CLINICAL TRIAL PROTOCOL

TITLE: Comparative Effectiveness of Repetitive Versus Deep Transcranial Magnetic Stimulation for Major Depression: A Randomized Controlled Trial

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1. THE NEED FOR A TRIAL

1.1 The problem to be addressed

Major depressive disorder (**MDD**) is a significant public health issue with a considerable personal and societal toll. MDD is estimated to affect over 300 million individuals around the globe and is now ranked as the leading cause of disability worldwide [1]. In Canada, the lifetime prevalence of MDD is 12%, and ~1.9 million Canadians live with MDD in any given year [2]. First-line treatments for MDD include pharmacotherapy and psychotherapy [2]. Unfortunately, around 30 to 40% of patients develop treatment-resistant depression (**TRD**), classically defined as the failure to respond to one or two adequate trials of antidepressants [3–5]. TRD affects about ~2% of the population (~760,000 Canadians) and represents about 30 to 50% of the total treatment cost for MDD [6]. Given the public health imperative, novel therapeutic approaches are needed.

Transcranial magnetic stimulation (**TMS**) has been gaining ground in the last decade for the treatment of TRD, with evidence of superiority over pharmacotherapy after two (2) failed antidepressant trials [7,8]. TMS uses rapidly alternating magnetic fields to safely stimulate specific cortical areas, allowing modulation of underlying dysfunctional brain networks. Even though TMS is a now well-established treatment for TRD [9], optimizing protocols to maximize effectiveness remains an active area of research.

The primary aim of this trial is to compare the effectiveness of two different TMS techniques in TRD, repetitive TMS (**rTMS**) and deep TMS (**dTMS**). Compared to rTMS, dTMS delivers a broader magnetic field, which in turn reduces coil positioning error and maximizes the probability of optimal cortical stimulation [10]. A past RCT comparing both approaches found a greater depression score decrease and response/remission rates for dTMS, but was short of reaching significance for remission rates (primary outcome) [11]. Critical components of this RCT were suboptimal, including too few treatment sessions and insufficient statistical power, both of which could have obscured an actual difference between modalities. **Proof of a more effective type of TMS over another would translate into increased odds of improvement for TRD patients who live with a chronic and disabling illness.**

The exploratory aim of this trial is to study the predictive value of candidate biomarkers for TMS in MDD. Two scalable techniques have shown the potential to develop biomarkers in pilot studies: electroencephalography (**EEG**) and electrocardiography (**ECG**). These highly scalable approaches could easily be implemented in regular clinical psychiatric settings. **Predicting an individual's chances of improvement to TMS before the start of treatment could expedite remission, spare futile interventions, and protect limited clinical resources.**

The results of this trial will have clinically significant benefits for MDD patients. Evidence of the superiority of dTMS could lead to more favorable clinical outcomes for patients suffering from TRD and offer an additional treatment option to individuals who have not responded to rTMS. Identifying scalable biomarkers ready for clinical use could also positively impact the care trajectory of patients suffering from TRD and reduce the current trial-and-error approach for treatment selection.

1.2 Research questions

Primary: To assess the superiority of dTMS over rTMS in TRD.

Hypothesis: dTMS will achieve significantly greater reduction in depressive symptoms and higher response/remission rates than rTMS.

Exploratory: To evaluate the predictive capacity of scalable candidate biomarkers.

Hypothesis: Specific biomarker features at baseline will predict response to TMS overall, irrespective of the specific TMS modality.

1.3 The need for a trial

1.3.1 The need to increase the effectiveness of TMS for TRD

The evidence for the effectiveness of TMS in TRD is supported by well over 200 RCTs and dozens of meta-analyses [5,9,12]. Health Canada approved TMS in 2002, and U.S. Food and Drug Administration (**FDA**) followed suit for TRD in 2008. The most recent literature indicates that TMS

consistently achieves response (≥50% improvement from baseline) and remission (little to no symptoms left) rates of 40-55% and 25-35% in TRD, respectively [5]. TMS involves the use of a powerful alternating magnetic field to modulate neuronal activity. Electromagnetic pulses are delivered through coils of various designs. Standard rTMS uses figure-8 coils offering focal and superficial stimulation [13]. Even though rTMS is effective in TRD, remission rates are still below those for electroconvulsive therapy (**ECT**), which remains the gold standard for TRD [14]. **Given the low patient acceptability of ECT [15], work must continue to optimize the effectiveness of therapies such as TMS, which possess an advantageous safety, tolerability, and acceptability profile [5].**

1.3.2 Rationale for testing the clinical efficacy between dTMS and rTMS

Several ways to increase the effectiveness of TMS have been studied, including increasing the number of pulses per session, various frequencies, bilateral treatment, treatment acceleration, and functional imaging. So far, none have yielded consistent results [16–24]. One approach of interest has been to improve coil technology [25]. Figure-8 coils used for rTMS have been developed for neurophysiological experimentation, where more focus stimulation is preferred for precise target engagement. Unfortunately, the high individual variability of the prefrontal cortex (**PFC**) and the probabilistic nature of figure-8 coil positioning renders them theoretically more prone to error in clinical use. Neuronavigation systems have been developed to optimize targeting [26], but these tools are expensive and technically complex, currently precluding widespread use.

H-coils used in dTMS, on the other hand, were developed for specifically for clinical use (**Fig. 1 of the Appendix**). H-coils create a much broader and deeper magnetic field than figure-8 coils, reducing coil positioning error and maximizing the probability of optimal cortical stimulation. Indeed, even though the average thickness of the cortical gray matter strip is only 2 mm, the highly convoluted pattern of organization (gyri and sulci) means that some parts of the gray matter may remain sub-optimally stimulated with figure-8 coils compared to H-coils. H-coils are, therefore, better adapted to engage the underlying PFC circuitry. The initial H-coil developed for TRD was the H1. More recently, another H-coil has received FDA clearance for MDD: the H7 [27]. The H7 has the advantage of stimulating 4x deeper than figure-8 coils (compared to 2.5x for the H1-coil), translating into a total stimulated brain volume of 40.3 cm^3 for the H7, compared to 18 cm^3 for the H1, and only 3 cm^3 for figure-8 coils. Because of this, the H7 can stimulate large portions of the PFC, including the dorsolateral and dorsomedial prefrontal regions. These areas, which are of significant interest in MDD [28], can only be simultaneously stimulated by the H7. The clinical advantage of broader PFC stimulation provided by dTMS is supported by the effectiveness of ECT, which causes widespread whole-brain depolarization. ECT still, to this day, remains the gold standard in terms of clinical outcomes in TRD, with remission rates of ~50%, according to the most recent data [14]. **The recruitment of larger PFC areas by dTMS may therefore be expected to augment the antidepressant effect.**

Because of this, some have theorized the therapeutic superiority of dTMS over rTMS in MDD [29]. While some evidence suggests this [11], the issue is still vigorously debated. **Resolving this research question is vital to enhance the effectiveness of TMS for TRD.**

1.3.3 rTMS vs. dTMS

dTMS was shown to be effective for TRD in its landmark trial [30]. Subsequently, an RCT compared rTMS (N = 75) and dTMS (N = 72) in a way that led to inconclusive findings [11]. Even though the proportion of remitters was greater in the dTMS group (dTMS 60% remission, CI95% 48–71%; rTMS 43% remission, CI95% 31–55%), this was not statistically significant (OR 1.74, CI95% 0.79–3.83, p = 0.17). Regarding secondary endpoints, response was significantly greater with dTMS (OR 2.33, CI 95% 1.04–5.21, p = 0.040). The 17-item Hamilton Rating Scale for Depression (**HRSD-17**) decrease was also significantly greater in the dTMS group (p = 0.048). Still, this trial was underpowered and only used a limited 20-session course, which is insufficient [31] and probably prevented full therapeutic effects. **These equivocal results require a well-designed and appropriately powered head-to-head RCT. Such a trial would be vital to improving the overall effectiveness of TMS and guide the**

implementation and choices of optimal technology in clinical settings. Additionally, this trial did not follow up with patients beyond the treatment period (4 weeks). It is now established that trajectories of outcomes vary between individuals treated with TMS and that some do not reach a plateau of improvement by treatment end [32] and can continue to improve afterward [33]. Research health metrics such as functioning and quality of life may also require longer follow-up periods.

Lastly, that trial used the original 10 Hz stimulation protocol initially approved by the FDA for rTMS. More recently, intermittent theta burst stimulation (**iTBS**) has been introduced for rTMS and received FDA approval. The landmark iTBS-rTMS trial (THREE-D study co-chaired by DMB and ZJD) established the non-inferiority of this approach to the 10 Hz stimulation protocol [18]. iTBS is delivered in only ~3 min, compared to 37.5 min for 10 Hz, which makes it much more efficient (time-saving and cost-effective) and has led to its adoption by many clinics worldwide [34].

1.3.4 The search for biomarkers

In addition to treatment optimization, biomarkers are another key strategy in improving outcomes in MDD. Predicting the chances of improvement to TMS before the start of the procedure could help treatment centers better orient patients to optimal therapies, spare them futile interventions and improve the use of limited clinical resources. Encouraging results have emerged from neuroimaging studies [35], but scalable, reliable, and cost-effective candidates are needed [36]. **This work aligns with our group's expertise in TMS and biomarkers** [33,37–49].

Individual alpha frequency: EEG biomarkers have shown great promise in MDD [35,48,49]. EEG has the advantage of being a low-cost, broadly available, and already established tool in routine clinical care [48]. Initial studies suggested pathologic frontal alpha asymmetry in MDD [50], and interference with this abnormal rhythm by TMS has been theorized to reset dysfunctional thalamocortical oscillators and lead to therapeutic improvement [51]. A research question arising from this observation has been determining if specific TMS stimulation frequencies are more efficient at interfering with these abnormal rhythms**.** It was initially determined in a pilot study that participants (N = 35) undergoing rTMS experienced a greater improvement when their individual alpha frequency (**iAF**) was closer to the 10 Hz [52]. **Collaborator MA on this proposal later replicated this finding in a larger cohort (N = 59**) [53]. So far, this promising approach remains to be explored with other frequencies, such as those proposed here (18 Hz/dTMS and iTBS/rTMS). Such evidence could help clinicians assign patients to an optimal TMS protocol based on their iAF, an example of the recently-discussed Stratified Psychiatry concept [36]. **Our hypothesis is that individuals with baseline iAF closer to 10 Hz will respond better to TMS overall.**

Reward positivity: EEG event-related potentials (ERPs) are also recognized as promising biomarkers. Decreased reward positivity (**REWP**), an ERP elicited by reward feedback, is associated with MDD [58]. REWP originates from the anterior cingulate and is highly sensitive to insults to the mesocorticolimbic reward system [58–61]. REWP has been shown to reflect the anterior cingulate electrophysiological response to dopaminergic reward prediction error signals [60,62]. A substantial body of evidence implicates dopamine and anterior cingulate dysfunction in MDD and a series of studies demonstrated that REWP amplitude can serve as a biomarker for depression [58]. Importantly, TMS applied to the PFC can enhance dopamine release, neuronal activity, and cerebral blood flow in the cingulate cortex [63–66]. **We previously demonstrated that 10 Hz rTMS applied to the DLPFC enhanced REWP in substance users** [45,46]. **In healthy subjects, we demonstrated that 600 pulses of iTBS applied to the left DLPFC suppressed the amplitude of REWP across two independent studies** [47]. To date, the effects of dTMS on REWP amplitude are unknown, which adds to the innovation of the proposed work. Since REWP studies have shown the cingulate is critically involved in MDD [58,59], it may be hypothesized that a similar mode of action involving the cingulate, as measured by the REWP, is the case in the treatment of MDD. REWP is thus well-positioned to serve as an RDoC-type predictive biomarker of reward-related psychopathology in MDD. While other ERPs have been studied in MDD, REWP has the most extensive literature supporting its use in the context of cingulate dysfunction and

MDD. In line with this work, we hypothesize that a TMS-induced modulation of cingulate activity could be objectively evaluated using REWP, particularly for a condition with mesocorticolimbic reward system dysfunction like MDD. **Our hypothesis is that participants with lower baseline REWP will respond better to TMS overall.**

ECG: Cardiac function abnormalities and autonomic nervous system dysfunctions have been extensively described in MDD, focusing on decreased vagal control, which could represent a failure of the PFC to inhibit sympathetic activity [67]. At the neurobiological level, subcortical hyperactivity is thought to be responsible for increased sympathetic tone in response to stress [68]. The PFC regulates sympathetic and parasympathetic activity by top-down mechanisms through the vagus nerve via the subgenual anterior cingulate [67]. In MDD, these mechanisms could be compromised, given the known dysfunctions of the PFC in MDD. Since TMS is theorized to normalize PFC activity, its effects could therefore be captured by cardiac activity recording [69]. ECG-based biomarkers represent a low-cost and scalable approach that merits further investigation. **Our team has already shown** that greater baseline ECG corrected QT interval length was associated with greater improvement in vagus nerve stimulation [38] and that even though baseline resting-state heart rate variability was not associated with improvement to TMS [49], lower baseline resting-state heart rate (**HR**) was associated with greater improvement [70]. **Our hypothesis is that participants with higher baseline corrected QT interval and lower baseline resting-state HR will respond better to TMS overall.**

1.4 Knowledge transition

We will engage in knowledge translation with the scientific and clinical communities via 1) publication of study findings in high-impact peer-reviewed open-access journals with a broad readership and 2) presentations at international scientific conferences, including both leading neuroscience (e.g., Society of Biological Psychiatry, American College of Neuropsychopharmacology), brain stimulation (e.g., International Brain Stimulation Conference), national (e.g., Canadian Psychiatric Association) and provincial (Association des Médecins Psychiatres du Québec) annual meetings. We will also summarize our findings in plain language and use media deemed to be highly effective for knowledge users. We will also disseminate our findings via social media platforms. Knowledge translation will also be facilitated through our members' affiliation and collaboration with the *Réseau Québécois sur le suicide, les troubles de l'humeur et les troubles associés*. We will liaise with radio, television, and press journalists to ensure media coverage of this study and its potential benefits. The media and federal and provincial governmental organizations frequently solicit our research team members for their expertise. Information that identifies participants or that reasonably could be used to identify participants will not be included in such publications. **A timeline of our planned knowledge translation activities is provided in Table 1 of the Appendix.**

1.5 Risk management

TMS is a well-tolerated procedure with limited side effects and a well-established safety track record [71,72]. Both rTMS and dTMS systems are approved by Health Canada. **For most patients, adverse events are minimal**, the most common side effects being mild discomfort at the stimulation site and mild headaches/fatigue after stimulation (20-30%). Nausea, irritability, and sleep disturbance are rarely seen (< 5%) [71]. Seizures are the most severe potential adverse event reported with TMS but are extremely rare (0.01%, ten times lower than antidepressants) [71]. No difference in adverse events (types or frequency) has been reported between rTMS and dTMS [11], an observation supported by our pilot data. Standard operating procedures regarding the emergence of side effects are in place, including a specific procedure in the event of a seizure/loss of consciousness, which mobilizes the blue code team. Regarding adverse events monitoring, we will follow the same protocol as in the THREE-D study [18]. At each session, participants will be queried for any suicidal ideation and adverse events. All adverse events will be recorded for analysis. Participants will also report pain levels to the TMS procedure on a verbal analog scale (from 1 [no pain] to 10 [intolerable pain]). We will also record the number of serious adverse events and reasons for treatment discontinuation when such events occur. A psychiatrist will

always be available in case of adverse events, assessment of emergent/worsening suicidal ideation, or any other emergencies.

2. THE PROPOSED TRIAL

2.1 Recruitment

Potential participants will be selected among regular clinical patients referred by their medical doctor via the secretariat of the psychiatric neuromodulation clinic of the CHUM (email: neuromodulation.psychiatrie.chum@ssss.gouv.qc.ca, tel: 514-890-8000 #26489, fax: 514 412-7792), or by their medical doctor via the lab website (www.labo-unp.ca). As part of the clinical routine administrative functioning, a clinical nurse will contact all patients referred for neuromodulation treatments and evaluate them. The nurse will then schedule a medical appointment with one of the psychiatrists of the study. If the participant meets eligibility criteria, the psychiatrist will offer to the patient to participate in the study. If the participant is interested, the research coordinator will contact the participant to describe the study and the treatment (treatment schedule), side effects as well as to answer any question the participant might have. The research coordinator will then schedule an appointment with the participant to obtain informed consent.

2.2 Design

The trial will now be conducted as a randomized, single-center, two-arm, parallel-group pilot study, primarily aimed at assessing feasibility and preliminary outcomes involving **50 adult** outpatients with TRD over two (2) years starting in January 2024. Using a computerized random permuted block method, participants will be **randomly allocated (1:1)** to one of the two intervention groups (rTMS or dTMS). Before the study initiation, we will obtain written approval from the Research Ethics Board, and this protocol will be registered on clinicaltrials.gov.

2.3 Interventions

After consent and enrollment, patients will undergo a screening visit to obtain demographic, clinical, and baseline data to determine their eligibility for the trial according to inclusion and exclusion criteria (section 2.5 below). Participants will be randomized to receive either rTMS on a MagPro X100 research grade stimulator (MagVenture) equipped with a B70 fluid-cooled coil or dTMS on a research Brainsway system equipped with an H7-Coil. Following randomization, patients will undergo baseline assessments and motor threshold testing to determine the appropriate site and strength of stimulation according to standard methods, and then begin treatment [18,30,73]. For dTMS, the MDD FDA-cleared 18 Hz stimulation protocol will be used (2 sec ON, 20 sec OFF, 55 trains; 1980 pulses per session; 20 min 10 s duration; 120% hand motor threshold [27]). For rTMS, the MDD FDA-approved iTBS protocol will be used (triplet 50 Hz bursts repeated at 5 Hz, 2 s ON and 8 s OFF; 600 pulses per session; total duration of 3 min 9 s, 120% hand motor threshold [18]).

2.4 Randomization

Subjects will be randomized into the study and stratified by treatment failure, defined by the failure to two adequate trials vs. those with more than two adequate trial failures, as assessed by an Antidepressant Treatment History Form (**ATHF**) score of more than 3 in the current episode [74]. The degree of treatment resistance has been a significant predictor of improvement in treatment in prior TMS trials. It is essential to ensure that the groups are balanced for this variable [75–77]. Randomization will be based on a stratified permuted block design, using random block sizes to decrease the likelihood of predictability of group assignments. An independent statistician external to the study will manage the computer-generated randomization list. Research staff will not have access to the randomization schedule.

2.5 Blinding

Given the study's design, blinding participants and TMS operators will not be possible. Still, staff responsible for participant assessments and data analysis will be blinded to treatment conditions and

external to the clinic staff. Patients will be instructed not to reveal their group assignment to the raters. Patients will not be given the specifics of the treatment parameters and will be instructed not to talk to each other during the study period. Both treatments will be presented as effective to them. Lastly, the data management center will strictly control access to the randomization code.

2.5 Eligibility criteria

Inclusion criteria: Adults aged 21–70 years with a Mini-International Neuropsychiatric Interview (**MINI**)-confirmed diagnosis of MDD [78], at least moderate intensity, single or recurrent episode, HRSD-17 score of at least 18 [18,79], no improvement to at least two adequate courses of antidepressants (based on the ATHF) or were unable to tolerate at least two separate trials of antidepressants of inadequate dose and duration, and have been on a stable antidepressant regimen for the past four weeks before screening. Patients with a chronic depressive episode >2 years and who have previously received ECT or ketamine will be eligible to participate.

Exclusion criteria: Having previously received TMS; substance use disorder within the last three months; diagnosis of bipolar or psychosis spectrum disorder; anxiety or personality disorder that is assessed by a study investigator to be the primary cause and causing greater impairment than MDD; concomitant major unstable medical or neurological illness, intracranial implant, cardiac pacemaker or implanted medication pump; significant laboratory abnormality; active suicidal intent; pregnancy; if participating in psychotherapy, must have been in stable treatment for at least three months before entry into the study, with no anticipation of change; currently taking more than the equivalent of 2 mg of lorazepam of a benzodiazepine daily or any dose of an anticonvulsant due to the potential to limit TMS effectiveness. If participants do take benzodiazepines, they will be instructed not to take them before treatment, only after and no later than at bedtime.

Discontinuation criteria: Participants will be withdrawn if: i) they experience worsening in depression, defined as an increase in HRSD-17 from baseline of more than 25% during two consecutive assessments, or development of active suicidal intent or attempted suicide; ii) the Principal Investigator believes that for safety reasons, it is in the best interest of the participant to stop participation. Discontinued participants will receive whichever treatment plan is optimal for their situation. Participants will be permitted to miss scheduled treatment days due to illness or scheduling conflicts, and sessions will be added to complete the scheduled 30 sessions. However, participants who miss four consecutive treatment days will be excluded from the study, although we will attempt to continue collecting outcome data.

2.6 Treatment period duration

Participants will undergo one (1) daily treatment session over six (6) consecutive weeks (Monday to Friday) for a total of 30 sessions, which is the standard in TMS studies [31].

2.7 Frequency and duration of follow-up

Biomarkers will be acquired at baseline (W0). Clinical measures will be completed at W0, immediately post-treatment on the last day (W6), and at follow-ups post-treatment: 1-week (W7), 4-week (W10), 12-week (W18).

2.8 Outcomes

Primary: (1) dTMS and rTMS score changes from baseline to W6 on the HRSD-17 scale; (2) Response (yes/no) defined as a reduction ≥50% on the HRSD-17 scale from baseline to W6; (3) Remission (yes/no) defined as a score ≤ 7 on the HRSD-17 scale at W6.

Secondary: dTMS and rTMS score changes, response, and remission at other timepoints (W7, W10, and W18); outcomes on other symptomatic scales (see below in section 2.9 *clinical assessments*), global measures of severity/improvement and quality of life and functionality; tolerability, self-reported adverse events, treatment-associated pain, numbers of all-cause dropouts.

Exploratory: iAF, REWP, resting-stage ECG features, and ~~NCG-TMS~~ pupil measures at baseline.

2.9 Assessments (see Table 2 of the Appendix)

Clinical assessments: The primary outcome measure will be measured by the HRSD-17, which has been the standard scale in both TMS and pharmacotherapy trials in TRD for decades [18]. Other scales include the HRSD-28, Hamilton Anxiety Rating Scale (**HAMA**) [80], 16-Item Quick Inventory of Depressive Symptomatology Self-Report (**QIDS-SR-16**) [81], General Anxiety Disorder-7 (**GAD-7**) [82], Snaith–Hamilton Pleasure Scale (**SHAPS**) [83], Columbia-Suicide Severity Rating Scale (**C-SSRS**) [84], Rumination Response Scale (**RRS**), Adult ADHD Self-Report Scale [85], The McLean Screening Instrument for Borderline Personality Disorder (**MSI-BPD**) [86] and various cognitive tests (**see Table 2 of the Appendix**). At each session, participants will be queried for any suicidal ideation and adverse events, which will be recorded for analysis. Participants will also report pain levels to the TMS procedure on a verbal analog scale (from 1 [no pain] to 10 [intolerable pain]). We will also record the number of serious adverse events and reasons for treatment discontinuation when such events occur. Medical history, an electrocardiogram (ECG), blood tests, BMI, vital signs, and urine analysis (including drug screen) will be obtained at baseline.

Biomarker assessments: Biomarkers will be collected at baseline. Participants will also undergo resting state ECG and EEG recordings using standard procedures [87,88]. EEG recording will be acquired through a 32-channel device (Natus Trex HD with video). In line with previous investigations [53], resting state EEG will be recorded for 5 minutes with eyes closed followed by 5 minutes with eyes open while the subject fixates on a red dot on a screen. Participants will be asked to stay relaxed during the acquisition, and electrooculogram (EOG) electrodes will be installed to record eye movements. Skin impedance will be maintained below 10 kΩ for all electrodes. EEG recordings will be sampled at 512 Hz. Following resting-state EEG, recording will continue during the completion of the Probabilistic Selection Task, a well-established reward task that elicits robust REWP and is believed to be sensitive to dopamine and reward functioning [46]. REWP is measured by subtracting the amplitude (in microvolts) of the EEG reward-related potentials from non-reward-related potentials.

Brain Vision Analyzer 2.0 will be used to process EEG recordings. **1) Preprocessing:** Preprocessing will be undertaken to filter EEG recordings and remove artifacts and discontinuities. Finite impulse response Butterworth filters will be used to bandpass EEG recordings into the frequency band of interest (0.3-100 Hz). A notch filter will be implemented to reject powerline interferences (60 Hz). The forward-backward technique will keep the signals' phase intact [89]. By filtering the input EEG data in both the forward and reverse directions, this method allows to perform zero-phase digital filtering with no phase distortion and thus preserves features in the filtered time-series at precisely the same timepoint on which they occur on the unfiltered time series. The *Autoreject* algorithm will be used for artifact detection and correction. This adaptive method uses cross-validation to identify an optimal peak-to-peak amplitude threshold. In addition, the Gratton technique (regression-based) will be used to EOG-correct the data. Finally, data will be re-referenced to the average reference; **2) Segmentation:** Resting state EEG recordings will be segmented into non-overlapping windows of 4 s epochs; **3) Feature extraction:** In line with previous investigations within the context of TMS outcome prediction, iAF will be calculated for electrodes F3 and F4 during eyes closed resting states [52,53]. Power spectrum will be evaluated by applying a Fast Fourier Transform to 4 s EEG epochs (50% overlap, Hamming window), where iAF corresponds to the maximum value on the power spectrum within the alpha frequency range (7-13 Hz). Patients with no clear/dominant iAF will be excluded from the analysis. A dominant iAF frequency will be defined as a maximum value within the alpha frequency range higher than 1.5 Z-score below the mean. The proportion of excluded subjects (those who do not show a dominant iAF) will be compared to those reported in Corlier and colleagues (15.1%) and Roelofs and colleagues (12.6%) [52,53].

Regarding pupil measure procedures, they will follow what was described in a recent study[91]. All recordings will be obtained through a pupillometer NeurOptics PLR-3000 (NeurOptics Inc., Irvine, ca, USA). Pupil data will be obtained from both eyes. No calibration is required, and data will be stored on the device with results uploadable to an external computer.

2.10 Sample size

In light of budget constraints, we revised our study design to accommodate a smaller sample size, aligning it with the scope of a pilot study. The original plan to recruit 220 participants (110 per group) was based on calculations that assumed a 3-point difference in change from baseline between groups on the HRSD-17 scale and a standard deviation of 7.5 for the change in HRSD-17 in each group. These calculations suggested that 198 patients (99 per group) would be necessary to determine if dTMS is superior to rTMS with 80% power and a 5% two-sided significance level [88], adjusted for an anticipated attrition rate of up to 10% [18]. However, due to a lower than expected budget, we have revised our sample size to a total of 50 participants, with 25 in each group. This reduction necessitates a reclassification of the study as a pilot study. Pilot studies are valuable for testing the feasibility of larger trials, refining study protocols, and providing preliminary data. While the smaller sample size may limit the power to detect the originally hypothesized effect size, it remains sufficient for exploring trends and generating hypotheses. The findings from this pilot study will be crucial for informing the design and sample size calculations of subsequent, larger-scale trials.

2.11 Quality of life and health service research metrics

Patient functioning and quality of life is an increasingly recognized aspect of improvement with antidepressant treatment. The following scales will be measured at baseline and follow-ups. The Clinical Global Impression Severity/Improvement (**CGI-S, CGI-I**) scales will be used as a global measure of severity and improvement [93]. Quality of life will be assessed by the World Health Organization Quality of Life Short Version (**WHOQOL-BREF**) [94] and functionality by the Sheehan Disability Scale (**SDS**) [95].

2.12 Planned recruitment rate

It is anticipated that a timeline of 5 years will be necessary to complete all facets of the proposed trial (**the study timeline is presented in Table 1 of the Appendix**). Given significant outreach efforts in the past six months and our new partnerships with nearby hospitals, we have averaged 6.5 new referrals per week, which would lead to ~340 new referrals per year. On average, >75% of referrals to our clinic are accepted for treatment. If we expect at least 25% of those patients to be eligible and accept participating in the trial, we are confident that recruitment will proceed at a rate of at least ~15 participants per trimester, reaching the target of 220 participants over the 4-year enrollment period.

2.13 Compliance

Dropout rates to TMS in the literature and at our clinic are less than 5% [18], but we used a more conservative 10% for sample size calculation.

2.14 Loss to follow-up

Attrition rate to TMS in the literature and at our clinic for the 1-month follow-up is less than 5% [18]. Active strategies to reduce dropout and attrition rates will be employed, such as calls by the study team in case of no show and reminders for upcoming follow-ups.

2.15 Number of centers involved

This will be a single-center trial. Even though a multicenter trial would accelerate recruitment and study completion, we are unaware of any other academic research institution with rTMS (MagVenture) and dTMS (Brainsway) equipment and who would be available to collaborate on this project. We have the necessary infrastructure to carry out the trial successfully.

2.16 Statistical analyses

We sought a statistical consultation at our research center for this section, **and a biostatistician will be responsible for the statistical plan and analyses**. The primary analysis will follow the intent-to-treat principle. To assess if dTMS is superior to rTMS, an analysis of covariance (**ANCOVA**) will be performed, with the HRSD-17 total score at W6 as the outcome. Independent variables will include the treatment attribution (rTMS or dTMS), the HRSD-17 score at baseline and the stratification variable (treatment failure to 2 trials or >2 antidepressant trials). ANCOVAs are known to have more power and increased precision in an RCT context over ANOVA [96]. Additionally, it is often recommended to adjust for the stratification variables in the primary analysis, especially for moderately sized trials [97,98].

Estimates for the mean difference between groups will be produced with the corresponding 95% confidence interval. Also, rates of response and remission (as defined in section 2.8) between the intervention groups will be compared using chi-squared tests. As secondary analysis, a generalized linear mixed model (GLMM) will be used to analyze repeated measures of study outcomes (HRSD-17 score, response, and remission) for timepoints of interest (W6, W7, W10, and W18) while accounting for the HRSD-17 score at baseline [99]. The model will include time, treatment group and their interaction as fixed effects. Different structures of variance-covariance matrix will be considered, but one will be selected based on the Akaike Information Criterion [100].

Subsequently, biomarkers distribution by sex and age group will be described using mean, standard deviation, median and interquartile ranges. Univariate generalized linear models (**GLM**) will be used to assess whether, individually, baseline biomarkers predict changes in HRSD-17 post-TMS for each timepoint [101]. A multivariate GLM will also be used to evaluate the ability of all baseline biomarkers to accurately predict changes in HRSD-17 when used together. Potential confounders such as sex and age will be included in the multivariate regression model. Correlations between biomarkers will be assessed using a spearman correlation matrix. Stratified analysis per treatment group will be conducted to verify the hypothesis that baseline biomarkers are predictors of changes in HRSD-17 regardless of the treatment received (rTMS or dTMS). Finally, we will investigate the relationship between the biomarkers and the response using the set of analyses described above with appropriate adjustments for categorical outcome.

2.17 Frequency of analyses

While no interim analyses are planned, the final analyses at the conclusion of this pilot study will be instrumental in determining the feasibility and potential trends indicating the efficacy of the interventions. Should these results demonstrate promising trends, they will serve as a foundation for seeking additional funding and designing a larger-scale study to further investigate these findings.

2.18 Planned subgroup analyses considering sex and gender

We are planning a subgroup analysis to investigate sex-based differences in outcomes between the two treatment groups in analyses stratified by sex [102]. In addition, we will include measures of gender identity, gender role identification, and sexual orientation. We will perform preliminary and exploratory analyses to begin addressing the knowledge gap regarding the effect of these variables in MDD. Our team includes a CIHR Sex and Gender Science Chair who will guide us through these analyses.

2.19 Has any pilot study been carried out using this design?

We compared preliminary clinical outcomes of 63 TRD patients who received (1) rTMS-iTBS [N=28], (2) dTMS-H1 [N=17], (3) dTMS-H7 [N=16] using the clinician-rated MADRS scale. Our preliminary results suggest greater therapeutic effects for dTMS-H7 compared to the two other modalities. Average percent improvement for the dTMS-H7 group was 34.4% (SD 35.3), while it was 26.1% (SD 29.9) for the dTMS-H1 group and 23.2% (SD 25.3) for the rTMS-iTBS group. There is a similar trend using the self-rated BDI-II. All TMS modalities were well-tolerated, with no difference between groups regarding adverse events or dropout rates. This preliminary data supports our hypothesis that larger coils can have increased therapeutic effects, with the more significant effects mediated by the H7, which generates the most extensive electromagnetic field.

Fig. 2 of the Appendix outlines biomarker pilot data gathered for this proposal. In summary, it was determined by one of our collaborators (MA) that patients with an iAF closer to 10 Hz experienced greater improvement (**Fig. 2A**). Our group also recently reported the potential predictive role of resting-state baseline HR to TMS (**Fig. 2B**) [70]. We also determined that a higher corrected QTc interval on baseline ECG predicted response to TMS (**Fig. 2C**) [38].

3. TRIAL MANAGEMENT

3.1 Trial management

The trial will be conducted at the *Centre Hospitalier de l'Université de Montréal* (**CHUM**), which has a high recruitment capacity and is configured for maximal collaboration between clinical and research teams. Trial management procedures will leverage existing staff and infrastructures at our brain stimulation clinic. Our research center (Centre de Recherche du CHUM - **CRCHUM**), a unique hospital-based research center incorporating basic, preclinical, clinical, and public health research, will provide research support. CRCHUM's methodological and statistical platform (**CITADEL**) will provide statistical expertise and data monitoring/management services and was involved in the methodological design and statistical planning of the proposed study. This capacity includes the generation of randomization tables and clinical outcome data collection via a RedCap server hosted at CITADEL with web-accessible, privacy-compliant input of patient data on-site.

3.2 Ethical considerations

Source documents will always be kept in a locked filing cabinet to limit access, and in the case of electronic source documents, files will be password-protected and saved in a secure CHUM or CRCHUM server. However, our case report forms (CRF's) will not contain any personal health information. Only the subject number will be recorded in the CRF, and if the subject name appears on any other document (e.g. laboratory report), it must be obliterated on the copy of the document retained in the Trial Master File or made available for audit. Study data will be kept for 10 years after the end of the study, in accordance with data protection laws. Subjects will be informed that representatives of other parties (including pharmaceutical companies), ethics committee (IEC)/institutional review board (IRB) or regulatory authorities may inspect their records to verify the information collected, and that all personal information made available for inspection will be handled in the strictest confidence and in accordance with data protection laws. The investigator will maintain an encrypted and password protected personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified and retrieved.

3.3 Team and applicants

The research team is led by **NPA** and **ECR** *Jean-Philippe Miron* (MD, PhD; 10hrs/week), brain stimulation psychiatrist, and research director of the CHUM's Unité de Neuromodulation Psychiatrique (UNP). *Paul Lespérance* (MD, MSc; 10hrs/wk) is a brain stimulation psychiatrist and founder of the CHUM's UNP. Both will be responsible for participant recruitment and management. *Daniel M. Blumberger* (MD, MSc; 1hr/wk) is a clinician scientist at the Centre for Addiction and Mental Health in Toronto with solid expertise in clinical trials of TMS for MDD. All three have expertise in TRD and brain stimulation RCTs, have contributed to the trial design and characterization, and will ensure that clinical trial guidelines, regulations, and procedures are met. *Didier Jutras-Aswad* (MD, MSc; 1hr/wk) will further assist in RCT regulations and policies locally. *Élie Bou Assi* (PhD; 1hr/wk - EEG), *Dang Khoa Nguyen* (MD, PhD; 1hr/wk - EEG), *Travis E. Baker* (PhD; 1hr/wk – EEG and REWP), *Martijn Arns* (PhD; 1hr/wk – EEG and NCG-TMS), *Zafiris J. Daskalakis* (MD, PhD; 1hr/wk) will assist in the biomarker aspects of the study, quality control, and biomarker data analysis.

3.4 Trial steering committee

The trial steering committee will be composed of Dr. Miron, Dr. Lespérance, and two outside experts with complementary knowledge of TMS/TRD/trials/methodology/statistics and will meet two times a year. The committee will monitor and discuss the following: recruitment, device management, budgets, consent procedures, consent forms, safety plans before study initiation, monitoring of the progress of the study, retention of subjects, adverse events, serious adverse events, reasons for participant withdrawal, adherence to the timeline of the study, quality of data, protocol violation and make directives about the continuation, modification, or termination of the study (based on the balance of adverse events and beneficial outcomes). Throughout the study, notification of any SAEs and proposed investigator-initiated protocol changes will be submitted to the committee for further evaluation. A Data and Safety Monitoring Board will not be necessary since we use TMS equipment already approved by Health

Canada. Lastly, our trial management group (executive committee), composed of Dr. Miron, Dr. Lespérance, our research coordinator will meet every two weeks.

3.5 Funding

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