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Review

Transcranial magnetic stimulation (TMS) for geriatric depression

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ABSTRACT

Background: The prevalence of treatment-resistant geriatric depression (GD) highlights the need for treatments that preserve cognitive functions and recognize polypharmacy in elderly, yet effectively reduce symptom burden. Transcranial magnetic stimulation (TMS) is a proven intervention for treatment-resistant depression in younger adults but the efficacy of TMS to treat depressed older adults is still unclear. This review provides an updated view on the efficacy of TMS treatment for GD, discusses methodological differences between trials in TMS application, and explores avenues for optimization of TMS treatment in the context of the ageing brain.

Methods: A systematic review was conducted to identify published literature on the antidepressant efficacy of TMS for GD. Databases PubMed, Embase, and PsycINFO were searched for English language articles in peer-reviewed journals in March 2021.

Results: Seven randomized controlled trials (RCTs) (total n = 260, active n = 148, control n = 112) and seven uncontrolled trials (total n = 160) were included. Overall, we found substantial variability in the clinical response, ranging from 6.7% to 54.3%.

Conclusions: The reviewed literature highlights large heterogeneity among studies both in terms of the employed TMS dosage and the observed clinical efficacy. This highlights the need for optimizing TMS dosage by recognizing the unique clinical features of GD. We showcase a set of novel approaches for the optimization of the TMS protocol for depression and discuss the possibility for a standardized TMS protocol tailored for the treatment of GD.

1. Introduction

According to the World Health Organization, the world is facing a longevity revolution. The number of people aged 60 years and older in the population is growing at an unprecedented rate and will accelerate in future decades. In 2019, the number of people aged 60 years and over was 1 billion. This number will grow to 1.4 billion by 2030 and double to 2 billion by 2050 (United Nations et al., 2020).

Depression is a common condition worldwide and is the most common manifestation of psychological distress and emotional suffering in later life. Depression is the primary cause of disability worldwide, associated with significant impairment across numerous areas of functioning and a substantial decrease in the quality of life in older adults (Friedrich, 2017). Depression is also the most common neuropsychiatric precursor of dementia identified in older adults (Roberto et al., 2021). Ultimately, depression increases the perception of poor health and the resulting request for health care services with related costs represents an estimated economic burden in the USA of over 200 billion dollars annually (Greenberg et al., 2015; Olchanski et al., 2013).

Presently, the risk of mental health problems and decompensation from pre-existing depression is particularly high due to stressors caused by the COVID-19 pandemic (Lee et al., 2020). The risk of depression in the context of social isolation and loneliness is extraordinarily high among older adults, who are also at a particularly high risk of severe complications of infection with COVID-19 (Ettman et al., 2020).

Approximately 20–40% of patients with depression do not benefit

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sufficiently from the conventional antidepressant interventions, including medication and psychotherapy (Greden, 2001). Pharmacological treatments have limited efficacy, side effects are common (Carvalho et al., 2016), and one-third of patients are medication-resistant, failing to achieve remission after using two or more antidepressants (Fava, 2003; Rush et al., 2006) and experiencing chronic depressive episodes (Nemeroff, 2007).

The prevalence of treatment-resistant depression is higher in older adults who often show a lack of robust efficacy for conventional antidepressant treatments that significantly benefit depressed younger adults (Tedeschini et al., 2011). Older adults with geriatric depression (GD) frequently have an unfavorable course of disease with an increased risk of relapse (Licht-Strunk et al., 2009) and decreased probability of treatment response (Knöchel et al., 2015). A major challenge in optimally treating GD is the presence of comorbidities. GD patients often have physical frailty, vascular pathologies (Alexopoulos et al., 2008; Potter et al., 2016), greater risk of falling (Iaboni and Flint, 2013), more psychomotor impediment, and more disability (Fiske et al., 2009). They may also become more significantly cognitively impaired, especially in executive dysfunction (Lockwood et al., 2002). They have more psychological stressors such as social isolation and caregiver dependence (Moos et al., 2005). They are also vulnerable to elder abuse - including physical, verbal, psychological, financial, and sexual abuse; abandonment; neglect; and severe losses of dignity and respect. Elder abuse can lead to severe psychological consequences (Dong et al., 2013; Luo and Waite, 2011). Eventually, chronic treatment-resistant depression is the cause of persistent disability, increased risk of suicide, and greater medical morbidity (Russell et al., 2004; Sporinova et al., 2019).

The high frequency of occurence of treatment-resistant GD highlights the critical need for treatments that preserve cognitive capacities, consider polypharmacy and physical frailty, yet effectively reduce symptom burden. One established nonpharmacological intervention for treatment-resistant depression is transcranial magnetic stimulation (TMS).

1.1. Transcranial magnetic stimulation (TMS)

TMS is a form of non-invasive brain stimulation by which a brief magnetic field passes through the scalp and induces an electrical current in the cerebral cortex. Barker et al. (1985) at the University of Sheffield, UK introduced the first, 'modern-era' TMS device. Prior to that, explorations around electromagnetic induction for brain activation went back to the seminal discoveries by Michael Faraday in 1831, and included a number of filed and issued patents around notions of therapeutic uses in brain sciences, including for the treatment of depression (Horvath et al., 2011; Walsh and Pascual-Leone, 2003). The operating mechanism of a TMS stimulator includes a capacitive high-voltage, high-current charge-discharge system connected via an electronic switch (thyristor) to the inductor of the stimulation coil (Wagner et al., 2007).

Passing a short and strong pulse of current via a coil positioned on the scalp generates a magnetic field that penetrates skin and skull, and reaches the brain where it induces electrical currents according to the physical principle discovered by Michael Faraday (Barker et al., 1985; Wassermann et al., 2008). A TMS pulse can modulate neural activity directly in a spatially and temporally focused manner to depolarize neurons, modify intracortical excitability, and activate distant cortical-subcortical and spinal structures along specific connections. The impact of a TMS pulse on the brain is dependent on several different factors, including the power of the magnetic flux, the shape of the stimulation coil, the shape and duration of the pulse, the distance and orientation between the coil and the cortical surface, the direction of the induced electrical currents, the specific repetition of electric pulses, and the underlying cortical structure and activity.

Early studies were conducted to measure the ability for TMS to interact with brain activity and behavior, for example, inducing speech arrest (Pascual-Leone et al., 1991, 2000). More recently, the combination of TMS with other neuroimaging technologies such as PET, EEG, and fMRI has made it possible to show that the changes induced by TMS are propagated throughout the rest of the brain by dynamic network interactions (Bestmann et al., 2008; Shafi et al., 2012).

Application of repetitive pulses of TMS at specific frequencies and patterns, enables modulation of cortical excitability beyond the duration of the TMS train itself, and opens up the possibility of therapeutic applications (Pascual-Leone et al., 1994). Initial studies showing the efficacy of repetitive TMS (rTMS) targeting the dorsolateral prefrontal cortex in the treatment of medication-resistant depression (Pascual--Leone et al., 1996) were followed by a rapidly expanding number of randomized and multi-site clinical trials (Perera et al., 2016) and eventually, the Food and Drug Administration (FDA) approved the Neuronetics TMS device for the treatment of medication-resistant depression in 2008 (George et al., 2010; O'Reardon et al., 2007). Since then, the use of rTMS has rapidly expanded (Zheng et al., 2020): A number of other devices have also gained FDA clearance and obtained the CE mark, many health care systems and health insurances have endorsed TMS and cover its treatment costs, safety recommendations for TMS use and for training in TMS delivery have been developed and endorsed by the International Federation of Clinical Neurophysiology (Rossi et al., 2021), and many patients are being helped worldwide.

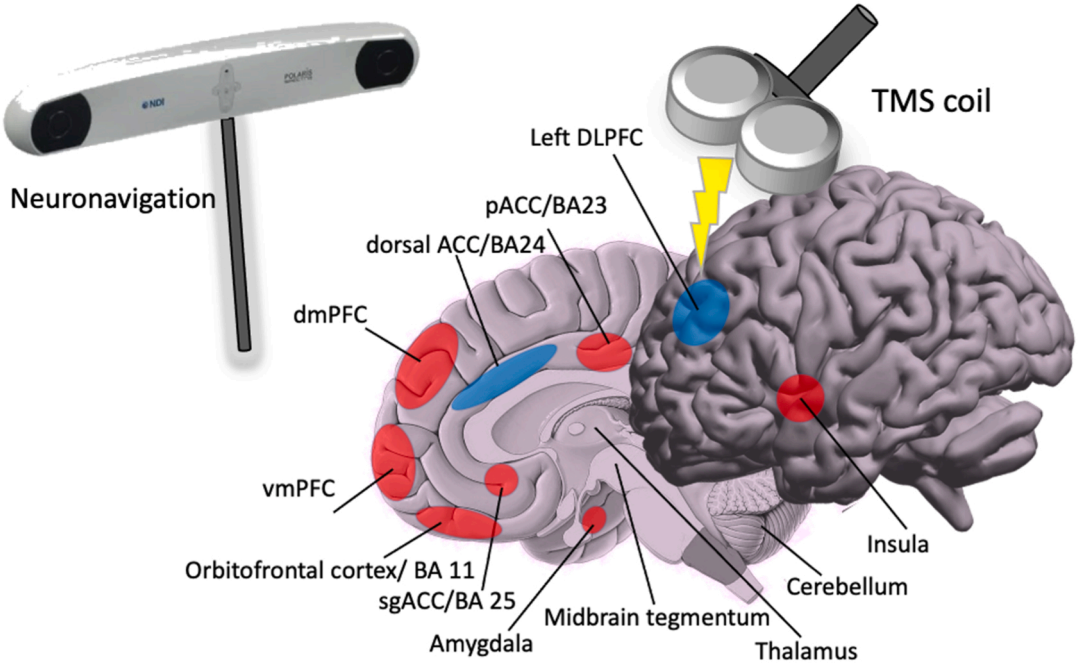
1.2. Pathophysiology and neural networks relevant to geriatric depression

Current models conceptualize depression as a network disorder associated with alterations in a distributed set of brain regions (Price and Drevets, 2010) Fig. 1. The left dorsal lateral prefrontal cortex (L-DLPFC) and the subgenual anterior cingulate cortex (sgACC) have been consistently related to depression symptomatology (Mayberg, 2001, 2003; Pizzagalli, 2011). Specifically, the sgACC is hyperactive in depression, and a decrease in this hyperactivity is related to the antidepressant response. On the contrary, the L-DLPFC is hypoactive in depression, and an increase in activity is associated with antidepressant response.

In GD, the pathophysiology diverges from younger depressed individuals for several reasons. For example, aging disease-related processes such as inflammation, vascular disease, and amyloid accumulation are more prevalent among older adults, promoting dysfunction in frontal-subcortical networks, mediating the expression of depression, and promoting chronicity and recurrence (Lindenberger, 2014). Other contributing factors such as hypertension, diabetes, obesity, hormonal modifications, changes in neuroplasticity, and synaptogenesis start in mid-life, continue during aging and are more evident in older adults (Fiske et al., 2009). Moreover, older adults are prone to social isolation, and in some communities, they have limited access to health care, even more during the COVID-19 pandemic. All these stressors may also trigger inflammatory and other maladaptive responses leading to brain network disorders (Maydych, 2019; Moos et al., 2005; Slavich and Irwin, 2014).

Structural and functional brain network abnormalities have been reported in GD. Diffusion tensor imaging studies of GD have found microstructural lesions in white matter tracts that connect the prefrontal cortex with subcortical and posterior cortical regions, which have been associated with executive dysfunction (Alexopoulos et al., 2008; Gunning-Dixon et al., 2008). These structural and functional changes are associated with an executive dysfunction depressive syndrome that has been described in older adults with distinct clinical presentation characterized by anhedonia, apathy, psychomotor retardation, lack of insight, and inadequate response to antidepressants.

For example, hypoactivity in resting functional connectivity in the cognitive control network (CCN), including the dorsal anterior cingulate cortex (dACC) and the DLPFC during depressive episodes, has been found in older adults (Alexopoulos et al., 2012). Behavioral tasks engaging the CCN show a hypoactivation of the DLPFC and decreased functional connectivity between the DLPFC and the dACC in GD as compared to non-depressed older adults (Aizenstein et al., 2009).



Brain Networks in Geriatric Depression

Cognitive Control Network (CCN)	DLPFC dorsal ACC	Hypoactivity	Executive Dysfunction
Default Mode Network (DMN)	dmPFC pACC	Hyperactivity	Self-referential thinking, rumination
Salience Network (SN)	Amygdala Insula	Hyperactivity	Apathy, negative thinking, negative bias

Fig. 1. Transcranial magnetic stimulation (TMS) and brain networks in geriatric depression. An illustration of a TMS coil inducing a magnetic field to target the L-DLPFC as guided by a neuronavigation device, an apparatus that helps guide the TMS coil to the cortical target, depicted on the left. Brain regions associated with depressive symptomatology are highlighted (red indicates hyperactivation and blue indicates hypoactivation). Brain networks involved in GD are described in the table alongside their psychological phenotype as well as whether they are hyper- or hypo-activated. DLPFC = dorsolateral prefrontal cortex, pACC = pregenual anterior cingulate cortex, BA = Brodmann area, dmPFC = dorsolateral PFC, vmPFC = ventromedial PFC, sgACC = subgenual anterior cingulate cortex.

Conversely, GD's hyperactivity within the default mode network (DMN) is consistent with previous findings in depressed adults (Sheline et al., 2010). The DMN mediates self-referential thinking, including the processing of the past events and planning for the future evaluating beliefs and intentions of others (Raichle et al., 2001; Raichle and Snyder, 2007; Sheline et al., 2009). The DMN includes connections between the medial prefrontal cortex (mPFC) and posterior cingulate cortex (pACC) and is inhibited during cognitive activities and active during internal mentation. Also, the salience network (SN), comprising the insula and amygdala, is hyperactive in GD, degrading the ability to assess the significance of external stimuli and assigning emotional and motivational value to those stimuli (Hermans et al., 2014; Mulders et al., 2015).

TMS is particularly appealing for treatment of GD because of its ability to modulate brain network interactions inducing electrical currents in the DLPFC to rebalance the cortico-limbic governance (Fox et al., 2012). TMS for treatment-resistant depression (TRD) in the adult population has proven to be safe, well-tolerated, and effective in multiple randomized controlled trials (George et al., 2010; Levkovitz et al., 2015; Pascual-Leone et al., 1996). TMS provides additional advantages in older adults, including lack of side effects compared to antidepressant medication, and lack of cognitive side effects compared to electroconvulsive therapy (ECT). Nevertheless, only around 50% of patients with medication-resistant depression treated with TMS obtain improvement of depressive symptomatology, of whom only 25–30% attain remission (Blumberger et al., 2018; Fitzgerald, 2020). These limits in the clinical efficacy highlight the need to optimize the TMS treatment. For this reason, many recent attempts have been devoted to the refinement of the TMS protocol (e.g., dosage and targeting) to improve antidepressant efficacy. However, these attempts are based on brain models of younger individuals, raising questions about applicability to treatment of GD, particularly considering the effects of aging on the anatomy and neurochemistry of the brain. For example, age-related brain atrophy might cause more distance between the coil and the brain tissue as well as increase cerebral spinal fluid influencing the propagation of the current generated by a TMS pulse (Murphy et al., 1992; Scahill et al., 2003; Wagner et al., 2008). This suggests that specific efforts should be devoted to optimizing TMS therapy for GD taking into consideration structural and functional brain changes in older adults.

Some have argued that older individuals might be less likely to respond to TMS treatment for depression, but subsequent studies have

not supported such claims, suggesting that TMS is a promising treatment for GD. In 2015, Sabesan et al. considered the factors that can moderate the clinical effect of TMS in GD (Sabesan et al., 2015). In 2018, Iriarte and George reviewed the factors that influence the response to TMS in elderly (Iriarte and George, 2018). In 2020, van Rooij et al. discussed the influence of the aging brain on rTMS efficacy for GD and highlighted the importance of developing specialized rTMS protocols for treating depression in the elderly (van Rooij et al., 2020). To build on these previous publications, in the present paper, we provide a brief introduction to TMS and an updated systematic review of the current literature surrounding TMS treatment for GD, and simultaneously explore potential avenues for the optimization of TMS intervention for GD. Our first aim is to offer a systematic review of the evidence regarding efficacy of TMS for treating depression in older adults. Our second aim is to give the reader an illustration of the methodological commonalities and differences of the studies published so far. The third aim is to discuss the recent evidence about the optimization of TMS protocols to improve antidepressant efficacy taking into consideration some aspects specific to older adults that might affect TMS efficacy. Finally, we propose a framework of determinants to take into consideration for future investigation.

2. Methods

2.1. Literature search

A literature search was conducted using the PubMed, Embase, and PsycINFO databases in March of 2021. The following search terms were used: "(Transcranial Magnetic Stimulation OR TMS) AND (geriatric OR elderly OR old OR late life) AND depress*". Peer-reviewed articles written in English and published before the date of the literature search were included.

2.2. Eligibility criteria

We sought to include randomized controlled trials (RCTs) that directly investigated the efficacy of rTMS in samples of GD patients. Due to the limited number of published studies that fit these criteria, the search was expanded to include uncontrolled trials. A criterion for inclusion was the implementation of a standardized depression rating scale (e.g., Hamilton Depression Rating Scale (HAM-D) or Beck Depression Inventory (BDI)) as the study's primary outcome. One co-author assessed the eligibility of publications for inclusion based on their title and abstract. The selected publications were then evaluated by a second co-author before their inclusion was finalized. Lastly, the reference lists of the included publications were searched for additional relevant trials.

3. Results

We found 14 studies that met the inclusion criteria. Patient characteristics, experimental design, outcome measures, and main results are summarized in Table 1. The parameters of TMS stimulation employed in these studies are shown in Table 2 for RCTs and uncontrolled studies. In Fig. 2 we summarize the TMS parameters used by the RCTs and we highlight the dosing of the RCTs compared to the approved protocol by the FDA. Table 3 and Fig. 3 show the number of patients that responded or remitted after TMS intervention.

3.1. RCTs rTMS for geriatric depression

We found 7 RCTs which evaluated the efficacy of rTMS for GD. All participants included in these trials were at least 50 years old. Manes et al. (2001) conducted the first RCT on the efficacy of rTMS in a sample of patients with GD ($n = 20$, age ≥ 50, $m = 60.7$, $SD = 9.8$). Patients received 5 daily rTMS sessions to the L-DLPFC at 20 Hz with an intensity of 80% of motor threshold (MT) or sham stimulation. Even though they found no group significant difference in the change in HAM-D score from baseline to post-treatment between the active (22.7–14.4) and sham (22.7–15.5) group ($p = 0.66$), the 6 participants who responded to the treatment (defined as a decrease in HAM-D score of at least 50% and no longer meeting the criteria for major or minor depression) had significantly larger frontal volume than compared to non-responders ($p = 0.03$).

A similar study was conducted by Mosimann et al. (2004) with a sample of 24 GD patients (40–90 years old, $m = 62$, $SD = 12$) who underwent 10 rTMS sessions of either 20 Hz of active stimulation at 100% MT to the L-DLPFC or sham stimulation. Participants in both the active and the sham group improved in HAM-D scores by between 17% and 20%. However, no between-group effects were observed. Jorge et al. (2008) conducted two experiments with patients with GD. In the first experiment 30 participants (age ≥ 50, $m = 62.9$, $SD = 7.2$) received 10 daily rTMS sessions. Participants either received 10 Hz stimulation over the L-DLPFC at 110% MT or sham. The difference in HAM-D-17 scores between the active group (33.1% decrease) and the sham group (13.6%) reached statistical significance ($p = 0.04$). In the second experiment, 62 participants (age ≥ 50, $m = 64.3$, $SD = 7.2$) received 15 rTMS sessions using the same parameters as in the first experiment or sham. Again, the difference in HAM-D-17 scores between the active group (39.4%) and the sham group (6.9%) reached significance ($p = 0.003$). Interestingly, the response rates (defined as a larger than 50% decrease in HAM-D-17 score between baseline and post-treatment) were negatively associated with age and positively associated with frontal gray matter volume.

Both Manes et al. (2001), as well as Jorge et al. (2008) indicate a relationship between lower rTMS efficacy rates and frontal atrophy. To address this, Kaster et al. (2018) explored the efficacy of high-dose deep rTMS, in 52 GD participants (age $m = 72.4$, $SD = 2.10$). Participants had 20 sessions of either 18 Hz stimulation to the L-DLPFC and ventrolateral PFC at 120% of MT or sham. There were significant differences in both the response and remission rates (defined as a 50% decrease in post-treatment score relative to baseline for 2 consecutive weeks, and a post-treatment HAM-D-24 score equal to or below as well as a 60% decrease in HAM-D-24 compared to baseline for 2 consecutive weeks, respectively) between the active (response: 44%, remission: 40%) and sham group (response: 18.5%, remission: 14.8%) ($p < 0.05$). Trevizol et al. (2019) investigated whether bilateral rTMS displays superior efficacy for GD relative to unilateral and sham rTMS. Data from two mixed-age sample studies with similar methodologies were pooled (Blumberger et al., 2012, 2016) and only a subset of the data comprised of elderly patients was analyzed (age range = 60–85). 42 participants (age = 60–85, $m = 65.7$, $SD = 6$) underwent 15 sessions of low frequency 1 Hz rTMS either bilateral or to the right-DLPFC followed by high frequency 10 Hz rTMS to the L-DLPFC, or sham. There were significant differences in the response and remission rates (defined as a 50% reduction in HAM-D-17 scores from baseline, and a HAM-D-17 score equal to or lower than 10, respectively) between the three conditions (response - bilateral: 45%, unilateral: 0%, sham: 16.7%, $p = 0.016$, remission – bilateral: 40%, unilateral: 0%, sham: 0%, $p = 0.014$) with the effect driven by the bilateral condition. Leblhuber et al. (2019) investigated the efficacy of 10 rTMS sessions to the PFC bilaterally at 3 Hz compared to sham for 29 (sham = 10) GD patients (age $m = 72.4$, $SD = 2.10$). A significant decrease in HAM-D-7 scores was observed post-treatment, relative to baseline, for the active group (baseline: $m = 12.9$, $SD = 0.89$ – post-treatment: $m = 10.2$, $SD = 0.67$,

Table 1
Characteristics of trials investigating the efficacy of TMS in treating geriatric depression (defined here as a sample with mean age > 55).

Author and year	n	Age	Diagnosis	Design	Outcome measures	Results
Randomized Control Trials						
Manes et al. (2001)	20 (sham = 10)	M = 60.7(≥ 50), SD = 9.8	Major or Minor Depression	Double Blind RCT	HAM-D MMSE	No significant difference between sham and active. HAM-D change (active: 22.7–14.4, sham: 22.7–15.5, p > 0.66) MMSE change (active: 28.7–29.6, sham: 28.6–29.2, p > 0.41)
Mosimann et al. (2004)	24 (sham = 9)	M = 62(40–90), SD = 12	MDD	Double Blind RCT	HAM-D-21 BDI-21 items 1, 6, 15, and 18 from the NIMH scale VAS	No significant difference between sham and active. HAMD-21 (active: 20% decrease (SD = 17), sham: 17% decrease (SD = 15)).
Jorge et al. (2008)	30 (sham = 15)	M = 62.9(> 50), SD = 7.2	Vascular Depression	Double Blind RCT	HAM-D-17	The difference in HAM-D-17 score change between the active group (33.1% decrease) and the sham group (13.6%) reached statistical significance (p = 0.04). Age was inversely correlated with response.
Jorge et al. (2008)	62 (sham = 29)	M = 64.3(> 50), SD = 9.4	Vascular Depression	Double Blind RCT	HAM-D-17	The difference in HAM-D-17 score change between the active group (42.4% decrease) and the sham group (17.5%) reached statistical significance (p < 0.001).
Kaster et al. (2018)	52 (sham = 27)	M = 65.2(60–85), SD = 5.5	MDD	Double blind RCT	HAM-D-24	No significant difference between groups in HAM-D-24 score (p = 0.08).
Trevizol et al. (2019)	43 (sham = 12)	M = 65.7(60–85), SD = 6	TR-MDD	Double blind RCT	HAM-D-17	Response (≥ 50% reduction in HAMD-17) differences were significant (bilateral: 45% of n, unilateral: 0% of n, sham: 16.7%, p = 0.016) Remission rates (= HAMD-17 ≤ 10) were significantly different between groups (bilateral: 40% of participants, unilateral: 0% of participants, sham: 0% of participants, p = 0.014).
Leblhuber et al. (2019)	29 (sham = 10)	M = 72.4(range unspecified), SD = 2.10	TRD	Open Label RCT	HAM-D-7	Significant decrease in HAM-D score in active group ($p = 0.001$) but not in sham group (n.s.).
Uncontrolled Trials						
Mosimann et al. (2002)	13	M = 56.4(40–74), SD = 12.7	TRD	Open label	HAM-D	Significant decrease in HAM-D score (21.2% reduction, SD = 18.0%, p < 0.001). Significant negative relationship between HAM-D reduction and cortico-scalp distance.
Nahas et al. (2004)	18	M = 61.2(55–75), SD = 7.3	TRD	Open label	HAM-D-28 GAF CGI BDI	Significant change in average HAM-D score from 29.7 (7.5) to 23.6(8.3) (p = 0.001). Response: 28% (defined as > 50% improvement in score) Remission: 22% (defined as HDRS scores ≤ 8) Scalp to cortex distance positively correlated with age for the Prefrontal cortex (p = 0.1) but not for Motor Cortex (p = 0.83).
Fabre et al. (2004)	11	M = 67.9(> 55), SD = 6.7	TR-Vascular Depression	Open label	HAM-D	Response: 5/11 (≥ 25% decrease in HAM-D score). Inverse correlation between frontal atrophy and response.
Abraham et al. (2007)	19	M= 66.8(≥ 60), SD = 6.4	TR-depressive disorder/unipolar or bipolar type	Open label	HAM-D-21 HAM-A BDI VAS for depression, anxiety, and physical discomfort CGI MMSE	Significant decrease in average HAM-D score (baseline: 25.3(5.8), post-treatment: 17.3(6.5), p = 0.0003). Response 6/19 patients (defined as decrease in HDRS ≥ 50%). Remission 2/19 (defined as HAM-D score < 8).
Milev et al. (2009)	49	M = 69(58–89), SD = 6.7	TRD	Open label	HAM-D-21 BDI CGI VASfor depression HAM-A VAS for anxiety and physical discomfort MMSE	Significant decrease in HAM-D score (p < 0.0001). Response 18% (score decrease ≥ 50%) Remission 8% (score < 8)
Dardenne et al. (2018)	10	M = 73.9(65–82), SD = 5.7	TRD	Open Label	HAM-D-17 BDI	Significant decrease in HAM-D (change score: 10.6(7.9), p = 0.004) and BDI scores (change score: 10.8(7.1), p = 0.004). Response HAM-D = 4. Response BDI = 2(defined as at least 50% decrease in scores for both).

(*continued on next page*)

Table 1 (*continued*)

Author and year	n	Age	Diagnosis	Design	Outcome measures	Results
Sayar et al. (2013)	70	M = 66.6(> 60), SD = 5.8	TRD	Open Label	HAM-D-17	Remitters HAM-D = 2(score ≤ 7). Remitters BDI = 2 (score ≤ 9). Significant decrease in HAM-D score (baseline: 21.94 (5.12), post-treatment: 11.28(4.56), p < 0.001). Response = 58.46% (decrease in score ≥ 50%). Remission = 50% (post-treatment score < 8).

RCT: Randomized Controlled Trial, HAM-D: Hamilton Depression Rating Scale, MMSE: Mini Mental State Exam, MDD: Major Depressive Disorder, BDI: Beck Depression Inventory, NIMH: National Institute of Mental Health, VAS: Visual Analogue Scale, HAM-A: Hamilton Anxiety Rating Scale, TR: Treatment Resistant, TRD: Treatment Resistant Depression, GAF: Global Assessment of Function, CGI: Clinical Global Impression. EFD: Executive Function Defect. MADRS: Montgomery Asberg Depression Scale. NIH Toolbox executive measures include the Flanker test, which measures visuospatial inhibitory attention, and the Dimensional Sort Card Test, which measures cognitive flexibility. Primary outcome measures are listed first in the outcome measures column. Age range is specified between brackets in the age column.

Table 2
TMS parameters of randomized controlled trials (RCTs) and uncontrolled studies.

Author and year	TMS devices	Coil type	Coil position	Target localization	Intensity	Frequency Hz	Pulse count	Number of sessions
Randomized Controlled Trials								
Manes et al. (2001)	Magstim	figure 8	Left DLPFC area 46	3-D MRI surface reconstruction	80% MT	20	4,000	5 (1week)
Mosimann et al. (2004)	Magstim	figure 8	Left DLPFC	5 cm rostral from APB hotspot	100% MT	20	16,000	10 (2weeks)
Jorge et al. (2008)	Magstim	figure 8	Left DLPFC	3-D MRI surface reconstruction	110% MT	10	12,000	10 (2weeks)
Jorge et al. (2008)	Magstim	figure 8	Left DLPFC	3-D MRI surface reconstruction	110% MT	10	18,000	15 (2weeks)
Kaster et al. (2018)	Brainsway deep	H1 coil	Bilateral DLPF & VLPF	–	120% MT	18	120,240	20 (4weeks)
Trevizol et al. (2019)	Magventure	B-65 figure 8	Bilateral DLPFC	5 cm rostral from APB hostpot & 3-D MRI surface reconstruction	Adjusted for coil to cortex distance	10 (Left) & 1 (Right)	18,225–31,500	15 (3weeks)
Leblhuber et al. (2019)	Theracell	Magnetic Loop	Bilateral PFC	No specific method due to magnetic loop apparatus	Adjusted to reliably induce visible bilateral contractions of *verum* muscles	3	54,000	10 (2weeks)
Uncontrolled Trials								
Mosimann et al. (2002)	Magstim	figure 8	Left DLPFC	5 cm rostral from APB hotspot	100% MT	20	22,400	14 (2weeks)
Nahas et al. (2004)	Neuronetics 3600	figure 8	Left PFC	5 cm rostral from APB hotspot	Adjusted for coil to cortex distance (range = 103–141% MT)	5	24,000	15 (3weeks)
Fabre et al. (2004)	Magstim	figure 8	Left PFC	5 cm rostral from APB hotspot	100% MT	10	16,000	10 (2weeks)
Abraham et al. (2007)	Dantec	figure 8	Left DLPFC	5 cm rostral from APB hotspot	100% MT	10	16,000	10 (2weeks)
Milev et al. (2009)	Not reported	figure 8	Left DLPFC Right DLPFC	5 cm rostral from APB Hotspot	80–100% MT	101	16,000	10 (2weeks)
(Dardenne et al., 2018)	Magstim	figure 8	Left DLPFC	3-D MRI surface reconstruction	110% MT	20	31,200	20 (4 days)
(Sayar et al., 2013)	Magstim	figure 8	Left PFC	5 cm rostral from APB hotspot	100% MT	25	18,000	18 (3weeks)

VLPFC = ventro-medial pre-frontal cortex, DLPFC = dorsolateral prefrontal cortex, APB = abductor pollicis brevis, MT = motor threshold.

p = 0.001) but not for the sham group (baseline: m = 13.2, SD = 1.43, post-treatment: m = 13.3, SD = 1.48).

In summary, across 7 RCTs a total of 260 patients were studied (148 in the active and 112 in the sham groups). Most of the RCTs employed a conventional rTMS protocol with a figure-8 coil (except for Kaster et al., 2018 and Leblhuber et al., 2019, who employed an H1 coil and a Theracell magnetic loop, respectively). The RCTs with a conventional rTMS protocol and a figure-8 coil employed stimulation parameters that differ significantly from those prescribed by the FDA approved protocol with conventional rTMS and a figure-8 coil. Firstly, the FDA protocol prescribes a total pulse count of 90,000 pulses, whereas these RCTs incorporated a lower pulse count, effectively underdosing TMS. Secondly, the FDA protocol stipulates 4–6 weeks (20–30 sessions) of TMS and the use of 10 Hz at 120% MT intensity (McClintock et al., 2018).

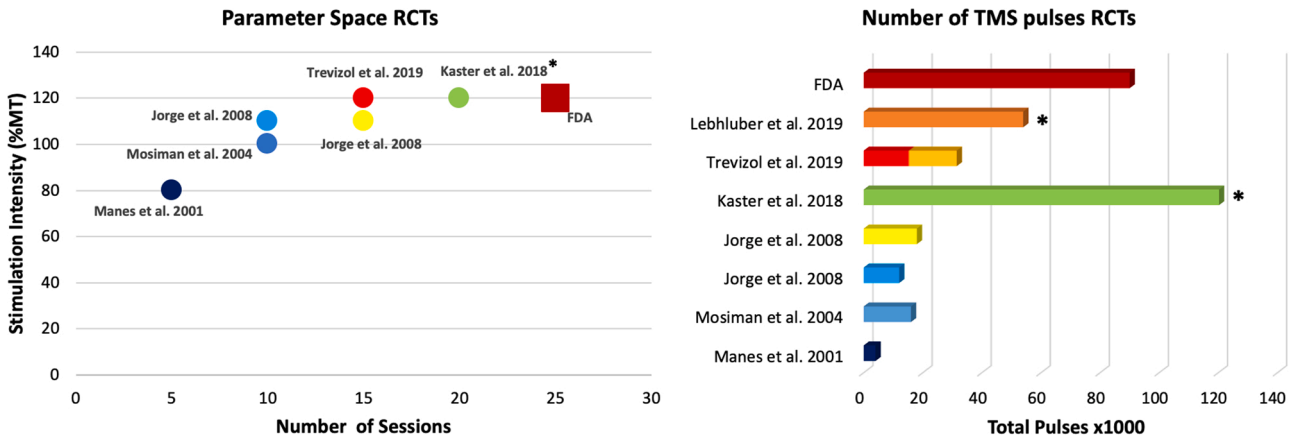


Fig. 2. Parameters space for randmoized controlled trials (RCTs) TMS studies for geriatric depression. On the left the stimulation intensity and the total number of sessions are plotted for each RCT alongside the FDA approved protocol. On the right the total pulse counts for each RCT and the FDA protocol are plotted. It is striking that the vast majority of RCTs used parameters that effectively under dosed rTMS relative to the corresponding FDA-cleared protocol. Most protocols (including the FDA's) incorporated conventional rTMS and a figure-8 coil, except for Leblhuber et al. (2019) and Kaster et al. (2018), signified by the asterisks. Leblhuber et al. (2019) varied stimulation intensity per participant and is thus not included in the parameter space graph on the left. Trevizol et al. (2019) employed two different TMS protocols, one with a total pulse count of 18,225, and another with a total pulse count of 31,500 (represented on the right with red and yellow, respectively).

However, the reviewed RCTs did not match these parameters. Fig. 2 plots the parameters space for the published RCT's versus the FDA stipulations for the conventional rTMS protocol. To accurately define the clinical profile of TMS for GD it would be essential that studies dose similar to the FDA protocol that matches their treatment design.

3.2. *Uncontrolled studies of rTMS for geriatric depression*

We included 7 uncontrolled studies that investigated the efficacy of TMS in seniors with GD. Mosimann et al. (2002) conducted an open label study with 13 patients (mean age = 56.4, SD = 12.7) who received high frequency rTMS (20 Hz) to the L-DLPFC (1600 pulses/14 sessions). A significant decrease in the HAM-D score was observed. They also found that cortico-scalp distance, which is causally related to frontal atrophy, was negatively correlated to reductions in HAM-D score. To address this issue, Nahas et al. (2004) adjusted the stimulation intensity according to patients' DLPFC atrophy levels for a sample of 18 GD patients (range = 55–75). Again, a significant reduction in HAM-D scores was observed. The average reduction in scores was larger than the one observed by Mosimann in 2002 (35.2% ± 28.8 versus 21.2% ± 18.0) (Mosimann et al., 2002), potentially reflecting the success of adjusting for the scalp-cortical distance. Fabre et al. (2004) stimulated the L-DLPFC of 11 GD patients (age range > 55, mean = 67.9, SD = 6.7) at 10 Hz (10 sessions, 100% MT). Five participants responded to the treatment (defined as a greater than 25% decrease in HAM-D score). Notably, these five participants had less frontal atrophy and better cognitive functioning, especially demonstrated by higher scores on the Trail Making Test as well as the Digit Span test. Abraham et al. also stimulated the L-DLPFC at 10 Hz and 100% MT for 10 sessions of 19 GD patients aged over 60 years (mean = 66.8, SD = 6.4) and found a significant decrease in HAM-D scores. Out of these 19 patients six met criteria for response (> 50% improvement in HAM-D) and two met criteria for remission (End Score HAM-D ≤ 8) (Abraham et al., 2007). Another study was conducted at two different sites. At the first site 20 patients with GD were stimulated to the L-DLPFC at 10 Hz. At the second site, a total of 29 patients were split into three groups: 11 received 10 Hz to the L-DLPFC, 14 received 1 Hz to the right DLPFC, and 4 participants received a combination of the two (although the authors did not specify how the two stimulations were combined) (Milev et al., 2009). They found a significant decrease in depressive symptoms as measured by the HAM-D and BDI, with no statistically significant difference in the change of HAM-D score between patients stimulated to the L-DLPFC (26.1% reduction) and the Right-DLPFC (26.7% reduction) (p = 0.40). Dardenne et al. (2018) conducted a trial with 10 seniors (age range = 65–82, mean = 73.9, SD = 5.7) who were stimulated at the L-DLPFC with high-frequency (20 Hz) at 110% MT for 20 sessions. Both HAM-D and BDI scores displayed a significant reduction. A large open-label study with 70 GD patients (age range > 60, mean = 66.6, SD = 5.8) employed 25 Hz rTMS at 100% MT for 18 sessions (Sayar et al., 2013). Consistent with the previous studies, a significant decrease in the HAM-D score was observed.

In summary, a total of 160 participants were included across the 7 open label trials. There was significant variance in the TMS parameters employed by the different trials, for example in the rTMS frequency. Authors often did not present explicit reasoning behind their choice of a specific frequency or set of stimulation parameters. To the best of our knowledge, there is no solid physiological evidence to suggest that one frequency would lead to higher efficacy than another. Therefore, we suggest that future studies adhere to the conventionally used frequencies (10 Hz or 1 Hz) since their clinical value is already established or articulate a testable hypothesis and gather data to evaluate it. For example, it is reasonable to assume that personalized stimulation parameters, e.g. optimizing rTMS frequency to an individuals' EEG oscillatory frequencies as in 'synchronized' TMS (sTMS), might prove more effective (Leuchter et al., 2015). However, further studies are needed to fully test such notions. Most importantly, similar to the above reviewed RCTs, most open label studies significantly under dosed the TMS pulse count when compared to the equivalent FDA approved protocol (conventional rTMS and figure-8 coil).

3.3. *Safety of rTMS for geriatric depression*

Overall, TMS is a safe intervention for GD. Most of the reviewed studies did not report any significant adverse events (Dardenne et al., 2018; Fabre et al., 2004; Kaster et al., 2018; Leblhuber et al., 2019; Manes et al., 2001; Milev et al., 2009; Mosimann et al., 2002; Nahas et al., 2004; Sayar et al., 2013). The adverse events that were reported were mild and transient. These events included discomfort or pain on the head around the stimulation site, headaches, as well as nausea and crying (Abraham et al., 2007; Jorge et al., 2008; Mosimann et al., 2004). The frequency of these adverse events was low, and the controlled trials did not observe a significant difference in the number of reported adverse events between the active and the sham groups. Tolerability for TMS as intervention for GD was high. Most studies did not report any

Table 3
Remission, response, and non-response following TMS treatment in geriatric depression (GD) for randomized controlled rials (RCTs) and uncontrolled trials.

Author and year	n	Responders	p value	Remitters	p value
Randomized Control Trials					
Manes et al. (2001)	20 (sham = 10)	Active group: 3, sham group: 3 (50% or greater decrease in HAM-D score & no longer meeting criteria for major or minor depression).	n.s.	Active group: 2, sham group: 2 (HAM-D score ≤ 8).	n.s.
Mosimann et al. (2004)	24 (sham = 9)	Active group: 1, sham group: 0 (Decrease in HAM-D score ≥ 50%). Partial responders, active group: 3, sham group: 2 (Decrease in HAM-D score ≥ 30%).	n.s.n.s.	–	–
Jorge et al. (2008)	30 (sham = 15)	Active group: 5, sham group: 1 (Decrease in HAM-D score ≥ 50%).	0.08 (n.s.)	Active group: 2, sham group: 1 (HAM-D score ≤ 8 & no longer meeting criteria for major or minor depression).	0.50 (n.s.)
Jorge et al. (2008)	62 (sham = 29)	Active group: 13, sham group: 2 (Decrease in HAM-D score ≥ 50%).	0.03	Active group: 9, sham group: 1 (HAM-D score ≤ 8 & no longer meeting criteria for major or minor depression).	0.01
Kaster et al. (2018)	52 (sham = 27)	Active group: 11, sham group: 5 (Decrease in HAM-D score ≥ 50% relative to baseline on 2 consecutive weeks).	< 0.05	Active group: 10, sham group: 4 (HAM-D score ≤ 10 & ≥ 60% reduction from baseline for 2 consecutive weeks).	< 0.05
Trevizol et al. (2019)	43 (sham = 12)	Active group: 9, sham group: 2 (Decrease in HAM-D score ≥ 50%).	0.016	Active group: 8, sham group: 0 (HAM-D score ≤ 10).	0.004
Uncontrolled Trials					
Nahas et al. (2004)	18	5 (Decrease in HAM-D score ≥ 50%).		4 (HAM-D score < 8).	
Fabre et al. (2004)	11	5 (Decrease in HAM-D score ≥ 25%).		–	
Abraham et al. (2007)	19	6 (Decrease in HAM-D score ≥ 50%).		2 (HAM-D score < 8).	
Milev et al. (2009)	49	16 (Decrease in HAM-D score ≥ 30%).		4 (HAM-D score < 8).	
(Dardenne et al., 2018)	10	4 (Decrease in HAM-D & BDI scores ≥ 50%).		2 (HAM-D score ≤ 7 & BDI score ≤ 5).	
(Sayar et al., 2013)	70	38 (Decrease in HAM-D score ≥ 50%).		19 (HAM-D score < 8).	

HAM-D = Hamilton Depression Rating Scale, BDI = Beck Depression Inventory. Mosimann et al., 2004 did not report on remission rates (Mosimann et al., 2004). Leblhuber et al., 2019 and Mosimann et al., 2002 are not included in this table because they did not report on neither response nor remission rates (Leblhuber et al., 2019; Mosimann et al., 2002).

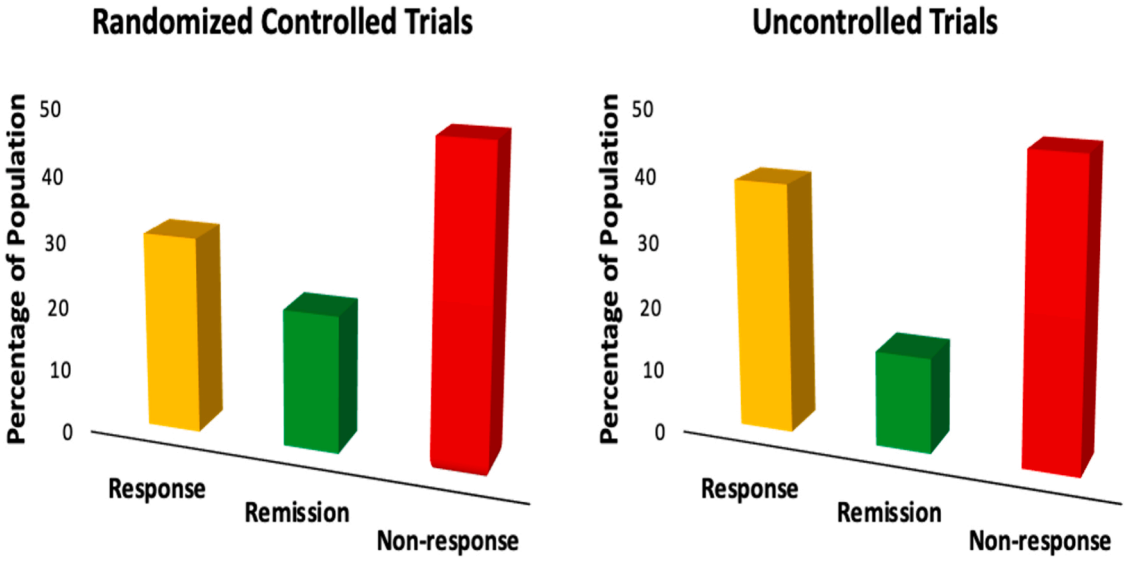


Fig. 3. Remission, response, and non-response following TMS treatment in geriatric depression (GD) for randomized controlled trials (RCTs) and uncontrolled trials.

treatment-related participant withdrawals (Dardenne et al., 2018; Fabre et al., 2004; Jorge et al., 2008; Leblhuber et al., 2019; Manes et al., 2001; Mosimann et al., 2002, 2004; Nahas et al., 2004). In the few studies where treatment-related withdrawals were reported, the dropouts were limited, ranging between 1 and 3. For example, Abraham et al. (2007) reported one participant drop out due to local pain on the scalp at the stimulation site during treatment (n = 20). Kaster et al. (2018) reported a participant withdrawal due to stimulation induced discomfort (n = 52). Milev et al. (2009) reported that a participant withdrew because of discomfort and the occurrence of headaches (n = 49). Trevizol et al. (2019) had a single participant drop out because they could not tolerate the treatment (n = 43). Lastly, Sayar et al. (2013) reported three withdrawals due to worsening of symptoms or stimulation-induced discomfort (n = 70). This evidence indicates that

TMS dropouts are very few, supporting the tolerability of TMS in geriatric patients.

4. Discussion

Depression is highly prevalent in the elderly: about 14% are diagnosed with a depressive disorder, of which at least 2% meet the criteria of MDD (Ageing, n.d). As the average population gets gradually older, GD is becoming a growing and important public health problem. Here, we provide a systematic review of the current literature on the efficacy of TMS in treating GD. The reviewed evidence supports a high degree of tolerability and safety and has also proven significant therapeutic efficacy for TMS in patients with GD. Importantly, there are some potential advantages to using TMS in older adults and there is also no evidence against the value of rTMS in the elderly with depression.

4.1. Therapeutic efficacy of TMS for geriatric depression

The reviewed studies indicate that TMS treatment for GD is favorable, although the variance in response and remission rates between the trials indicates room for optimizing the treatment. Out of the reviewed RCTs, three of the six that reported on response rates found a significant difference in the number of responders between the active and the sham groups. Three of the five RCTs that reported on remission rates found a significant difference between the active and the sham group (Table 3). Seven of eight of the uncontrolled trials observed responders to the treatment and six observed remitters (Table 3). Importantly, there was considerable variability in the response and remission rates for both RCTs and the uncontrolled trials, ranging from 6.7% to 54.3% for response and 8.2–40.0% for remission . In the following paragraphs we discuss some potential factors that could be driving this heterogeneity.

4.2. TMS Intensity and cortex-scalp distance

The variability in efficacy rates could be related to the idiosyncrasies of the samples. Studies have shown that frontal atrophy levels are very variable among elderly (Peters, 2006). Studies have shown that a larger distance between the scalp and the frontal cortex is related to a lower clinical outcome in rTMS treatment for GD, which has been recently reviewed by Sabesan et al. (Manes et al., 2001; Mosimann et al., 2002; Sabesan et al., 2015). This is most likely due to the decreased strength of the electrical field at the stimulation target site. Therefore, the discrepancy in clinical outcome between and within the trials could be a consequence of significant differences in frontal atrophy levels between samples of different trials. Unfortunately, an insufficient number of the reviewed trials recorded participant frontal atrophy to conduct a formal analysis. (Nahas et al., 2004). For example, Manes et al. (2001) stimulated the L-DLPFC at 80% MT and did not find a difference in either response or remission rate between the active and the sham group, while Jorge et al. (2008) stimulated the L-DLPFC at 110% MT and found a significant difference in both the response and remission rate between the treatment and control group. Therefore, Nahas et al. (2004) proposed that adjusting the stimulation intensity according to individual cortico-scalp distance may be a way to compensate for the frontal atrophy.

Besides the direct effects of the frontal atrophy, the concomitant increase of cerebrospinal fluid may influence the direction of the current, and consequently the electric field generated in the targeted region of the cortex (Fishman, 1992). We suggest for future studies to consider conducting a formal analysis of this phenomenon.

Alternatively, it has been shown that atrophy of the motor cortex in older adults is associated with lower resting MT (List et al., 2013; Mimura et al., 2021; Zadey et al., 2021). These findings suggest that brain atrophy may be associated with an increase in cortical excitability. This would suggest that accounting for frontal atrophy with a higher stimulation intensity is more complex than simply modifying stimulation intensity solely based on measures of scalp-to-cortex distance. More research is needed to elucidate the optimal stimulation intensity in GD.

4.3. TMS number of pulses

The total pulse count seems to influence the clinical outcome as well. Jorge et al. conducted two experiments, in the first one, participants received 12,000 total pulses over the course of the intervention, in the second they received 18,000. The authors found a higher response (39.4% versus 33.3%) and remission rate (27.3% versus 13.3%) with 18,000 compared to 12,000 total pulses. This is in line with a recent study showing that increasing treatment duration, and thus total pulse count, leads to a concomitant increase in the proportion of participants who reach clinically-meaningful response (Yip et al., 2017). Worth noting is that most studies reviewed here, which employed a conventional rTMS protocol with a figure-8 coil, under dosed in terms of pulse count compared to the FDA approved protocol that employed a similar treatment design (conventional rTMS with a figure-8 coil). If a higher pulse count is related to superior clinical outcome, the efficacy rates observed in these studies could be substantially higher if the studies had delivered a higher pulse count. Therefore, this highlights the importance for future studies to adequately dose. The issue of number of pulses seems particularly relevant for older adults given the evidence of altered, hypoactive, mechanism of plasticity with advancing age (Freitas et al., 2011; Pascual-Leone et al., 2011). Modulation of brain plasticity is thought to play a critical part in the therapeutic effects of rTMS (Hallett, 2007). If so, a hypothesis could be formulated that in older adults, given hypoactive mechanisms of plasticity, rTMS would require a greater number of pulses and a longer treatment course than in younger patients to achieve efficacy. In the future, considering that the current FDA approved TMS protocols for depression have only shown moderate superiority over sham (around 10%), even among young populations (McClintock et al., 2018), it is pertinent to take into consideration how rTMS protocols can be optimized specifically for GD.

4.4. Advantages of TMS for GD compared to electroconvulsive therapy (ECT) and pharmacological interventions

TMS is generally safe and well-tolerated. Serious adverse effects include generalized tonic-clonic seizures, but the risk is low and appears to be comparable to that for antidepressant medications. By comparison ECT is an effective treatment for depression, but it is not tolerated by some patients and declined by others. Many patients experience some adverse cognitive effects during and after a course of ECT, including acute confusion, anterograde amnesia, and retrograde amnesia. However, objective tests indicate that neuropsychological impairment caused by ECT is generally short lived, and impaired cognition due to depression typically improves after a course of ECT. In addition, ECT does not appear to be associated with an increased risk of dementia (Duke, 2011; Kerner and Prudic, 2014).

Furthermore, the mortality rate of ECT, at 0.2%, has been shown to be equal to control (Kaster et al., 2021). This makes ECT one of the safest procedures performed under general anesthesia. Serious adverse events are mostly related to cardiopulmonary events (Kerner and Prudic, 2014). TMS offers a generally more favorable side effect profile than ECT or antidepressant medications.

4.5. Recent advances in protocol optimization to improve TMS clinical efficacy within the framework of geriatric depression

In this section, we present recent advancements in TMS protocol for depression and discuss their limitations in the context of GD. Our current understanding of the antidepressant mechanisms of TMS is still limited, and its therapeutic efficacy also remains sub-optimal (Herwig et al., 2003). Overall, using current TMS protocols, 50% of patients attain

improved depressive symptomatology, of whom half obtain remission (Blumberger et al., 2018; Fitzgerald, 2020). Consequently, current attempts have sought to update the TMS protocol by improving targeting and dosage, and, more recently, focusing on personalizing the intervention based on single patient symptomatology in the adult population. However, these approaches fail to consider that growing older progressively affects the anatomy and the neurochemistry of the human brain and these changes should be considered in the context of TMS for GD. For example, growing older has been linked to reduced brain size and weight, expanded cerebral ventricles and sulci, rarefication of the cerebral vasculature, deformation of neurons, and reduced synaptic density (Lindenberger, 2014). DTI studies showed that the integrity of white matter is also reduced in older adults compared to young adults (Moseley, 2002; Sullivan and Pfefferbaum, 2006). Further, the degree of age-related volume losses is different across regions. The prefrontal cortex and the hippocampus are among the regions that show considerable individual differences in age-related reduction (Fjell et al., 2009). So far, no studies have yet systematically investigated how white matter abnormalities influence plasticity induced by TMS. All these brain-related changes might alter how the magnetic field generated by TMS reaches the brain cortex and influences treatment response.

The following paragraph will review recent studies that advanced optimization of TMS protocols for depression (see Fig. 4) and discuss their limitations in the context of GD. Fox et al. (2012) have adopted fMRI to measure if BOLD-based resting-state functional connectivity can predict the clinical response to TMS. The authors found that different L-DLPFC stimulation sites have a different degree of connectivity with the subgenual anterior cingulate cortex (SGC), and that these differences in degrees of connectivity explain variations in the clinical efficacy of TMS for depression. Specifically, a positive response to rTMS treatment was predicted by strong anticorrelation of the SGC with the stimulation site in the DLPFC. This study importantly highlights that different stimulation targets are associated with diverse levels of clinical efficacy due to different connectivity profiles. More specifically, it indicates that DLPFC sites with better clinical efficacy are more anticorrelated with the SGC. Altogether, this study also expands our knowledge of the physiological mechanisms underlying antidepressant effects and shows encouragement for identifying the appropriate stimulation targets to optimize the clinical response of TMS treatment for depression. However, it is not obvious that this approach can be applied to GD because the functional connectivity between regions in the default mode network (DMN) is diminished (Damoiseaux et al., 2008; Grady et al., 2006, 2010). This is even more important, considering that this reduction in functional connectivity correlates with age-related cognitive deterioration (Onoda et al., 2012), white-matter alterations (Coelho et al., 2021), and decreases in structural connectivity in aging (Greicius

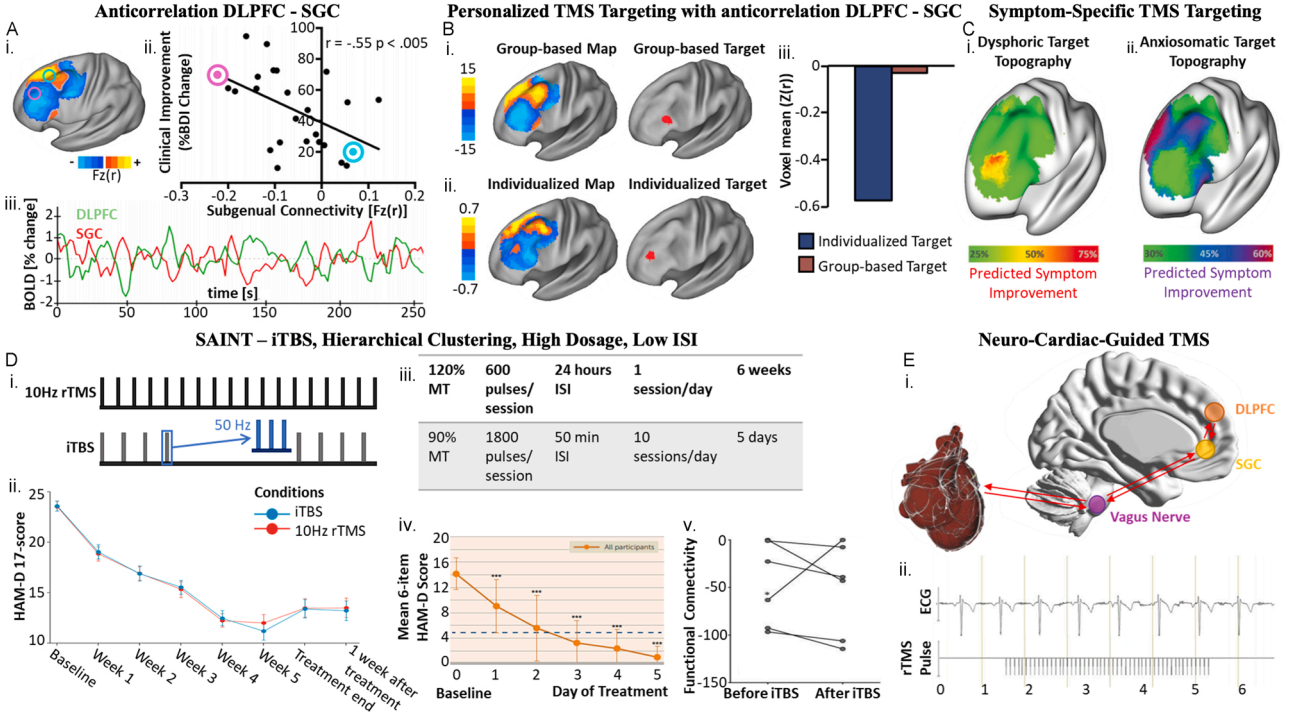


Fig. 4. Recent studies advancing the optimization of TMS protocols for depression. (A) Anticorrelation between DLPFC and Subgenual Anterior Cingulate Cortex (SGC). i. Map of cortical functional connectivity with the SGC (Fz(r)), masked to highlight the DLPFC. ii. The anticorrelation of the TMS stimulation site with the SGC predicted the degree of treatment efficacy. iii. Example functional anti-correlation between TMS target in the DLPFC and the SGC (Weigand et al., 2018). (B) Personalized TMS targeting based on the individual functional map of anticorrelation between the DLPFC and the SGC. i. Map of averaged functional connectivity with the SGC based on averaged group data, with optimal TMS stimulation site. ii. Map of functional connectivity with the SGC for a single subject, with optimal TMS stimulation site. iii. The TMS target based on data from the single subject is more strongly anti-correlated with the SGC than the target generated from the group data (Fox et al., 2013). (C) TMS targeting based on subset of depressive symptomology. Two optimal TMS targeting maps were identified for dysphoric symptoms (i.) and anxiosomatic symptoms (ii.). (Siddiqi et al., 2020a). (D) Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT). i. iTBS allows for shorter stimulation durations (Cole et al., 2020). ii. iTBS is non-inferior to FDA-approved protocol (Blumberger et al., 2018). iii. SAINT administered a significantly shorter treatment duration and yet a similar total pulse count (total of 5 days, 10 session per day, a 50-min intersession interval (ISI), 1800 pulses per session) to the FDA-approved treatment course. iv. Significant decreases in HAM-D 6-item score were observed for 21 participants (Blue line indicates remission (HAM-D score $\leq$ 5)) (Cole et al., 2020). v. Functional anti-correlation between the DLPFC and SGC increased for participants after iTBS. (E) Using heart rate to determine the optimal TMS stimulation site. i. Iseger et al. (2020) propose a crucial depression network between the DLPFC, SGC, and the Vagus Nerve. They argue that, since the DLPFC is functionally connected to the Vagus Nerve and the heart through the SGC, the degree to which rTMS modulates heart rate should predict how successfully the DLPFC stimulation is affecting the network. ii. They found that stimulating the left frontal area at given L-DLPFC locations successfully decreases heart rate after rTMS trains (Iseger et al., 2017).

et al., 2009; Honey et al., 2009).

Building on Fox's findings, Siddiqi et al. (2020b, 2021) identified specific neural networks associated with improvement in different clusters of depression symptomology. Subsequently, they discovered two distinct TMS circuit targets, one effective for decreasing dysphoric symptoms and another for reducing anxiety and somatic symptoms. Moreover, these two symptom-specific targets were distinct to active TMS compared with sham stimulation. This innovative approach demonstrates that different clusters of depressive symptoms responded better to different TMS sites, thereby paving the way for symptoms specific TMS treatments.

Recent advancements come also from Iseger et al. who proposed a novel approach to TMS stimulation targeting called Neuro-Cardiac Guided TMS targeting (NCG-TMS). This technique is built on the finding that the DLPFC and the SGC are nodes in a larger network that is functionally intertwined with the vagus nerve (VN), which is largely responsible for regulating heart rhythm (Thayer et al., 2009). Leveraging this frontal-vagal network, it has been shown that TMS to the DLPFC decreases heart rate (Makovac et al., 2017). The core idea of NCG-TMS is that the optimal stimulation target for rTMS depression treatment can be located by determining the region of the DLPFC that most successfully decreases heart rate, since this region of the DLPFC will be most strongly connected to the frontal-vagal network. The authors have conducted three studies with healthy volunteers (total $n = 75$, (Iseger et al., 2019, 2017, 2021)) presenting evidence for the reliability of activating the DLPFC-SGC-VN network, which has been independently replicated by Kaur et al. (2020). If NGC-TMS retains its promise when tested on a clinically depressed population, the technique could present itself as a reliable and cost-effective approach for locating the optimal DLPFC stimulation target for rTMS depression treatment.

Williams et al. have proposed a more radical attempt to improve TMS protocol for depression. The authors developed and tested a new protocol called the Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) (Cole et al., 2019). The SAINT protocol incorporates a few innovative components, it consists of multiple sessions per day at separate intervals, applying a higher total pulse count, and improving targeting. The authors increased the dosage by applying multiple daily sessions of intermittent Theta Burst (iTBS), which is a stimulation paradigm that involves bursts of three TMS pulses at 50 Hz, repeated at 5 Hz (Huang et al., 2005). Specifically, in SAINT, iTBS is administered for 10 sessions a day every 50 min for 5 consecutive days. A total of 18,000 pulses/day with a total of up to 90,000 over the treatment. Which overall is the pulse count of a six-week course of conventional rTMS.

The intersession intervals of 50 min were chosen based on studies stimulating hippocampal slices showing that 50–90 min has a cumulative effect on synaptic strengthening and enlargement of dendrites in the hippocampus (Kramár et al., 2012). Extrapolating this knowledge to the DLPFC may be faulty. Further, the authors refer to previous studies showing improvements in clinical symptoms using iTBS on the motor cortex and parietal cortex. This does not necessarily warrant a generalization of these findings to the frontal areas.

Translation of this data in the context of GD is not obvious. For example, previous studies showed a general trend towards a decrease in TMS evoked motor cortex plasticity in the aged population compared to young adults (for review see Guerra et al., 2021). In this regard, Opie et al. (2017) demonstrated that iTBS increased M1 plasticity in young subjects, this wasn't the case for in the older group. Other studies measured TMS effects outside the motor cortex combining TMS with EEG to measure TMS-evoked potentials (TEPs). This approach allows for measuring TMS effects applied on DLPFC, which is the targeted region in depression. It has been shown that after stimulation of DLPFC a reduction in N45 amplitude is found in older adults when comparing the results with a group of healthy controls, suggesting impaired glutamatergic plasticity in older adults (Noda et al., 2017). Nevertheless, there is some literature that suggests that iTBS is applicable to the treatment of GD. Three case studies report on individual GD patients that gained clinical benefit after a course of iTBS treatment (Chatterjee et al., 2020; Hodzic-Santor et al., 2021; Konstantinou et al., 2020). Moreover, an open label trial with 13 GD patients found a 1/3 response rate and a 1/3 remission rate after 20 sessions of iTBS over 4 weeks (Cristancho et al., 2020), similar to the previously mentioned rates for conventional rTMS protocols (Blumberger et al., 2018; Fitzgerald, 2020). More research is needed to corroborate the clinical value of iTBS for treatment of GD. Moreover, the authors choice to stimulate at 90% resting motor threshold**,** was based on a study investigating plasticity on the motor cortex on 16 healthy young adults (Nettekoven et al., 2014), but we know that ageing is related with disproportionately large frontal compared to motor area atrophy. All in all, it is unclear whether these mechanisms can translate to DLPFC stimulation, and it is also unclear if these apply in depressed older adults. Nevertheless, the remarkable remission rate of $> 90\%$ reported by SAINT is superior to conventional rTMS protocols and needs to be replicated in a controlled design.

5. Conclusion

Overall, we found that TMS treatment for GD is safe, well-tolerated, and shows very encouraging efficacy results. We discussed the determinants impacting clinical efficacy and conclude that most studies use different methodology, and the majority of studies adopted a pulse count substantially lower than what is prescribed by FDA protocol. Further, a lack of consistent clinical improvement among patients indicates that the treatment has potential for optimization. A number of researchers have laid out techniques for optimizing TMS targeting, dosage, and treatment duration. However, the applicability of these techniques to treating GD must be evaluated in light of idiosyncrasies of the ageing brain. We suggest that future studies recognize the importance of sufficiently dosing the TMS protocol for GD and optimize parameters and interventions to the older adults.

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Dr. A. Pascual-Leone is a co-founder of Linus Health and TI Solutions AG; serves on the scientific advisory boards for Starlab Neuroscience, Magstim Inc., Radiant Hearts, and MedRhythms; and is listed as an inventor on several issued and pending patents on the real-time integration of noninvasive brain stimulation with electroencephalography and magnetic resonance imaging.

CRediT authorship contribution statement

Davide Cappon: Conceptualization, Methodology, Writing – original draft, Supervision. **Tim den Boer:** Conceptualization, Methodology, Writing – original draft. **Caleb Jordan:** Writing – review & editing. **Wanting Yu:** Writing – review & editing. **Eran Metzger:** Writing – review & editing. **Alvaro Pascual-Leone:** Conceptualization, Methodology, Writing – review & editing, Supervision.

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