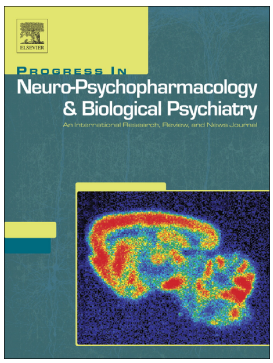
Journal Pre-proof



Effects of repetitive transcranial magnetic stimulation on suicidal behavior: A systematic review

Gianluca Serafini, Giovanna Canepa, Andrea Aguglia, Andrea Amerio, Davide Bianchi, Magnani, Bernardo Dell'Osso, Maurizio Pompili, Paul B. Fitzgerald, Mario Amore

PII: S0278-5846(20)30297-9

DOI: https://doi.org/10.1016/j.pnpbp.2020.109981

Reference: PNP 109981

To appear in: *Progress in Neuropsychopharmacology & Biological Psychiatry*

Received date: 5 April 2020

Revised date: 20 May 2020

Accepted date: 20 May 2020

Please cite this article as: G. Serafini, G. Canepa, A. Aguglia, et al., Effects of repetitive transcranial magnetic stimulation on suicidal behavior: A systematic review, *Progress in Neuropsychopharmacology & Biological Psychiatry* (2019), https://doi.org/10.1016/j.pnpbp.2020.109981

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 Published by Elsevier.

Journal Pre-proof

Effects of repetitive transcranial magnetic stimulation on suicidal behavior: a systematic review

Gianluca Serafini[1,2*], Giovanna Canepa[1,2], Andrea Aguglia[1,2], Andrea Amerio[1,2], Davide Bianchi[1,2], Luca, Magnani[1,2], Bernardo Dell'Osso[3,4,5,6], Maurizio Pompili[7], Paul B. Fitzgerald[8], Mario Amore[1,2]

[1]*Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Section of Psychiatry, University of Genoa, Genoa, Italy;*

[2]*IRCCS Ospedale Policlinico San Martino, Genoa, Italy;*

[3] *Department of Mental Health, Department of Biomedical and Clinical Sciences, Luigi Sacco Hospital, ASST Fatebenefratelli Sacco, University of Milan, Milan, Italy;*

[4] *Department of Psychiatry and Behavioral Sciences, Bipolar Disorders Clinic, Stanford University, CA, USA;*

[5] *CRC "Aldo Ravelli" Center for Neurotechnology and Brain Therapeutic, University of Milan, Milan, Italy;*

[6] *Centro per lo studio dei meccanismi molecolari alla base delle patologie neuro-psico-geriatriche, University of Milan, Italy;*

[7]*Department of Neurosciences, Suicide Prevention Center, Sant'Andrea Hospital, University of Rome, Rome, Italy;*

[8]*Epworth Centre for Innovation in Mental Health, Epworth Healthcare and Monash Universitty Department of Psychiatry, Camberwell, VIC, Australia;*

Submitted as research article to "Progress in Neuropsychopharmacology & Biological Psychiatry": Abstract (242-words); Key words: (5); Text (4939-words); References (53); Tables (2); Figures (1)

Running title: Repetitive transcranial magnetic stimulation and suicidal behavior

Corresponding author: *Gianluca Serafini M.D., *Ph.D.*, Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), Section of Psychiatry, University of Genoa, IRCCS Ospedale Policlinico San Martino, Largo Rosanna Benzi 10, 16132, Genoa, Italy; Tel. 00390103537668 (office), 00393475372316 (mobile), Fax. 00390103537669; e.mail: gianluca.serafini@unige.it

Abstract

The efficacy and tolerability of transcranial magnetic stimulation (rTMS) in major depression is well-known and documented by existing studies. However, whether rTMS may be effective on suicidal behavior is unclear and needs to be further investigated. This systematic review is aimed to investigate the available literature about the effects of rTMS on suicidal behavior and provide a comprehensive overview of the available evidence. A systematic search regarding the association between rTMS and suicidal behavior was carried out. All relevant articles concerning this association were comprehensively searched on PubMed, Scopus, Science Direct, and PsycInfo databases. After a careful search, 16 articles (7 sham-controlled studies, 5 uncontrolled studies, 4 case-series) meet inclusion criteria and were selected in this systematic review. Overall, the left dorsolateral prefrontal cortex (DLPFC) was identified as the most frequent stimulation target by most studies. Unfortunately, actually it is not clear whether suicidal behavior reduction may be mediated, at least in some cases, by depression attenuation. While some methodological heterogeneity was found in terms of stimulation parameters (e.g., frequency, number of sessions, intensity of stimulation), most of the analyzed articles showed that rTMS is a safe, applicable, well tolerated and reproducible method in treating suicidal behavior. The main findings suggest that TMS is globally safe, well-tolerated and effective in treating suicidal behavior. The most effective treatment seems to be bilateral TMS as well as the combination with antidepressants. Further longitudinal studies are required in order to replicate the mentioned study results. **[Keywords:** rTMS; suicidal behavior; major depression; left dorsolateral prefrontal cortex; brain-derived neurotrophic factor**]**

Journal Pre-proof

1. Introduction

Suicidal behavior is a significant, global public health concern with approximately 800.000 deaths annually across the globe, being the second leading cause of death among 15–29-year-olds. It is estimated that for each person who dies by suicide, more than 20 other individuals attempt suicide. Suicidal behavior refers to various clinical conditions including suicidal ideation and thoughts, suicide attempts, suicidal acts and completed suicide (World Health Organization, 2019; Meyer et al., 2010; Pompili et al., 2012, 2013). The proposed mechanisms underlying suicidal behavior include hyperactivity of the hypothalamic-pituitary-adrenal axis, lower serotonin levels and activity (Menon Kattimani, 2015), overactivity of the noradrenergic system (Meyer et al., 2010), reduced GABAergic cortical inhibition (Lissemore et al., 2018; Kang et al., 2016; Lewis et al., 2018), lower brain-derived neurotrophic factor (BDNF) levels in the prefrontal cortex (PFC) and hippocampus, white matter hyperintensities (related to disruptions in the neural circuits involved in emotional regulation) (Meyer et al., 2010), particularly in brain areas such as frontal cortex and basal ganglia connections. Moreover, functional and structural neuroimaging studies showed blunted prefrontal cortex (PFC) regional flood blow (Cox et al., 2014), hypoactivation patterns in left dorsolateral prefrontal cortex (DLPFC) (Thompson et al., 2018), reduction in cell density and thinner cortex in left DLPFC (Sobanski et al., 2015) and impaired functional connectivity in default mode network (DMN) (Chen et al., 2013) in suicidal patients. Reduced serotonergic input into the ventromedial prefrontal cortex (VMPFC), orbitofrontal cortex (OFC), and DLPFC may result in impaired affect regulation as well as in diminished behavioral control and, thereby, in a greater propensity to exert powerful emotions such as suicidal or aggressive feelings. The study of Tik et al. (2017) comprehensively summarized the most relevant neural circuits modulated by TMS in major depression (MDD).

Transcranial magnetic stimulation (TMS) is a non-invasive and painless neuromodulatory tool affecting underlying neuronal excitability. Modulation is achieved by inducing a short capacitor discharge of electric current into a coil generating a magnetic field, which later induces neural cell membrane potentials depolarizing in cortical tissue under the coil and affect the related nerve loop activity. Repetitive TMS (rTMS) has been used in the treatment of a variety of psychiatric and neurological disorders, although at this time it is only approved as a treatment for major depressive episode with unsatisfactory response to antidepressant by the US Food and Drug Administration. Research found that high frequency (HF) stimulation (≥5 Hz) induces excitatory effects, whereas low-frequency (LF) stimulation (≤1Hz) causes inhibitory effects in the brain (Chen et al., 2013). The efficacy of HF-rTMS of the left dorsomedial prefrontal cortex (l-DLPFC) in depression is well-established, with a Level A recommendation according to European guidelines, whereas the efficacy of rTMS of the right DLPFC (r-DLPFC) is considered as probable (Level B recommendation) (Lefaucheur et al., 2014). Studies have shown that superior efficacy is achieved when delivering >1000 pulses per session and stimulation intensity >100% of motor threshold. Evidence found that better efficacy was achieved when using higher intensity pulses, more sessions of stimulations, or longer courses of treatment (Chung et al., 2018).

The efficacy of decreasing the r-DLPFC activity via low-frequency rTMS may be connected to the increase of activity in l-DLPFC through transcallosal connections or inhibition itself. Furthermore, recent studies demonstrated efficacy for a DMPFC (Downar et al., 2014) and right orbitofrontal (r-OFC) (Feffer et al., 2018) in MDD. The DLPFC is easily accessible to TMS application and is

synaptically connected to the limbic system involved in mood regulation (e.g, striatum, thalamus, and anterior cingulate cortex) (Li et al., 2004).

Studies hypothesized that rTMS of the DLPFC might modulate brain networks, which are implicated in the pathophysiology of MDD (Li et al., 2004). Further research in animals and patients suffering from MDD revealed that frontal rTMS can also affect various neurotransmitter systems, neurotrophic factors, and cortical excitability (Hung et al., 2020).

To date, whether rTMS may be effective in the treatment of suicidal behavior needs to be further investigated. Possible mechanisms involved in the rTMS treatment of suicidal behavior may be, similarly to MDD, the increase in serotonin neurotransmission in PFC and hippocampus, changes in local hippocampal inhibitory circuits and cortical inhibition, modulation of the functional connectivity in the frontostriatal network and subgenual area, changes in functional connectivity between the DLPFC and DMN, promotion of hippocampal neurogenesis and synaptic plasticity and increase of BDNF plasma levels (Peng et al., 2018). Suicidal behavior has been associated with specific executive deficits while suicidal ideation was linked to cognitive rigidity (Westheide et al., 2008). Patients who experience major affective disorders often suffer from cognitive impairments that significantly impact on their functional recovery (Crowe et al. 2020). DLPFC is a frontal brain area that may be critically involved in the executive functions of inhibition, decision making, working memory, abstract reasoning and attention (Funahashi, 2017). However, recent studies suggested that DLPFC-mediated cognitive control functions may also pertain to emotions. Specifically, functional imaging studies demonstrated the recruitment of l-DLPFC during the regulation of negative emotions through reappraisal/suppression strategies and activation of r-DLPFC during tasks involving the control over positive distraction (Zilverstand et al., 2017). Importantly, there are studies reporting that suicidal ideation is associated with an abnormal PFC activation during a verbal fluency task (Pu et al., 2015) during or emotion regulation functional magnetic resonance imaging task (Miller et al., 2018) in depressed patients.

Failure to recruit left DLPFC in the face of negative distraction has been associated with MDD, anxiety, trait negative affect and schizotypy (Grimshaw et al., 2014). The authors proposed the asymmetric inhibition model postulating that each frontal region is fundamental for the inhibition of different types of emotions, with l-DLPFC being particularly responsible for inhibiting negative stimuli, and r-DLPFC being responsible for inhibiting positive stimuli. This model is consistent with data regarding the clinical efficacy of stimulating l-DLPFC and inhibiting r-DLPFC. These results are in line with previous neuropsychological studies showing that after damage to the left PFC regions some patients became increasingly depressed, while damage to the right frontal regions resulted in increasing levels of manic symptoms.

Given that additional research is really needed to determine whether and to what extent TMS is effective in treating suicidal behavior, the present systematic review is aimed to comprehensively investigate the current literature about this topic and provide an updated overview of the available evidence.

2. Methods

2.1 Eligibility Criteria

We adopted the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" guidelines (Liberati et al., 2009). We included papers that explicitly mentioned the association between TMS AND suicidal behavior in adolescence or adulthood. When a title or abstract appeared to describe a suitable study, the full-text paper was closely examinated to evaluate its significance for our study. Exclusion criteria were the following: (1) papers published before 1980; (2) studies without abstracts or with abstracts that did not explicitly mention the association between TMS and suicidal behavior; (3) studies that were not published in English; (4) systematic reviews or meta-analytic studies on the topic (with the exception of Weissman et al. 2018, which analyzed the data of two articles not reporting the above mentioned keywords) and (5) studies on animals.

2.2 Information Sources

We performed a systematic search through four major electronic databases concerning medical and social science studies (e.g., PubMed, Scopus, Science Direct, PsychInfo) for titles and abstracts pertinent to our research questions. We also examined the reference lists of the selected articles to search further papers which might be potentially relevant for inclusion. Overall, the papers we examined covered the period between 2011 and 2020.

2.3 Search Terms

Overall, the following search query was used in Pubmed: suicid*[Title/Abstract]) AND rTMS [Title/Abstract]; suicid*[Title/Abstract]) AND TMS [Title/Abstract]. The following search query was used in Sciencedirect: rTMS AND suicide [title-abstract-keywords]; TMS AND suicide [title-abstract-keywords]; rTMS AND suicidal [title-abstract-keywords]; TMS AND suicidal [title-abstract-keywords] as well. In addition, the following search query was used in Scopus: rTMS AND suicide [article title-abstract-keywords]; TMS AND suicide [article title-abstract-keywords]; rTMS AND suicidal [article title-abstract-keywords]; rTMS AND suicidal [article title-abstract-keywords].

2.4 Selection of Studies

Articles were examined and selected in a two-step process in order to reduce bias. First, two independent researchers (GC, DB) performed the literature search. In case of any discrepancies between the two reviewers, these were solved by consulting the senior researchers (GS and MA). In the second phase, full-text papers meeting our inclusion criteria were obtained and independently analyzed by senior authors who discussed the design and the main characteristics of the studies in order to choose whether they could be included.

In case of doubts, the study was put on a "pending list" of those awaiting assessment and more information, and later was carefully reanalyzed for possible inclusion. In case of disagreement at this step, the eventual inclusion was discussed between reviewers. Figure 1 summarizes the main results of the search strategy (i.e., the identification, screening, eligibility, and inclusion process) used for selecting studies.

[Insert here Figure 1]

2.5 Data collection process

GC and DB acquired the following data from the 16 papers included in this review (see "Study Sample" below): author/s and publication year, study design, sample size, presence/absence and type of control group (e.g., sham rTMS, other treatment), psychiatric diagnosis and sample characteristics, psychometric instruments, TMS protocol, shortcomings/limitations, main findings and conclusions (for more details, see Table 1).

2.6 Summary Measures

The quality of the studies was assessed using the following criteria: (1) representativeness of the sample (0–2 points); (2) presence and representativeness of control group (0–2 points); (3) presence of follow-up (0–2 points); (4) evidence-based measures of sucidality [e.g., Columbia Suicide Severity Rating Scale (C-SSRS), Scale of Suicidal Ideation (SSI), Beck Scale for Suicide Ideation (BSI)], (5) presence of raters who identified independently the presence of suicidal behavior (0–2 points); and (6) statistical evaluation of interrater reliability (0–2 points). Quality scores ranged from 0 to 12. Studies were differentiated with respect to their quality as follows: (1) good quality (9–12 points), if most or all the criteria were fulfilled or, where they were not met, the study conclusions were considered very robust; (2) moderate quality (4–8 points), if some criteria were fulfilled or, where they were not met, the study conclusions were deemed robust; and (3) low quality (0–3 points), where few criteria were fulfilled or the conclusions were not considered robust.

3. Results

3.1 Study Sample

The searches in PubMed, Scopus, Science Direct, and PsycInfo revealed, after the removal of duplicates, a total of 16 potentially relevant articles about TMS and sucidality. Overall, including duplicates, the search in PubMed generated 47 articles; the search in Scopus generated 161; the search in Science Direct generated 35. Of all these stusies, 227 were excluded as they are duplicates, or they are lacking an abstract, or they had an abstract that did not explicitly mention the use of TMS in a sample of suicidal patients, or they were not written in English.

3.2 Study Types and Sample Characteristics

Five sham-controlled clinical trials, including a total of 441 patients (1 study included 2 previous RCTs), 1 accelerated rTMS-controlled clinical trial including a total of 119 patients, 1 ECT-controlled clinical trial including a total of 73 patients, 3 uncontrolled clinical trials - including a total of 66 patients, 4 case series/case reports including a total of 6 patients – and 2 retrospective studies including a total of 341 patients were included in the present systematic review. Clinical

samples included predominantly patients with suicidal ideation or suicidal attempts and one of the following psychiatric diagnoses: MDD, treatment resistant depression (TRD), and in some cases bipolar disorder (BD).

3.3 Study Quality Assessment

According to our quality score system, the mean quality score of the 5 sham-controlled clinical trials was 6.6, the mean score of the 2 accelerated TMS or ECT - controlled clinical trials was 6.5; the mean score of the 3 uncontrolled clinical trials was 3.33; the mean score of the 4 case-series was 3.5, and the quality score of the retrospective analysis studies was 3.5. Quality scores ranged from 0 to 12. Studies were differentiated according to their quality, as follows: (1) good quality (8–12 points), if most or all the criteria were fulfilled or, where they were not met, the study conclusions were deemed very robust; (2) moderate quality (4–7 points), if some criteria were fulfilled or, where they were not met, the study conclusions were deemed robust, and (3) low quality (0–3 points), where few criteria were fulfilled or the conclusions were not deemed robust.

3.4 Sham-controlled clinical trials

Seven sham-controlled studies providing l-DLPFC rTMS, l-DLPFC iTBS or bilateral rTMS reported improvements in terms of suicidal ideation and mood disorders. The study of George and colleagues (2014) was specifically focused on depressed (unipolar or bipolar) patients admitted in an inpatient setting for suicidal ideation. The intense l-DLPFC rTMS protocol implementation was associated with a decline in suicidal ideation which was not significant when compared with the sham rTMS treatment effects. However, the study showed a trend toward improvement in the TMS group *vs.* sham at day 1. In particular, in completers on day 1 an average 50% reduction in SSI scores emerged with active rTMS as compared to a 25% reduction with sham. This difference normalized on day 2 and 3.

Similar results were documented by Yesavage et al. (2018) who conducted a clinical trial involving US veterans with TRD and providing low intensity but protracted l-DLPFC rTMS. Despite the reduction in suicidal ideation and depression, this was not significant when compared with sham-rTMS results. The overall remission rates in depression (40.7% in active rTMS group *vs.* 37.4% in sham rTMS group) were high in both groups. The most common serious adverse event was suicidal ideation, that was showed by 3 active and 4 sham participants. No suicides or seizures occurred during the study.

The study of Desmyter and colleagues (2016) was conducted with accelerated l-DLPFC intermittent Thetaburst Stimulation (iTBS), a TMS technique using bursts of high-frequency stimulation at repeated intervals, which is postulated to affect brain functions more profoundly when compared to the 'classic' rTMS protocols. Although the cross-sectional nature of this study design, the authors provided an intensive treatment including 20 sessions of iTBS (50 Hz, 1620 stimulations per sessions, 5 sessions per day over 4 days) and observed a significant decrease in suicide risk which was not linked to active or sham stimulation and unrelated to depression response. Treatment resulted safe and feasible. The significant decrease in suicidal risk was unrelated to depression

improvement, though it was not when compared with the sham treatment effect. Moreover, the improvement in suicidal ideation lasted up to one month after baseline.

Among clinical trials, only the study of Rao and colleagues (2019) evaluated the efficacy of low-frequency r-DLPFC rTMS on suicidal behavior and other clinical measures although this was in a group of unipolar depressed, antidepressant-free patients who developed depression following a TBI. Patients showed significant improvements in suicide ideation, depression, anxiety, sleep quality, clinical global condition and satisfaction with life, although the differences between sham and TMS treatment groups were not significant. No serious adverse events were registered.

Bilateral rTMS effectiveness in suicidal behavior was evaluated by Weissman and colleagues (2018), who analyzed the data extracted from two trials on this paradigm in TRD, compared with unilateral and sham rTMS. The l-DLPFC rTMS was not significantly more effective than sham treatment in reducing suicidal behavior, whereas bilateral rTMS was effective. Suicidal ideation resolved in 40.4%, 26.8% and 18.8% of participants randomized to bilateral, left unilateral and sham rTMS, respectively. Importantly, the relation between change in suicidal ideation and depression was significant, but the correlation was modest: the change in depression severity accounted for 15% of the change in suicidal ideation, and the rate in resolution of suicidal ideation was higher than that of depressive symptoms remission.

In addition, Keshtkar and colleagues (2011) compared a very low dose (408 pulses, 10 daily sessions) l-DLPFC protocol to having 10 electroconvulsive therapy (ECT) sessions in treating suicidal behavior in a sample of unipolar MDD patients. Both interventions significantly decreased depression and suicidal ideation, though ECT decreased them more than rTMS. However, TMS showed high rates of safety and tolerability.

Finally, Fitzgerald et al. (2018) compared l-DLPF rTMS with an accelerated rTMS protocol, using l-DLPF rTMS provided in an intensive rTMS schedule (3.500 pulses per session, 3 sessions per day over the first 3 days, followed by decreased intensity treatment, lasting overall 3 weeks) to TRD, in unipolar or bipolar patients. Both interventions resulted safe and effective and produced significant improvements in depression and suicidal ideation, though accelerated treatment was associated with a higher rate of reported discomfort. There were no between-group differences in terms of depression, suicidal behavior, and cognitive functioning. The accelerated group showed, after treatment, improved performance in trail making test, while the standard group showed improved performances in digital symbol coding test.

[Insert Table 1 here]

3.5 Uncontrolled clinical trials, ECT-controlled clinical trials, accelerated TMS-controlled clinical trials, retrospective studies

Five uncontrolled studies evaluated the effectiveness of l-DLPFC rTMS, using differently intensive protocols. Specifically, one study compared l-DLPFC rTMS with ECT and onother with accelerated rTMS, two retrospecive analyses evaluated the effectiveness of l-DLPFC, r-DLPFC, and a combination of these, ACC TMS and right and left prefrontal TBS.

The first study regarded a retrospective analysis implemented by Croarkin and colleagues (2018) in which the authors pooled data from 3 prior studies administering a low intensity but quite prolonged

(30 sessions over 6-8 weeks) l-DLPFC rTMS treatment to MDD adolescents failing to respond to at least one prior trial of antidepressant medication. Treatment was found to be safe and feasible. Findings suggested that suicidal ideation improved throughout treatment but this was presumably mediated by improvement in depressive symptom severity.

The retrospective analysis of Abdelnaim et al. (2020) stressed the effectiveness of different TMS protocols in improving suicidal ideation in 332 MDD patients. The heterogeneous protocols included 1, 10 and 20 Hz stimulation intensity, from 1400 to 2400 pulses per session and from 6 to 50 sessions. Suicidal ideation changes were correlated with improvements in depressive mood, guilt, and global energy.

A more intensive l-DLPFC rTMS protocol was implemented by Hadley et al. (2011), who treated adult depressed patients with either unipolar or bipolar TRD. Globally, suicidal ideation significantly decreased over time, especially in the first week of treatment, even tough 3 subjects showed a minor increase in suicidal ideation score after 1 week. The magnitude of the improvement in suicidal thinking ranged from 0% to 77%. Depression rates decreased too, and by 8 weeks, 66% of the subjects showed remission. Quality of life, emotional well-being, energy, physical and social functioning levels also increased. Interestingly, one subject receiving rTMS treatment for more than 2 years experienced relief from depressive symptoms, not reporting adverse effects.

Deep TMS (DTMS) was used by Berlim and colleagues (Berlim et al., 2014) with the aim of treating TRD unipolar patients. Patients showed significant improvements in suicidal ideation, anxiety, depression, global psychiatric conditions and quality of life, and no serious adverse events. Response and remission rates at week 5 were 70.6 and 41.2%, respectively. 20 Hz TMS stimulation was also implemented by Ozcan et al. (2020) with significant improvements in terms of depression, suicidal idation and behavior and hopelessness in TRD patients. These improvements were not related to the rates of emotion recognition skills that ameliorated, and of cognitive functions that remained stable.

3.6 Case reports and case series

Overall, we collected 4 case series studies, assessing the effectiveness of standard or accelerated rTMS. Accelerated TMS (10 Hz, 1980 pulses per session, 4 sessions per day, 5 sessions for a week for a month) was used by Fryml et al. (Fryml et al., 2018) in a TRD unipolar post-traumatic stress disorder (PTSD) 27 year old patient. the authors reported that at 4-weeks post-treatment follow-up suicidal thoughts disappeared and PTSD/depressive were improved. Unfortunately, it was not possible to test whether confounding environmental factors might have affected treatment response.

A less intensive rTMS protocol was additionally performed by Iliceto et al. (2018) who found that after 2 years follow-up the TBI depressed patient was recovered from both depression and suicidal behavior.

Despite the absence of manic episodes, 2 out 3 depressed and suicidal adolescents treated by Pan et al. (2018) developed hypomania after 4 days of the high dose rTMS treatment (6000 stimuli for a daily session, 10 Hz). Improvement rates in suicidal behavior were 40.01%, 100% and 75% as highlighted by Rachid et al. [44], who reported that TMS may possibly induce manic or hypomanic episodes in patients with depression, who are often taking an antidepressant. The authors added that TMS may induce manic switches even though light stimulus parameters are used or the patient is taking mood-stabilizers.

Finally, Kulkarni et al. (2018) reported the rTMS treatment (26 sessions over 4,5 weeks) of a depressed, suicidal inpatient with LF r-DLPFC. The patient improved gradually in depression rates and at 3-months follow-up, remission in depression and suicidal behavior was maintained.

[Insert Table 2 here]

4. DISCUSSION AND CONCLUSIONS

4.1 Summary of main findings

Overall, most of the included studies identified the l-DLPFC as the preferred stimulation area. Other selected brain regions were rDLPFC (inhibition stimuli, 1 Hz) and anterior cingulate cortex. The stimulation protocols were generally the standard ones of 10Hz, with a motor threshold of 100-120%, with several impulses ranging from 1200 used in the study of Kulkarni et al. (2018) to 6000 adopted in the study of Pan and colleagues (2018), George et al. (2014) and Hadley et al. (2011), with an average around 3000 pulses. Only one study (Abdelnaim et al., 2020) used DTMS, administered via a new "H1" coil, daily, for four weeks, in patients with severe TRD. DTMS was associated with improvements in suicidal behavior (ideation and behavior), depression and associated anxiety symptoms. Clinical safety was established for DTMS as well. Further studies implemented accelerated intermittent Theta Burst Stimulation (iTBS) (Desmyter et al., 2016) - a technique providing bursts of high-frequency stimulation (50 Hz), which is thought to affect brain function more thoroughly - and bilateral TMS. As DTMS showed similar outcomes to "classic" TMS, bilateral TMS resulted significantly more effective when compared with sham treatments. Moreover, accelerated TMS did not appear more effective than l-DLPFC TMS. Two studies (Desmyter et al., 2016; Kulkarni et al., 2018) focused on r-DLPFC and stressed the clinical efficacy of the treatment, which resulted nevertheless not significant when compared with sham TMS. Bilateral TMS resulted instead effective when compared with placebo (Weissman et al., 2018).

It is important to note that the number of subjects per study was very heterogeneous, ranging from 1 to 3 patients in case reports/series to more than one hundred (N=164 and 119, respectively) of participants in the study conducted by Yesavage et al. (2018) and Fitzgerald et al. (2018). The largest study was conducted by Abdelnaim (2020) on 322 patients, divided into 8 different treatments. An important discriminant in this study was the inclusion of a sham group, which is present only in controlled clinical trials to give a more significant statistical weight to the collected data.

Among controlled studies, bilateral TMS (George et al., 2014) resulted to be the most effective form of TMS when compared to placebo, but it has some technical limitations regarding the availability and applicability of a bilateral probe. Two reports (Keshtkar et al., 2011; Fitzgerald et al., 2018) compared instead l-DLPFC respectively with accelerated TMS and ECT. Accelerated TMS did not lead to different outcomes than standard TMS, as ECT demonstrated to be more effective than TMS. The most encouraging results in favour of DLPFC rTMS were those of Croarkin et al. (2018), Hadley et al. (2011), Ozcan et al. (2020) and Abdelnaim et al. (2020). In the study of Cloarkin et al. (2018), the reduction of suicidal risk was found to be mediated by depressive symptoms improvement. Conversely, in the study of Desemyter et al. (2016), changes in suicidal ideation were found to be independent of improvements in depression, and in Weissman et al. (2018) study the correlation between depressive and suicidal ideation changes was 0.38. In the

study of Hadley et al. (2011), improvements were found in suicidal ideation, especially in the first week of treatment, and depressive symptoms while Ozcan and colleagues (2020) clearly demonstrated the efficacy of TMS on suicidal ideation. Even in 2020, the retrospective study of Abdelnaim and colleagues (2020) based on a sample of 320 depressed patients, treated with various TMS protocols demonstrated a significant improvement in suicidal ideation, as well as depression and global energy. Given the importance and dramatic impact worldwide of suicidal behavior (Kuehn, 2020; Baryshnikov et al., 2020), these findings are very relevant as they directly indicate that suicidal ideation might be a specific target construct for TMS.

With regard to age, no significant differences were found in samples composed by adolescents (Croarkin et al., 2018; Pan et al., 2018) compared to adult groups. No differences were found in the treatment of MDD *vs.* TRD and between patients taking antidepressant *vs.* antidepressant free patients (Desmyter et al., 2016; Rao et al., 2019), although Fitzgerald and colleagues (2018) found a greater percentage of subjects who were not TMS responders among antidepressant free patients. This result is consistent with existing well-established evidence about the importance of implementing integrated treatments. Moreover, in line with previous findings (Serafini et al., 2015), TMS did not affect cognitive functions and according to Ozcan et al. (2020) ameliorated emotion recognition abilities.

With regards to safety, the use of rTMS may be considered a safe, applicable, well accepted and reproducible method. However, two of the three MDD adolescents treated by Pan and colleagues (2018) reported hypomanic episodes, after l-DLPFC rTMS treatment. This effect would be not apparently related to the high number of stimuli but to a possible incorrect diagnosis of MDD. Given these findings, it is highly recommended that patients with bipolar disorder, who are experiencing a depressive episode, may be treated with a mood stabilizer in combination to rTMS while patients diagnosed with MDD revaluated to consider the possibility that they might suffer from bipolar disorder, before rTMS treatment is initiated (Hede et al., 2019; Godman et al., 2019; Yee et al., 2019). In case treatment-emergent hypomania or mania occurs, rTMS discontinuation should be considered, while continuing mood-stabilizing medications. Overall, although safety in treating adolescents with TMS is overall well established (Krishnan et al., 2015), further studies are needed to assess the functioning of this technique in neurodevelopmental periods.

As TMS treatment combined with antidepressant medications for depressive symptoms has a certain therapeutic advantage *vs.* placebo (Wei et al., 2017), magnetic stimulation for suicidal behavior seems to lead to overall encouraging results, especially if the protocol involves bilateral stimulation. Although we are moving in the correct direction, providing more and more information regarding both safety and tolerability, further studies are required to refine the technique, being able to standardize treatments and guarantee useful therapeutic support for patients at risk, who do not respond to the most common guidelines.

4.2 Main strengths and limitations/shortcomings

To the best of our knowledge, this is the first review to systematically analyze the efficacy of TMS in treating suicidal behavior and this may be considered a strength of this study.

Anyway, our findings must be considered in the light of the following limitations. First of all, we were not able to perform a meta-analysis as outcomes were evaluated differently in the analyzed studies . Secondly, the comparison of such different studies in terms of protocol type (e.g., number

of trains per sessions, intensity, duration and intensity of treatments), possible concomitant use of psychoactive medications - not only antidepressants, and not always specified - age and type of patient unavoidably implies the presence of confounding factors. Moreover, the included studies were heterogeneous and some reports may have been underpowered (they had very small sample sizes) and/or did not include control groups. Furthermore, the inclusion/exclusion of specific studies may reflect the individual point of view and may subjectively reflect our experience in the field. Furthermore, some of the selected studies did not include control groups.

4.3 Main implications and future directions

In conclusion, TMS may be considered an effective, safe, and well-tolerated technique in treating suicidal behavior. Unfortunately, based on the analyzed studies, it is not clear whether suicidal behavior reduction may be mediated, at least in some cases, by depressive symptoms reduction. However, the anti-suicidal properties of rTMS protocols seem to be unrelated to active or sham stimulation and depression-response. The most effective treatment seems to be bilateral TMS, and TMS could be more effective in combination with antidepressants. Given the noninvasive nature of rTMS and its safety as a treatment for MDD, the use of this technique as an acute intervention in suicidal patients may be very helpful for both patients and clinicians and it is highly recommended in the clinical practice. Importantly, rTMS has been found to attenuate multiple suicidal dimensions (e.g., suicidal ideation, intensity of suicidal thoughts, suicidal behavior, and suicidal intent). Further well-designed, sham-controlled studies are urgently required to test more explicitly the efficacy and safety of high-dose rTMS in suicidal patients (both in subjects with active suicide ideation as well as those who have recently attempted suicide), and whether, with additional refinement, rTMS may represent an alternative method to rapidly attenuate suicidal behavior. As suicidal behavior might be a specific target construct for rTMS, the possible inclusion of patients with severe medical conditions (e.g., malignant cancer, cardiovascular diseases, etc.) who are even at suicide risk may be also considered in clinical settings. Unfortunately, the current practical and regulatory barriers restricted the conduction of interventional rTMS trials with suicidal patients (Lefaucheur et al., 2014).

Author contributions

Gianluca Serafini: Conceptualization, Writing- Original draft preparation; Giovanna Canepa: Data curation; Luca Magnani and Davide Bianchi: Investigation, Methodology; Paul B. Fitzgerald and Mario Amore: Supervision; Andrea Aguglia; Andrea Amerio: Writing - original draft; Maurizio Pompili; Bernardo Dell'Osso: Writing - review & editing.

Conflict of interest

The authors declare no conflict of interest

Journal Pre-proof

REFERENCES

Abdelnaim, M.A., Langguth, B., Deppe, M., Mohonko, A., Kreuzer, P.M., Poeppl, T.B. Hebel, T., Schecklmann, M., 2020. Anti-Suicidal Efficacy of Repetitive Transcranial Magnetic Stimulation in Depressive Patients: A Retrospective Analysis of a Large Sample. Front. Psychiatry 10,929.

Baryshnikov, I., Rosenström, T., Jylhä, P., Vuorilehto, M., Holma, M., Holma, I., Riihimäki, K., Brown, G.K., Oquendo, M.A., Isometsä, E.T., 2020. Role of Hopelessness in Suicidal Ideation Among Patients With Depressive Disorders. J Clin Psychiatry. 11,81.

Berlim, M., Eynde, F., Tovar-Perdomo, S., Chachamovich, E., Zangen, A., Turecki, G., 2014. Augmenting antidepressants with deep transcranial magnetic stimulation (DTMS) in treatment-resistant major depression. World J. Biol. Psychiatry 2014;15,570-578.

Chen, J., Zhou, C., Wu, B., Wang, Y., Li, Q., Wei, Y., Yang, D., Ma, J., Zhu, D., Zou, D., Xie, P., 2013. Left versus right repetitive transcranial magnetic stimulation in treating major depression: a meta-analysis of randomised controlled trials. Psychiatry Res. 210, 1260-1264.

Chung, S.W., Rogasch, N.C., Hoy, K.E., Sullivan, C.M., Cash, R.F.H., Fitzgerald, P.B., 2018. Impact of different intensities of intermittent theta burst stimulation on the cortical properties during TMS-EEG and working memory performance. Hum. Brain. Mapp. 39, 783-802.

Cox Lippard, E.T., Johnston, J.A., Blumberg, H.P., 2014. Neurobiological risk factors for suicide: insights from brain imaging. Am. J. Prev. Med. 47, S152-S162.

Croarkin, P.E., Nakonezny, P.A., Deng, Z.D., Romanowicz, M., Voort, J.L.V., Camsari, D.D., Schak, K.M., Port, J.D., Lewis, C.P., 2018. High-frequency repetitive TMS for suicidal ideation in adolescents with depression. J. Affect. Disord. 239,282–290.

Crowe, M., Porter, R., Douglas, K., Inder, M., Lacey, C., Jordan, J., Wells, H., 2020. Patients' experiences of cognitive functioning in recurrent depression: A qualitative study. Psychiatr Ment Health Nurs (in press).

Desmyter, S., Duprat, R., Baeken, C., Van Autreve, S., Audenaert, K., van Heeringen, K., 2016. Accelerated Intermittent Theta Burst Stimulation for Suicide Risk in Therapy-Resistant Depressed Patients: A Randomized, Sham-Controlled Trial. Front. Hum. Neurosci. 10, 480.

Downar, J., Geraci, J., Salomons, T.V., Dunlop, K., Wheeler, S., McAndrews, M.P.,. Bakker N7, Blumberger, D.M., Daskalakis, Z.J., Kennedy, S.H., Flint, A.J., Giacobbe, P., 2014. Anhedonia and reward-circuit connectivity distinguish nonresponders from responders to dorsomedial prefrontal repetitive transcranial magnetic stimulation in major depression. Biol. Psychiatry 76,176-185.

Feffer, K., Fettes, P., Giacobbe, P., Daskalakis, Z.J., Blumberger, D.M., Downar, J., 2018. 1 Hz rTMS of the right orbitofrontal cortex for major depression: Safety, tolerability and clinical outcomes. Eur. Neuropsychopharmacol. 28, 109-117.

Fitzgerald, P.B., Hoy, K.E., Elliot, D., Susan McQueen, R.N., Wambeek, L.E., Daskalakis, Z.J., 2018. Accelerated repetitive transcranial magnetic stimulation in the treatment of depression. Neuropsychopharmacology 43,1565–1572.

Fryml, L.D., Sahlem, G., Fox, J., Short, E.B., 2018. The role of rTMS for patients with severe PTSD and depression. Evidence-Based Mental Health 21,39-40.

Journal Pre-proof

Funahashi, S., 2017. Working Memory in the Prefrontal Cortex. Brain Sci.7,49.

George, M.S., Raman, R., Benedek, D.M., Pelic, C.G., Grammer, G.G., Stokes, K.T. Schmidt, M., Spiegel, C., Dealmeida, N., Beaver, K.L., Borckardt, J.J., Sun, X., Jain, S., Stein, M.B., 2014. A two-site pilot randomized 3 day trial of high dose left prefrontal repetitive transcranial magnetic stimulation (rTMS) for suicidal inpatients. Brain Stimul. 7, 421-431.

Godman, B., Grobler, C., Van-De-Lisle, M., Wale, J., Barbosa, W.B., Massele, A., Opondo, P., Petrova, G., Tachkov, K., Sefah, I., Abdulsalim, S., Alrasheedy, A.A., Unnikrishnan, M.K., Garuoliene, K., Bamitale, K., Kibuule, D., Kalemeera, F., Fadare, J., Khan, T.A., Hussain, S., Bochenek, T., Kalungia, A.C., Mwanza, J., Martin, A.P., Hill, R., Barbui, C., 2019. Pharmacotherapeutic interventions for bipolar disorder type II: addressing multiple symptoms and approaches with a particular emphasis on strategies in lower and middle-income countries. Expert Opin. Pharmacother. 20,2237-2255.

Grimshaw, G.M., Carmel, D., 2014. An asymmetric inhibition model of hemispheric differences in emotional processing. Front. Psychol. 5,489.

Hadley, D., Anderson, B., Borckardt, J., Arana, A., Li, X., Nahas, Z., George, M.S., 2011. Safety, Tolerability, and Effectiveness of High Doses of Adjunctive Daily Left Prefrontal Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression in a Clinical Setting. J. ECT 27,18-25.

Hede, V., Favre, S., Aubry, J.M., Richard-Lepouriel, H., 2019. Bipolar spectrum disorder: What evidence for pharmacological treatment? A systematic review. Psychiatry Res. 282,112627.

Hung, Y.Y., Yang, L.H., Stubbs, B., Li, D.J., Tseng, P.T., Yeh, T.C., Chen, T.Y., Liang, C.S., Chu, C.S., 2020. Efficacy and tolerability of deep transcranial magnetic stimulation for treatment-resistant depression: A systematic review and meta-analysis. Prog. Neuropsychopharmacol. Biol. Psychiatry 99, 109850.

Iliceto, A., Seiler, R.L., Sarkar, K., 2018. Repetitive Transcranial Magnetic Stimulation for Treatment of Depression in a Patient With Severe Traumatic Brain Injury. Ochsner J. 18,264–267.

Kang, J.I., Lee, H., Jhung, K., Kim, K.R., An, S.K., Yoon, K.J., Kim, S.I., Namkoong, K., Lee, E., 2016. Frontostriatal Connectivity Changes in Major Depressive Disorder After Repetitive Transcranial Magnetic Stimulation: A Randomized Sham-Controlled Study. J Clin Psychiatry 2016;77,e1137-e1143.

Keshtkar, M., Ghanizadeh, A., Firoozabadi, A., 2011. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for the treatment of major depressive disorder, a randomized controlled clinical trial. J. ECT. 27,310-314.

Krishnan, C., Santos, L., Peterson, M.D., Ehinger, M., 2015. Safety of noninvasive brain stimulation in children and adolescents. Brain Stimul. 8,76–87.

Kuehn, B.M., 2020. Rising Emergency Department Visits for Suicidal Ideation and Self-harm. JAMA 323,917.

Kulkarni, G., Mitra, S., Nahar, A., Mehta, U.M., Thippeswamy, H., Thirthalli, J., 2018. Low-Frequency rTMS as an alternative for suicidality and depression, in a patient with multiple medical comorbidities precluding ECT. Asian J. Psychiatr. 34,14-15.

Lefaucheur, J.P., André-Obadia, N., Antal, A., Ayache, S.S., Baeken, C., Benninger, D.H. Cantello, R.M., Cincotta, M., de Carvalho, M., De Ridder, D., Devanne, H., Di Lazzaro, V., Filipović, S.R., Hummel, F.C., Jääskeläinen, S.K., Kimiskidis, V.K., Koch, G., Langguth, B., Nyffeler, T., Oliviero, A., Padberg, F., Poulet, E., Rossi, S., Rossini, P.M., Rothwell, J.C., Schönfeldt-Lecuona, C., Siebner, H.R., Slotema, C.W., Stagg, C.J., Valls-Sole, J., Ziemann, U., Paulus, W., Garcia-Larrea, L., 2014. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin. Neurophysiol. 125, 2150-2206.

Lewis, C.P., Nakonezny, P.A., Blacker, C.J., Vande Voort, J.L., Port, J.D., Worrell, G.A., Jo, H.J., Daskalakis, Z.J., Croarkin, P.E., 2018. Cortical inhibitory markers of lifetime suicidal behavior in depressed adolescents. Neuropsychopharmacology 43,1822-1831.

Li, X., Nahas, Z., Kozel, F.A., Anderson, B., Bohning, D.E., George, M.S., 2004. Acute left prefrontal transcranial magnetic stimulation in depressed patients is associated with immediately increased activity in prefrontal cortical as well as subcortical regions. Biol. Psychiatry 55, 882-890.

Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gøtzsche, P.C., Ioannidis, J.P., Clarke, M., Devereaux, P.J., Kleijnen, J., Moher, D., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann. Intern. Med. 151 W65–W94.

Lissemore, J.I., Bhandari, A., Mulsant, B.H., Lenze, E.J., Reynolds, C.F. 3rd., Karp, J.F., Rajji, T.K., Noda, Y., Zomorrodi, R., Sibille, E., Daskalakis, Z.J., Blumberger, D.M, 2018. Reduced GABAergic cortical inhibition in aging and depression. Neuropsychopharmacology 43, 2277–2284.

Menon, V., Kattimani, S., 2015. Suicide and Serotonin: Making Sense of Evidence. Indian J. Psychol. Med. 37, 377-378.

Meyer, R.E., Salzman, C., Youngstrom, E.A., Clayton, P.J., Goodwin, F.K., Mann, J.J., Alphs, L.D., Broich, K., Goodman, W.K., Greden, J.F., Meltzer, H.Y., Normand, S.L., Posner, K., Shaffer, D., Oquendo, M.A., Stanley, B., Trivedi, M.H., Turecki, G., Beasley, C.M. Jr., Beautrais, A.L., Bridge, J.A., Brown, G.K., Revicki, D.A., Ryan, N.D., Sheehan, D.V., 2010. Suicidality and Risk of Suicide-Definition, Drug Safety Concerns, and a Necessary Target for Drug Development: A Brief Report. J. Clin. Psychiatry 71, 1040-1046.

Miller, A.B., McLaughlin, K.A., Busso, D.S., Brueck, S., Peverill, M., Sheridan, M.A., 2018. Neural Correlates of Emotion Regulation and Adolescent Suicidal Ideation. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 3,125-132.

Ozcan, S., Gica, S., Gulec, H., 2020. Suicidal behavior in treatment resistant major depressive disorder patients treated with transmagnetic stimulation(TMS) and its relationship with cognitive functions. Psychiatry Res. 286,112873.

Pan, F., Li, D., Wang, X., Lu, S., Xu, Y., Huang, M., 2018. Neuronavigation-guided high-dose repetitive transcranial magnetic stimulation for the treatment of depressive adolescents with suicidal ideation: a case series. Neuropsychiatr. Dis. Treat. 14,2675–2679.

Peng, Z., Zhou, C., Xue, S., Bai, J., Yu, S., Li, X., Wang, H., Tan, Q, 2018. Mechanism of Repetitive Transcranial Magnetic Stimulation for Depression. Shanghai Arch. Psychiatry 30, 84–92.

Pompili, M., Gibiino, S., Innamorati, M., Serafini, G., Del Casale, A., De Risio, L., Palermo, M., Montebovi, F., Campi, S., De Luca, V., Sher, L., Tatarelli, R., Biondi, M., Duval, F., Serretti, A., Girardi, P., 2012. Prolactin and thyroid hormone levels are associated with suicide attempts in psychiatric patients. Psychiatry Res. 200, 389-394.

Pompili, M., Shrivastava, A., Serafini, G., Innamorati, M., Milelli, M., Erbuto, D., Ricci, F., Lamis, D.A., Scocco, P., Amore, M., Lester, D., Girardi, P., 2013. Bereavement after the suicide of a significant other. Indian J. Psychiatry 55, 256-263.

Pu, S., Nakagome, K., Yamada, T., Yokoyama, K., Matsumura, H., Yamada, S., Sugie, T., Miura, A., Mitani, H., Iwata, M., Nagata, I., Kaneko, K., 2015. Suicidal ideation is associated with reduced prefrontal activation during a verbal fluency task in patients with major depressive disorder. J. Affect. Disord. 181,9-17.

Rachid, F., 2017. Repetitive Transcranial Magnetic Stimulation and Treatment-emergent Mania and Hypomania: A Review of the Literature. J. Psychiatr. Pract. 23,150-159.

Rao, V., Bechtold, K., McCann, U., Roy, D., Peters, M., Vaishnavi, S., Yousem, D., Mori, S., Yan, H., Leoutsakos, J., Tibbs, M., Reti, I., 2019. Low-Frequency Right Repetitive Transcranial Magnetic Stimulation for the Treatment of Depression After Traumatic Brain Injury: A Randomized Sham-Controlled Pilot Study. J. Neuropsychiatry Clin. Neurosci. 31, 306-318.

Serafini, G., Pompili, M., Belvederi Murri, M., Respino, M., Ghio, L., Girardi, P., Fitzgerald, P.B., Amore, M., 2015. The Effects of Repetitive Transcranial Magnetic Stimulation on Cognitive Performance in Treatment-Resistant Depression. A Systematic Review. Neuropsychobiology 71, 125-139.

Sobanski, T., Bär, K.J., Wagner, G., 2015. Neural, cognitive, and neuroimaging markers of the suicidal brain. Rep. Med. Imaging 9,71.

Thompson, C., Ong, E.L.C., 2018. The Association Between Suicidal Behavior, Attentional Control, and Frontal Asymmetry. Front. Psychiatry 9,79.

Tik, M., Hoffmann, A., Sladky, R., Tomova, L., Hummer, A., Navarro de Lara, L., Bukowski, H., Pripfl, J., Biswal, B., Lamm, C., Windischberger, C., 2017. Towards understanding rTMS mechanism of action: stimulation of the DLPFC causes network-specific increase in functional connectivity. NeuroImage 162, 289–296.

Wei, Y., Zhu, J., Pan, S., Su, H., Li, H., Wang, J., 2017. Meta-analysis of the Efficacy and Safety of Repetitive Transcranial Magnetic Stimulation (rTMS) in the Treatment of Depression. Shanghai Arch. Psychiatry 29,328–342.

Weissman, C.R., Blumberger, D.M., Brown, P.E., Isserles, M., Rajji, T.K., Downar, J., Mulsant, B.H., Fitzgerald, P.B., Daskalakis, Z.J., 2018. Bilateral repetitive transcranial magnetic stimulation decreases suicidal ideation in depression. J. Clin. Psychiatry 79, 17m11692.

Westheide, J., Quednow, B.B., Kuhn, K.U., Hoppe, C., Cooper-Mahkorn, D., Hawellek, B., Eichler, P., Maier, W., Wagner, M., 2008. Executive performance of depressed suicide attempters: the role of suicidal ideation. Eur. Arch. Psychiatry Clin. Neurosci. 258, 414-421.

World Health Organization. National suicide prevention strategies: progress, examples and indicators. who.int/mental_health/suicide-prevention/national_strategies_2019/en

Yee, C.S., Hawken, E.R., Baldessarini, R.J., Vázquez, G.H., 2019. Maintenance Pharmacological Treatment of Juvenile Bipolar Disorder: Review and Meta-Analyses. Int. J.

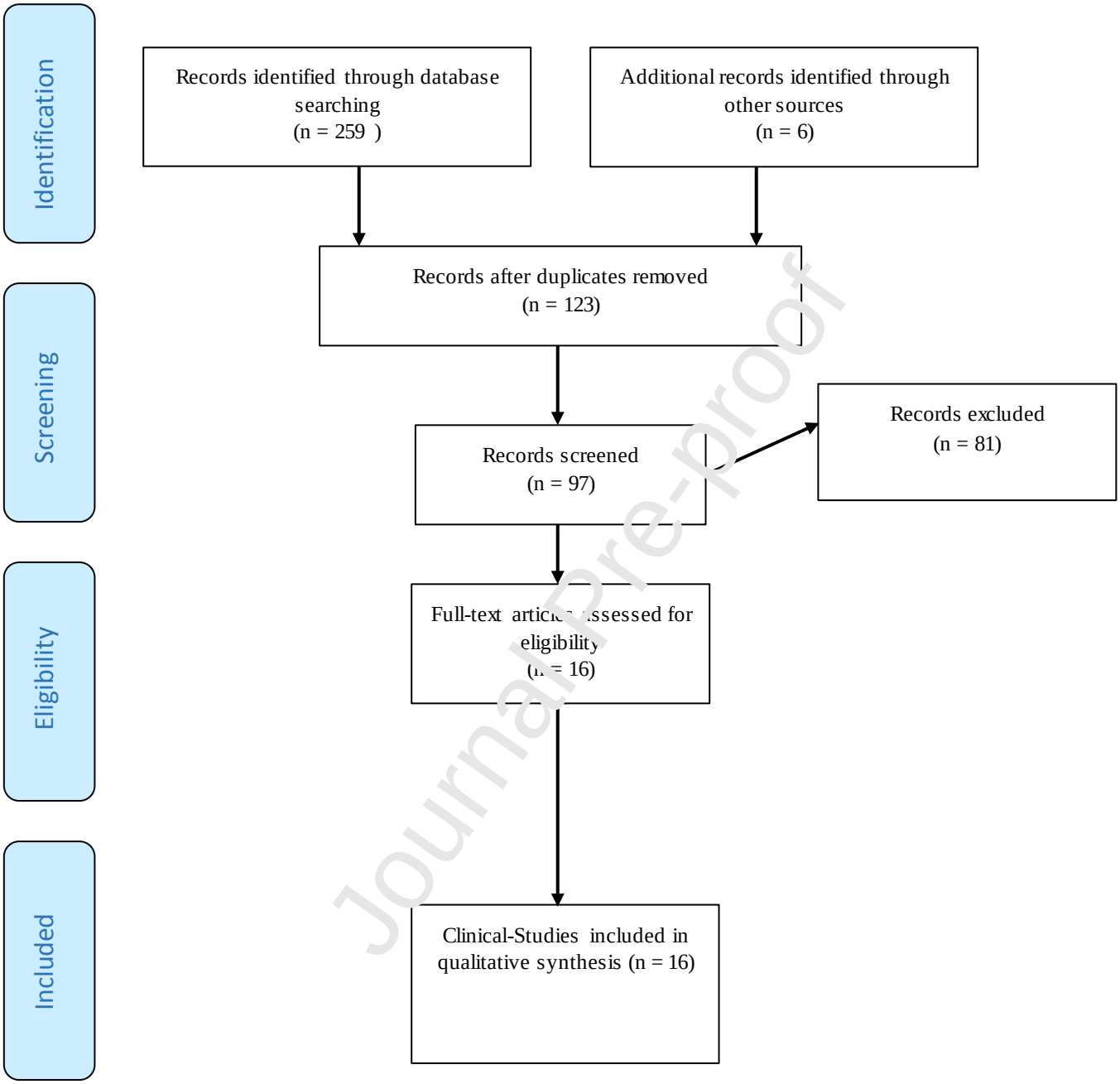
Neuropsychopharmacol. 22,531-540.

Yesavage, J.A., Fairchild, J.K., Mi, Z., Biswas, K., Davis-Karim, A., Phibbs, C.S., Formanm S.D., Thase, M., Williams, L.M., Etkin, A., O'Hara, R., Georgette, G., Beale, T., Huang, G.D., Noda, A., George, M.S., VA Cooperative Studies Program Study Team., 2018. Effect of Repetitive Transcranial Magnetic Stimulation on Treatment-Resistant Major Depression in US Veterans: A Randomized Clinical Trial. JAMA Psychiatry 75,884–893.

Zilverstand, A., Parvaz, M.A., Goldstein, R.Z., 2017. Neuroimaging cognitive reappraisal in clinical populations to define neural targets for enhancing emotion regulation. A systematic review. Neuroimage 151, 105-116.

Journal Pre-proof

Figure 1. Stages of the screening process



Journal Pre-proof

Table 1. Most relevant randomized controlled studies on the association between rTMS and suicidal behavior

Author(s), year	Study design	Sample characteristics	Stimulated brain region	Stimulation frequency and intensity	Control condition	Number of pulses/sessions	Psychometric instruments	Limitations	Main findings	Main conclusions	Quality assessment
Rao et al., 2019	Randomized. single-blind, sham controlled clinical trial. CG= r-DLPFC rTMS *vs*. sham rTMS.	30 TBI, MDD. unipolar, AF patients. MA=40 y. F=14.	r-DLPFC	1 Hz; 110%mt. 300-p trains, separated by 60-s II.	Sham rTMS	1200 p. 20 daily sessions over 4 weeks. 16-weeks post-treatment assessment. 4 patients dropped	BSSI: suicidal ideation	Small experimental group.	Time effect was significant, unlike time x treatment effect. There were no significant depression remission or response rate differences between groups.	TFS. SI, depression, anxiety, sleep quality, clinical condition and life satisfaction life improvement were found, but no SSDG.	I=1; II=1; II=2; IV=2; V=0; VI=0; TS=6; QD=moderate
Fitzgerald et al., 2018	2-arm single blind randomized controlled trial.CG=standard rTMS vs a-rTMS	119 TRD outpatients, partially taking antidepressant medications. MA= 49 y. F=66.	l-DLPFC	A-rTMS: 10 Hz, 120%mt. 4,2-s trains, separated by 15-s II. rTMS: 10 Hz, 120% mt. 4,2-s trains, separated by 25-s II intervals	rTMS	A-rTMS: 3500 p. Week 1: 3 sessions pd over 3 days, Week 2: 3 sessions over 2 days. Week 3: 3 sessions on a day. rTMS: 3150 p., 20 daily sessions, 5 days pw over 4 weeks. FU=4-5-weeks post-treatment. 115 patients completed the study	SSI: suicidal ideation.	Lack of blinding of patients. Lack of sham group.	SI evaluations showed at FU a significant main effect of Time(F (5428.550) = 2.652; p=0.022). There was no effect of treatment group, nor a significant time by group interaction. Depression results were similar. There were some significant	TSF. Improvements in SI and depression were found, but no SSDG. Significantly greater percentage of non-responders were AF. .	I=2; II=2; II=2; IV=2; V=0; VI=0; TS=8; QD=good

Journal Pre-proof

									cognitive improvements.		
Weissman et al., 2018	Randomized, double blind, controlled clinical trials.CG=l-DLPFC rTMS*vs.* bilateral rTMS*vs.* sham rTMS.	1) Blumberger et al., 2012. 68 TRD and SI outpatients, keeping antidepressants. MA=51, 5 years. F=28. 2) Blumberger et al., 2016. 121 TRD outpatients keeping antidepressants. MA=47 y. F=44. 33 patients without SI were removed.	l-DLPFC; BI; DLPFC	1) LU: 10 Hz, age<60: 100% mt; age>60: 120% mt. P pert: age<60: 50; age>60: 30. N of t: age<60: 29; age>60: 48+1. II: 30. BI: 30 Hz: R=1, L=10. Age<60: 100% mt; age>60: 120% mt. P pert: age<60: R=100, L=50; age>60. R=[illegible] L=[illegible]. N of t. age<60: R=4+1, L=15; age>60: L=4+1, R=25. II: 30. 2)LU: 10 Hz, 120%mt. P pert: 30. N of t: 70.II: 30. BI: Hz: R=1, L=10, 120% mt. P pert: R=100, R=30. N of t: R=6, L=50. II: 30	Sham rTMS	1)LU: 1540 p per session. BI: R=465 p per session, L=750 p per session. 15 sessions over 3 weeks, repeated if patient did not remit. 13 subjects withdrew. 2) LU: 2100 p per session. BI: R=600 p per session, L=[illegible] p per session. 15 sessions pw, repeated if patient did not remit. 16 subjects withdrew	HDRS-17 item 3 suicidal ideation	Lack of FU. Lack of specific measure.	SI resolved in 40,4%, 26,8% and 18, 8% of subjects randomized to BI, LU and sham rTMS, respectively. The difference in resolution between BI and sham rTMS was signficant (OR=3, 03; 95%CI= 1.19-7.1; p=0.2), unlike the difference between LU and sham rTMS (OR=1. 59; 95%CI= 0.61-4.2; p=.33). The correlation (Pearson r) between change in SI and in depression rates was .38 (p<.001).	TSF. Bilateral rTMS was effective in reducing suicidal ideation, whereas unilateral wasn't.	I=2; II=2; II=0; IV=1; V=0; VI=0: TS=5; QD=moderate

Journal Pre-proof

Yesavage et al., 2018	Double-blind, multicentri. sham-controlled randomized clinical trial. GC: l-DLPFC rTMS vs. sham rTMS.	164 veteran inpatients with TRD taking antidepressants. MA= 55 y. F=17,3%.	l-DLPFC	10 Hz, 120% mt. 4-s trains duration separated by 10-s intervals	Sham rTMS	4.000 p. 5 daily sessions pw over 4 weeks. Participants who remitted received additional sessions 3 weeks. 125 participants completed the study. FU=6 months	BSI: suicidal ideation. C-SSRS: suicidal ideation and attempts.	High proportion of men (80.5%)	The treatment effect of rTMS for suicidality was not significant compared with sham rTMS (BSI: OR= -0.54; C-SSR: OR= 1.02).	TSE but not effective on suicidality. The high proportion of males may be important as females may have a better response rate to rTMS.	I=2; II=2; II=2; IV=2; V=0; VI=0; TS=8;; QD=good
Desmyter et al., 2016	Randomized, double blind, sham controlled trial.CG: l-DLPFC accelerated- iTBS *vs.* sham iTBS.	50 MDD unipolar AF patients, failing to achieve remission after 1 antidepressant treatment. MA= 41,90 y. F=35.	l-DLPFC	50 Hz; 110% mt.54 trains of 10 bursts of 3 stimuli. Bursts were repeated every 200 ms.	Sham rTMS	1620 stimuli. 5 sessions pd over 4 days. FU: 1 month after baseline. Three patients dropped.	BSI: suicidal ideation	No evident limitations.	Post hoc paired *t*-tests showed significant decline ($p< 0.05$) unrelated to active or sham stimulation and to depression response.	TSE. SI and depression improved, but no DFBG was found The antisuicidal effect was independent of the antidepressant one.	I=2; II=2; II=2; IV=2; V=0; VI=0; TS=8; QD=good
George et al., 2014	2-site, 2 arm double blind randomized controlled trial.CG: rTMS vs sham rTMS.	41 SI and/or SA inpatients, in a depressive episode in MDD or BD II disorders, taking antidepressants. AD: PTSD, or TBI, or both. MA=42.5y. F=15%.	l-DLPFC	10 Hz, 120% mt. 5-s trains, separated by 10-second II.	Sham rTMS	6000 p. 3 sessions pd for 3 days. FU=6 months. 23 patients completed the study.	SSI: suicidal ideation. VAS questionnaire developed for suicidal ideation	Relatively small sample size.	At day 3 both groups improved when using SSI and VAS. Although there is more decline in the TMS group, the difference is not statistically significant (sham mean change= -24.9, 95%	TSE. rTMS showed a rapid and moderate effect, On SI by day 3, No DFBG was found.	I=1; II=1; II=2; IV=2; V=0; VI=0; TS=6; QD=moderate

Journal Pre-proof

									CI=34.4 -15.3; rTMS mean change= -43.8, 95% CI=57.2 -30.3, p=.028). There is no SDBG in SI and depressi on at FU.		
Keshtkar et al., 2011	2-arm double blind randomized controlled trial.CG: rTMS vs ECT	73 MDD patients taking antidepressants. MA=34, 8y. F=60%.	l-DLPFC	Hz not indicated, 90% mt. Stimulations and intervals duration not indicated. .	Bilateral ECT	408 p, 10 daily sessions. 60 patients completed the study. 1,5-week TMS treatment was compared with 3-week ECT treatment.	Suicidal ideation scales of BDI and HDRS	Poor details about rTMS protocol. Lack of FU.	Both ECT and rTMS groups improved in SI subscales of BDI (means: 1.4-0.5 and 1,5-1,2) and HDRS (means: 2.3-0.3 and 1.9-1.4); decreases were significantly higher in the ECT group.	TSE. rTMS was effective on SI and depression, tough ECT showed higher efficacy on both variables.	I=2; II=2; II=0; IV=6; V=0; VI=0; TS=5; QD=moderate

Note: ECT=Electroconvulsive Therapy; MDD; TS=Total score; DQ=Quality differentiation; rTMS=repetitive-transcranial magnetic stimulation; l-DLPFC= left Dorsolateral Prefrontal Cortex; r-DLPFC=right Dorsolateral Prefrontal Cortex; TRD= Treatment-Resistant Depression; C-SSRS=Columbia Suicide Severity Rating Scale; CDRS-R=Children's Depression Rating Scale, Revised; MDD= Major Depressive Disorder; SSI=Scale of Suicidal Ideation PTSD=Post-Traumatic Stress Disorder VAS= Visual-Analogue Scale; TBI= Traumatic Brain Injury; HDRS= Hamilton Depression Rating Scale; BDI= Beck Depression Inventory; BSI/BSSI= Beck Scale for Suicide Ideation; BSI-CV=Beck Scale for Suicide Ideation-Chinese Version; iTBS=intermittent Theta Burst Stimulation. BD=bipolar disorder; SIS=Suicidal Ideation Scale; ACC= anterior cingulate cortex; AF=Antidepressant-Free; MA=Mean Age; F=Females; CG=Comparison Groups; mt=motor threshold; s=seconds; p=pulses; t=trains; SI=Suicidal Idetation TSF=Treatment was Safe and Feasible; TS=Total Score; pd=per day; pw=per week; SSDG=Statistically Significant Differences between Groups; FU=Follow-Up; a-rTMS=accelerated rTMS; LU=Left Unilateral BI=Bilateral; II=Intertrain Interval; N=Number; y=years; ms=milliseconds: AD= Addictional Diagnosis; SA=Suicidal Attempts; EM=Emotional Recognition; HP=Hopelessness; LMCATI= left middle cerebral artery territory infarction; SRHD= severe rheumatic heart disease

Journal Pre-proof

Table 2. Most relevant uncontrolled, retrospective studies or case-reports/series on the association between rTMS and suicidal behavior

Author(s), year	Study design	Sample characteristics	Stimulated brain region	Stimulation frequency and intensity	Control condition	Number of pulses/sessions	Psychometric instruments	Limitations	Main findings	Main conclusions	Quality assessment
Ozcan et al., 2020	Uncontrolled clinical trial	30 TRD patients taking antidepressants	l-DLPFC	20 Hz, 100% mt. The stimulation duration of 2 s was delivered 20 times at 30 s intervals	No control group	1000 p, 5 days pw, for 4–6 weeks	SIS: suicidal ideation; BHS: hopelessness; C-SSRS: suicidal ideation/acts.	Lack of control group. Lack of FU.	Improvements in SI, SA, HP and depression were significant, as EM	TSE and effective on SI, SA, HP, depression and EM, this independently from SI and SA. No changes in cognitive functions.	I=2; II=0; II=0; IV=2; V=0; VI=0;TS=4; OD=moderate
Abdelnaim et al., 2020	Retrospective analysis	332 in- and out-patients with MDD. MA=47,3y. F=180.	l-DLPFC r-DLPFC ACC	1Hz, 10Hz and 20 Hz protocols. No information about motor threshold.	No control group	From 1000 to 2400 p for a minimum of 6 up to 50 sessions (17.0±6.5).	HAMD – item 3: suicidal ideation	Lack of sham group. Lack of follow-up. Poor details about protocol. Lack of specific measures.	47% of patients ameliorated in SI, 41.3% did not change in SI, and 11.7% increased in SI. . Positive association were found between SI and drive (item 7 HAM-D)	TSE and effective on Si and depression with a medium effect size.	I=2; II=0; II=0; IV=1; V=0; VI=0;TS=3; QD=low
Croarkin et al., 2018	Retrospective study	19 outpatient TRD adolescents with taking antidepressants. MA=16y.F=68.42%.	l-DLPFC	10 Hz, 120% mt. 4-s trains separated by 26-second II.	No control group	3000 p. 30 sessions over 6–8 weeks. 17 patients completed the study	C-SSRS-intensity of suicidal ideation scale. CDRS-R item 13: suicide attempts.	Lack of control group. Small experimental group. Lack of FU.	After adjusting for changes in depression severity, the decrease in SI and SA OR resulted non signficant.	TSE. Improvements in Si and SA were mediated by depression severity decrease, that was statistically significant	I=2; II=0; II=0; IV=1; V=0; VI=0; TS=3; QD=low
Fryml	Case-	A 27-years	l-	18 Hz,	No	1980 p. 4	No	Small	At FU SI	TSE	I=0;

Journal Pre-proof

et al., 2018	report	old female TRD and PTSD outpatient taking antidepressants	DLPFC	120% mt. 55 trains, separated by 12-s II.	control group	sessions pd, 5 days pw for 4 weeks. FU=3 weeks post-treatment	validated measures	sample. Lack of control group. Lack of psychometric measures.	was resolved; depression and PTSD were improved.	and effective on SI, depression and and PTSD.	II=0; II=2; IV=0; V=0; VI=0; TS=3; QD=low
Iliceto et al., 2018	Case-report	A 37 years old male outpatient in a depressive episode in a BD I, with SI and TBI, taking antidepressants	l-DLPFC	6 Hz, 120% mt. 4-s stimulations, separated by 26-s II.	No control group	3000 p. 5 sessions pw for 6 weeks. FU=2 years	No validated measures.	Small sample. Lack of control group. Lack of psychometric measur[illegible]	After 1 month SI was resolved; at FU SI and depression were resolved.	TSE and effective on SI and depression.	I=0; II=0; II=2; IV=0; V=0; VI=0; TS=3; QD=low
Kulkarni et al., 2018	Case-report	38-years-old female TRD and SA inpatient, taking antidepressants. AI= LMCATI, SRHD.	r-DLPFC	1Hz. 16 sessions: 100% mt. 10 sessions: 110% mt. 30-s II.	No control group	16 sessions: 1200 p; 10 sessions: 1500 p. 4,5 weeks. FU=3 mo[illegible]s.	No validat[illegible] d measur[illegible] s.	Small sample. Lack of control group. Lack of psychometric measures.	The patient experienced remission in depression and SI.	Treatment was safe, feasible and effective on suicidality and depression.	I=0; II=0; II=2; IV=0; V=0; VI=0; TS=3; QD=low
Pan et al., 2018	Case-report	3 MDD and SI adolescents taking antidepressants. F=2.MA= 16 y.	l-DLPFC	10 Hz, 100% mt. 5-s trains, separated by 15- s II.	No control group	600 p.7 daily sessions over 1 week	BSI-CV: suicidal ideation.	Small sample. Lack of control group. Lack of specific measures. FU not defined.	Improvement rates in SI were 40.01%, 100% and 75%. 2 patients developed hypomania.	TSE and effective in SI and depression.	I=1; II=0; II=1; IV=1; V=0; VI=0; TS=3; QD=low
Berlim et al., 2014	Uncontrolled clinical trial	17 TRD outpatient taking antidepressants. MA= 47.12y. F=13.	l-DLPFC	Deep TMS. 20 Hz, 120% mt. 75 trains, separated by 2-s IIl.	No control group	3000 p. 20 daily sessions over 4 weeks. 4 subjects dropped.	SSI: suicidal ideation	Small sample size. Lack of control group. Lack of follow-up.	Hedges ' g estimates for SI=0.6. Depression response= 70.60% ; remission 41.20%.	TSE and effective in SI and depression.	I=1; II=0; II=0; IV=2; V=0; VI=0; TS=3; QD=low
Hadley et al., 2011	Uncontrolled clinical trial	19 TRD (MDD or BD), taking antidepressants. MA=48 y. F=11.	l-DLPFC	10 Hz, 120% mt.5-s trains, separated by 10-s II.	No control group	6800 p. 5 sessions pw, over at least 2 weeks.7subjects dropped.	SSI: suicidal ideation	Lack of control group. Small experimental group. FU not defined	The SSI scores significantly decreased (t_{125} = 3.99, p = 0.0001). 66% of subjects showed depression remission.	TSE and effective in SI and depression.	I=1; II=0; II=1; IV=2; V=0; VI=0; TS=4; QD=moderate

Note: ECT=Electroconvulsive Therapy MDD; TS=Total score; DQ=Quality differentiation; rTMS=repetitive-transcranial magnetic stimulation; l-DLPFC= left Dorsolateral Prefrontal Cortex; r-DLPFC=right Dorsolateral Prefrontal Cortex; TRD= Treatment-Resistant Depression; C-

Journal Pre-proof

SSRS=Columbia Suicide Severity Rating Scale; CDRS-R=Children's Depression Rating Scale, Revised; MDD= Major Depressive Disorder; SSI=Scale of Suicidal Ideation PTSD=Post-Traumatic Stress Disorder VAS= Visual-Analogue Scale; TBI= Traumatic Brain Injury; HDRS= Hamilton Depression Rating Scale; BDI= Beck Depression Inventory; BSI/BSSI= Beck Scale for Suicide Ideation; BSI-CV=Beck Scale for Suicide Ideation-Chinese Version; iTBS=intermittent Theta Burst Stimulation. BD=bipolar disorder; SIS=Suicidal Ideation Scale; ACC= anterior cingulate cortex; AF=Antidepressant-Free; MA=Mean Age; F=Females; CG=Comparison Groups; mt=motor threshold; s=seconds; p=pulses; t=trains; SI=Suicidal Idetation TSF=Treatment was Safe and Feasible; TS=Total Score; pd=per day; pw=per week; SSDG=Statistically Significant Differences between Groups; FU=Follow-Up; a-rTMS=accelerated rTMS; LU=Left Unilateral BI=Bilateral; II=Intertrain Interval; N=Number; y=years; ms=milliseconds: AD= Addictional Diagnosis; SA=Suicidal Attempts; EM=Emotional Recognition; HP=Hopelessness. LMCATI= left middle cerebral artery territory infarction; SRHD= severe rheumatic heart disease

Journal Pre-proof

Journal Pre-proof

Highlights

- rTMS is effective, globally safe, and well-tolerated in treating suicidal behavior
- DLPFC was identified as the most frequent stimulation brain region in suicidal patients
- Bilateral TMS is more effective in reducing suicide risk in combination with antidepressants

Journal Pre-proof