over five consecutive days to the left dorsolateral prefrontal cortex (DLPFC). In the study, participants were divided into three groups: the first group received active iTBS stimulation while watching neutral videos, the second group received active iTBS stimulation while watching smoking-related videos, and the last group received sham stimulation while watching smoking-related videos.

The results presented in Chapter 2 demonstrate that aiTBS is a well-tolerated treatment that leads to similar reductions in cigarette consumption, nicotine dependence, craving, and perceived stress across all treatment groups. Moreover, the treatment's positive effects on nicotine dependence, general craving, and perceived stress persist for at least one week after the therapy. In Chapter 3, our follow-up study shows that the benefits of aiTBS on nicotine dependence and tobacco craving remain significant for at least one month after treatment completion, although their magnitude decreases after six months.

Our findings indicate that the therapeutic effectiveness of aiTBS, whether active or sham, does not differ significantly between groups exposed to smoking-related cues or neutral cues. These results add to the mounting evidence supporting TMS as a promising non-pharmacological approach for treating addiction and underscore the importance of accounting for placebo effects in assessing brain stimulation therapies' efficacy.

The results have important implications for developing targeted smoking cessation therapies, emphasizing the need to understand the mechanisms underlying the therapeutic benefits of brain stimulation techniques and to control for placebo effects during clinical investigations. An advantage of this study is the use of innovative placebo coil technology, which allows researchers to differentiate between the effects of the actual treatment and the placebo treatment.

In Chapter 4 of this thesis, our objective was to compare the immediate antidepressant efficacy of intramuscular (IM) ketamine and rTMS in patients with TRD in a real-world clinical setting. We collected clinical data from 24 TRD patients seeking treatment at a naturalistic mental health clinic. Half of the patients (n=12) received IM ketamine twice a week for eight sessions,

while the other half received 30 sessions of left DLPFC-iTBS. We conducted a retrospective evaluation of patients' symptom severity before and after treatment.

The study's findings indicate that both ketamine and rTMS treatments were effective in reducing depressive and anxiety symptoms in TRD patients, with no significant differences in efficacy between the two treatments. These results highlight the potential utility of both IM ketamine and rTMS as effective treatment options for TRD in a real-world clinical setting. Furthermore, findings revealed high remission and response rates in both groups, with no differences between the ketamine and rTMS groups.

This study tackles a critical challenge in mental health treatment, specifically the issue of treating patients with TRD. The findings contribute significantly to our existing knowledge on the effectiveness of ketamine and rTMS in treating depression, and provide valuable insights into their use in real-world clinical settings and research.

The study emphasizes the importance of personalized treatment plans for patients with TRD, as healthcare professionals can assess each patient's unique needs and preferences to determine the most suitable treatment option. Both ketamine and rTMS have shown potential as viable treatment options, but further research is necessary to identify the factors that influence the efficacy of each treatment and determine which patients would benefit most from each approach.

Overall, this study is a significant contribution to our understanding of how to improve the treatment of patients with TRD. Its insights can help clinicians better address the challenges of treating this population, ultimately leading to more effective and personalized treatment options.

Chapter 5 and 6 contain case reports that investigate the effectiveness of rTMS in treating two persistent neurological conditions: epilepsy and PD. Chapter 5 presents a case study of a patient with frontal lobe epilepsy, in which the feasibility, safety, and potential clinical effectiveness of bilateral orbitofrontal (OFC) low-frequency rTMS (LF-rTMS) for managing epileptic seizures are explored. This study provides valuable insights into the potential of LF-rTMS as a treatment option for patients with epilepsy and highlights the importance of further research in this area. By examining the specific case of this patient, we can better understand the potential benefits and limitations of using LF-rTMS for managing seizures and develop more effective treatment approaches for epilepsy patients. As managing frontal lobe epilepsy with medication alone is challenging, alternative treatments like rTMS are being investigated. After undergoing 30 sessions of rTMS, the patient reported a significant reduction in seizure frequency, and the fear and panic that previously preceded the seizures were eliminated. The patient continued to experience less seizures with reduced intensity and duration during the maintenance period. The patient reported a high level of satisfaction with the rTMS treatment, as it helped reduce the frequency of the focal attacks, allowed for a reduction in anti-seizure medication dosage, and resulted in a reduction in the side effects caused by the medication.

While the limitations of the study's design require careful interpretation of the findings, this case report provides valuable insights into the potential of rTMS as a treatment option for patients with refractory frontal lobe epilepsy. However, further studies with larger sample sizes and controlled designs are necessary to investigate the effectiveness of rTMS in managing refractory frontal lobe epilepsy more comprehensively. These studies would provide a more significant understanding of the treatment's potential and its limitations, which could help inform the development of more effective and personalized treatment plans for epilepsy patients. Overall, the findings from this case study suggest that rTMS may be a promising treatment option for patients with refractory frontal lobe epilepsy, but more research is needed to confirm its efficacy. In Chapter 6, a patient with PD is presented, who underwent an accelerated form of high-frequency rTMS (HF-rTMS). The study aimed to evaluate the clinical effectiveness of rTMS in managing health-related quality-of-life (QoL) symptomatology and depressive symptoms in PD, as well as the long-term effects of rTMS during the maintenance phase. PD is a debilitating neurodegenerative disorder, and depression is a common comorbidity that further worsens the quality of life of patients. The results indicate that HF-rTMS over the right M1 is a safe and well-tolerated treatment that improved the patient's health-related QoL and depressive symptoms, with these positive effects persisting for at least five months after treatment. Hence, HF-rTMS over the right M1 may be a potential treatment option for PD patients. However, it is important to note that this is a single case study, and therefore, further research is necessary to establish the safety and effectiveness of rTMS in larger patient populations. Both reports demonstrate that rTMS treatment can successfully suppress seizures in frontal lobe epilepsy and improve depressive symptoms and overall quality of life in PD. These findings suggest that rTMS may be a viable therapeutic option for certain cases of neurological disorders. However, further research is necessary to establish the safety and effectiveness of rTMS in larger patient populations, and the results may have implications for the development of new treatment strategies for other neurological conditions.

In Chapter 7 of the thesis we focus on safety concerns of TMS treatment, which have become increasingly important due to advancements in TMS coil technology. While TMS is generally considered safe and well-tolerated, the safety of new coil geometries is still not fully established. Inducing a seizure is a potential serious adverse event during any rTMS treatment. Although rTMS has shown promise in treating treatment-resistant obsessive-compulsive disorder (OCD), the optimal target area and stimulation frequency are still controversial. The case report in this chapter presents a patient with OCD who experienced a seizure during her 7th session of rTMS treatment using the FDA-approved 20-Hz protocol for OCD, applied bilaterally over the left and right dorsomedial prefrontal cortex (DMPFC) with a double-cone coil. However, it remains uncertain whether the seizure was a direct result of the rTMS treatment or if the patient had preexisting risk factors for seizures. Therefore, it is crucial to consider individual patient characteristics when selecting treatment protocols and to take appropriate measures to ensure patient safety. While caution is necessary during rTMS administration, the study's findings are limited by the use of a single case report, which may

restrict the generalizability of the results. In conclusion, this study provides valuable insights into the potential risks and benefits of TMS treatment and emphasizes the importance of careful patient selection, monitoring, and adverse effects management to ensure patient safety. This study lays the foundation for further research on the safety and efficacy of TMS treatment and the development of effective protocols to minimize the risk of adverse effects. However, more research is necessary to fully comprehend the potential risk factors and mechanisms underlying TMS-induced seizures and to develop effective strategies to prevent or manage such adverse effects.

The studies conducted in this thesis make a significant contribution to our understanding of the effectiveness and potential applications of rTMS in neuropsychiatry. The research findings provide valuable insights into the potential of rTMS as a treatment option for various mental health conditions, including depression, nicotine addiction, PD, and epilepsy. However, it is crucial to exercise caution and careful monitoring to avoid any potential adverse effects associated with rTMS treatment.

Furthermore, the thesis highlights the significance of the placebo effect in rTMS studies and the importance of exploring alternative treatment options such as ketamine. The placebo effect can have a significant impact on the outcomes of rTMS studies, and researchers must account for it when interpreting the results. Moreover, exploring alternative treatment options like ketamine could lead to the development of more effective and personalized treatment plans for patients with neuropsychiatric conditions.

In conclusion, the studies conducted in this thesis provide important insights into the potential applications of rTMS in neuropsychiatry. While caution is necessary to prevent any adverse effects, the findings suggest that rTMS could be a promising treatment option for various mental health conditions. Future research in this area should continue to explore the efficacy of rTMS and alternative treatments to further improve patient outcomes.

IMPACT PARAGRAPH

The impact of the thesis on the field is noteworthy due to its provision of valuable insights that hold practical implications for healthcare providers and clinicians. Therefore, I took the freedom to directly address clinicians and TMS practitioners here and provide them with hopefully useful suggestions and recommendation to consider in their clinical practice.

One of the recommendations for practice is that advanced placebo coil technology may be a useful tool in clinical trials to control for placebo effects. This technology can help researchers ensure that any treatment effects observed are genuinely due to the treatment itself and not just the placebo effect. However, clinicians should be aware of the potential for placebo effects in clinical practice and use them in a responsible and ethical manner. Additionally, it is crucial to acknowledge the power of placebo effects in clinical practice. Even if a treatment itself may not have a direct effect on a patient's condition, the placebo effect can still provide some benefit.

The thesis has also important more specific implications for the potential use of aiTBS as a smoking cessation treatment, given its findings. It suggests that aiTBS is a tolerable treatment option that could significantly impact smoking cessation outcomes. Therefore, healthcare providers should incorporate aiTBS into comprehensive smoking cessation programs, including other evidence-based interventions such as cognitive-behavioral therapy and medication-assisted treatment. Lastly, the thesis underscores the need for further research and refinement of non-invasive brain stimulation techniques for smoking cessation.

Furthermore, this thesis contributes to the ongoing discussion of treatment options for patients with treatment-resistant depression. The retrospective naturalistic study provides valuable insights into the efficacy of ketamine and rTMS and highlights the need for individualized treatment plans based on patient characteristics and preferences. As both ketamine and rTMS are potential therapies for individuals with treatment-resistant depression, healthcare providers must evaluate the unique needs and preferences of each patient to determine the most suitable treatment option. Ketamine may be more appropriate for patients requiring a faster response, while rTMS may be preferable for patients who cannot tolerate the side effects of ketamine. Although both therapies may be effective in reducing symptoms of treatment-resistant depression, the findings suggest that further research is necessary to determine the optimal treatment strategy for each patient. The study emphasizes the importance of continuing research in the field of neuromodulation as a potential alternative for patients with treatment-resistant depression.

In the treatment of frontal lobe epilepsy, clinicians should consider targeting the bilateral orbitofrontal cortex during rTMS. The results of the case report suggest that this area of the brain may be an effective target for reducing seizure frequency. However, it is important for clinicians to carefully monitor the safety and tolerability of rTMS in patients with epilepsy, as there is a risk of inducing seizures. When deciding on a treatment plan for epilepsy, clinicians

should weigh the potential benefits and risks of rTMS. While it may be effective for some patients, it may not be appropriate or effective for all patients. Therefore, clinicians should consider the individual needs and preferences of each patient when recommending a treatment plan for epilepsy.

For the management of PD, HF-rTMS has the potential to ameliorate depressive symptoms and enhance the quality of life of certain patients. Therefore, healthcare providers should contemplate this technique as a viable treatment option. Furthermore, the primary motor cortex could be a suitable brain region for targeting, and thus clinicians should take this into account when administering rTMS to individuals with PD.

Finally, clinicians should be aware of the potential risks associated with TMS. While TMS is generally considered safe, there is a risk of seizures, particularly in patients with a history of epilepsy or other seizure disorders. Therefore, clinicians should carefully screen patients for any history of seizures or other risk factors before recommending TMS. Another important implication is that clinicians should closely monitor patients during TMS sessions to identify any adverse effects or complications, such as seizures. Patients undergoing TMS should be monitored by trained personnel who are equipped to respond to any adverse events. This is crucial to ensure patient safety and minimize the risks associated with TMS treatment. Additionally, patients undergoing TMS should be fully informed of the potential risks associated with the treatment. Informed consent should be obtained before starting TMS treatment, and patients should be given a thorough explanation of the potential risks and benefits of the treatment. This will help patients make an informed decision about whether or not to undergo TMS treatment. Finally, health care providers should consider the potential risks and benefits of TMS when deciding on a treatment plan. While TMS can be an effective treatment for several neuropsychiatric disorders, it may not be appropriate for all patients. Clinicians should carefully consider the individual needs and preferences of each patient when recommending a treatment plan. They should weigh the potential risks and benefits of TMS against other treatment options and recommend the most appropriate treatment plan for each patient.

Overall, this thesis presents a comprehensive review of the use of rTMS in several neuropsychiatric disorders such as depression, smoking cessation, frontal lobe epilepsy, and Parkinson's disease. The findings from the studies presented in this thesis carry significant practical implications for healthcare providers.

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CURRICULUM VITAE

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LIST OF PUBLICATIONS

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Dr Mikellides is a fully London (UK) trained Consultant Psychiatrist who is currently working in Cyprus. He is Fellow of the Royal College of Psychiatrists UK and has a CCT in General and Liaison Psychiatry and an MD from Charles University. He had been an Honorary Clinical Lecturer for Queen Mary Medical School (London) and he is a Clinical Assistant Professor of Psychiatry at the University of Nicosia Medical School. Also, he was an Honorary Research Associate at the Institute of Psychiatry, Maudsley Hospital, King's College Hospital, London and a Special Scientist at the University of Cyprus.

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