RESEARCH PROJECT

# TREATMENT OF DEPRESSION IN THE ELDERLY WITH REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) USING THETA-BURST STIMULATION (TBS): RANDOMIZED, DOUBLE-BLIND, SHAM-CONTROLLED, CLINICAL TRIAL


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**ABSTRACT:**

**RATIONALE:** Recurrent transcranial magnetic stimulation (rTMS) is a consolidated procedure for the treatment of depression, with several meta-analyzes demonstrating its efficacy. The theta burst stimulation (TBS) method is a modification of the usual EMTr protocol, which provides cortical excitation by the application of magnetic stimuli with frequencies above 5 Hz. As a new intervention method, there are still few studies evaluating its efficacy in treatment of major depression. However, a recently published meta-analysis has pointed to benefits of this therapeutic modality. To date, there are no studies published with this method for the treatment of geriatric depression.

**OBJECTIVE:** To perform a randomized, controlled, double-blind clinical trial to evaluate the efficacy of theta-burst rTMS in the treatment of major depressive disorder in the elderly.

**METHODS:** A sample of 108 subjects were randomly assigned to the experimental (TBS) and comparative (sham) groups. Patients diagnosed with Major Depressive Episode (DSM-V) and at least 60 years of age will be included. Exclusion criteria: (i) contraindications to the use of EMT; (Ii) risk of suicide; (Iii) severe and / or out-of-control clinical comorbidities; (Iv) use of alcohol or drugs; (V) use of benzodiazepines in amounts greater than 10mg daily of diazepam or equivalent (other psychoactive drugs will be accepted as long as doses of the medications have been stable for at least 6 weeks). For patients on antidepressant treatment, it will be discontinued for a time equivalent to five half-lives of the drug in use, after which the intervention will be initiated by pacing protocol. The coil will be positioned in the prefrontal dorsolateral cortex, with iTBS mode on the left and cTBS on the right. In each application, 1800 pulses will be used on each side, totaling ten minutes in duration. There will be 20 consecutive sessions, one a day, except on weekends and holidays. The cycle of continuous intervention will last approximately four weeks, after which applications with the same technique will be performed at the end of weeks 4, 6, 8 and 12. The outcome measures will be measured on eight occasions: before the intervention (baseline) and after 1, 2, 4, 6, 8 and 12 weeks of onset. The main clinical outcome will be measured using the Hamilton Depression Scale (HDRS), comparing the baseline scores with those obtained at the end of 6 weeks after the intervention. As secondary endpoints, we will use the Global Clinical Impression Scale (CGI), the CIRS (Cumulative Illness Rating Scale), the Geriatric Depression Scale (GDS), the intermediate scores obtained on the HDRS scale, and variations in serum BDNF concentrations. All these evaluation tools have validated versions in Portuguese. As tolerability and safety parameters, the incidence of adverse events and the occurrence of manic and / or hypomanic symptoms by the Young Mania Scale (YMRS) will also be evaluated.

**EXPECTED RESULTS:** TBS stimulation will prove to be a safe, well-tolerated and effective intervention for the treatment of major depression in the elderly, becoming a more therapeutic option, particularly useful for patients with poor response or contraindications to the use of antidepressants.

**KEYWORDS**: depression; major depressive disorder; elderly; antidepressant; Repetitive transcranial magnetic stimulation (rTMS), theta-burst (TBS).

**Treatment of depression in the elderly with repetitive transcranial magnetic stimulation (rTMS) using theta-burst stimulation (TBS): randomized, double-blind, sham-controlled, clinical trial**

**a. Proposal:**

The aim of this study is to evaluate the efficacy of theta-burst (TBS) transcranial magnetic stimulation (TMS) in the treatment of major depressive disorder in elderly patients by means of a randomized, double-blind, sham-controlled trial.

**b. Qualification of the main problem**

With the increase in life expectancy and, consequently, the proportion of elderly people in the population, the morbidity of this age group will be increasingly relevant in terms of public health. As in other age groups, major depressive disorder (MDD) is a major problem for the elderly. The World Health Organization predicts that MDD will be the first or second major cause of functional impairment in 2020[1]. Several studies demonstrate that MDD also worsens the prognosis of cardiovascular and cerebrovascular diseases, the main causes of morbidity and mortality in the elderly. For example, it is known that MDD, besides being an independent risk factor for cardiovascular disease [2,3,4,5], it is also associated with other risk fator as arterial hypertension [6,7], diabetes mellitus [8] and smoking [9,10]. In addition, clinical trials in patients with cardiovascular diseases have demonstrated that antidepressant use decreases mortality [11],while the severity and persistence of depression in patients who had acute myocardial infarction increased mortality over subsequent years [12]. Finally, the presence of MDD is also associated with decreased cognitive and functional capacity [13], that are very relevant issues in this age group. In this way, the treatment of depression in the geriatric population is important not only from the psychiatric point of view, but also clinical and functional. In addition to cases of unipolar depression, the treatment of major depressive episodes manifested in the clinical course of bipolar disorder (BD) also presents with difficulties and peculiarities, especially in the elderly with BD [14].

The treatment of choice for geriatric unipolar depression is with antidepressants. The therapeutic response is considered to be similar to adult depression, remission rates that stabilize at 60-70% after more than three antidepressant treatments, and therefore approximately 30% of patients are resistant to pharmacological interventions [15]. However, there are not many clinical trials focusing specifically on the elderly population - in fact, much of the evidence for elderly antidepressant drug therapy is extrapolated from adult clinical trials or post-hoc analyzes of these trials, focusing on the elderly subgroup [16]. Interestingly, a clinical trial that recruited only patients over 75 years did not demonstrate superior efficacy of citalopram over placebo in the treatment of depression [17]. Still in the pharmacotherapy of geriatric depression, important issues are the side effects, drug interactions and restrictions of use of antidepressants in this age group. For example, the elderly are more sensitive to anticholinergic effects (constipation, urinary retention) characteristic of tricyclic antidepressants and the noradrenergic (dry mouth, tremor) effects of "dual inhibitors" [18]. Medications for therapeutic potentiation of antidepressants also have important side effects, such as lithium (intoxication by decreasing renal clearance, dehydration) and antipsychotics (weight gain, extrapyramidal symptoms) [18]. For these reasons, the therapeutic adherence to pharmacological treatment for depression in this age group is usually low [19].

Among the biological treatments, we highlight electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS). Both are treatments approved for depression and effective in the geriatric age group [20,21], however they have some issues that limit their use. ECT is associated in some cases with cognitive deficits in the long term and its application requires sedation - in fact, ECT is usually reserved only for cases of severe, refractory and / or psychotic depression [22].

*Repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression:*

The rTMS consists of the application of a magnetic field on the scalp, going beyond the cranial structures until reaching the cerebral cortex. During rTMS the affected cortex may undergo modifications such as becoming more excitable or more inhibited. The first situation occurs when using high frequencies (greater than 5 Hz) or when using theta burst method intermittently; Cortical inhibition occurs when low frequencies (1 Hz) or continuous theta burst method[23]. The rTMS is a consolidated treatment for depression, with several meta-analyzes demonstrating its efficacy [24,25]. However, there are few studies that have specifically evaluated the efficacy of rTMS in the geriatric population [26-30]. The rTMS may have some advantages over medications for the treatment of MDD in the elderly population. First, rTMS offers few side effects, with headache being the most common complaint [31]. The most serious adverse event is a seizure; however, using the safety parameters, it is an extremely rare event, with few reports of cases in the literature [31]. Additionally, the risk of drug interaction observed with the use of antidepressants and other medications of continuous use is null, a situation very common among depressed elderly people. Also, rTMS does not negatively interfere with patients' cognitive function, and may even improve it in some aspects [32]. No controlled studies with the *theta burst stimulation* (TBS) method have been performed in the treatment of geriatric depression; however, recent studies with the method have shown good prospects for the treatment of major depression in adults with meta-analyzes demonstrating a possible clinical superiority over conventional rTMS [33-38]. In addition, the session time in which the patient stays in the machine during TBS is much shorter, which facilitates patient compliance.

**c. Rationale and hypotheses of the study:**

Clinically, depression in the geriatric group is an important condition in which therapeutic alternatives have been poorly studied. In addition, the use of antidepressant medications in the elderly has important issues that limit their use, such as drug interactions. In this way, we can evaluate if TBS is a therapeutically effective alternative, and also with few side effects, for this population. This may bring short-term clinical gains for depressed elderly patients who do not tolerate antidepressants or have been refractory to antidepressants.

**d. Expected results:**

The expected main outcome is that TBS will be statistically superior to sham treatment for depression as assessed through the Hamilton Depression Rating Scale (HDRS). Other expected secondary outcomes consist of: TBS will be superior to sham treatment for improvement of depressive symptoms by the GDS (Geriatric Depression Scale), the MADRS (Montgomery-Asberg Depression Rating Scale) and the Global Clinical Impression Print Scale (CGI). Regarding serum markers, we expect that the TBS group active vs. sham will show a significant increase in BDNF levels. From the neurocognitive point of view, we expect that both groups will perform similarly.

**e. Scientific challenges and methods to overcome them:**

*Design and population:*

The study will be a randomized, double-blind, sham-controlled clinical trial in which volunteers will be recruited at the Clinical Hospital of the Medical School of University of São Paulo. They will be allocated to one of the groups: active TBS or sham stimulation. Participants will receive 20 consecutive days (excluding weekends and holidays) of TBS and will return at the end of 4, 6, 8 and 12 weeks for evaluation of clinical outcomes. Those who do not present clinical improvement and have been allocated to the sham group may choose to receive 20 days of active stimulation after the end of week twelve.

*Randomization and allocation of participants:*

The randomization will be in block, in which there will be permutation in the order and size of the blocks. The randomization will be generated through the website *www.randomization.com* by a researcher who will not be directly linked to the research. Patient allocation will be done through sealed, opaque and standardized envelopes. After the patient signs the informed consent form, the envelope will be opened and the envelope will be allocated to the treatment, in a coded form. The envelope will be identified with a random number that will be assigned to each patient.

*Inclusion and exclusion criteria:*

Patients older than 60 years, with initial HDRS greater than 17, who have MDD confirmed by M.I.N.I. The exclusion criteria will be: other mental disorders (alcohol or drug addiction, psychotic disorders, dementia, bipolar disorder); presence of serious neurological or clinical diseases; resence of severe suicidal ideation and CIRS (Cumulative Illness Rating Scale) score> 7, characterizing a set of clinical morbidities that could impair adherence to the research protocol, bipolar disorder and/or presence of manic symptoms (hypo) demonstrated with more than 8 points in the Young Mania Rating Scale. In addition, specific contraindications to the use of rTMS will also be excluded, such as metal implants, epilepsy or electronics in the cephalic segment. Patients who are receiving antidepressants will wash-out 5 half-lives of the medications prior to entry into the study. Patients receiving benzodiazepines will be included since receiving a maximum dose of 10mg of diazepam or equivalent. Other psychoactive drugs will be accepted as long as the doses of the medications have been stable for at least 6 weeks.

*Blinding:*

The study will be double-blind, evaluators and patients will not be aware of the randomized treatment until the end of the study. The blinding will be done with a sham coil, which consists of a coil that reproduces the sound that the true coil does, but without generating the magnetic field. A person only intended to apply the rTMS session will do the procedure and will not be involved with the evaluations or with the evaluators. A blinding scale will be applied to evaluators, applicators, and volunteers to see if blinding has been effective.

*Interventions:*

The coil will be positioned in the prefrontal dorsolateral cortex, with intermintent TBS (TBSi) mode on the left and continuous TBS (TBSc) on the right. 1800 pulses will be used on each side, totaling 10 minutes of total duration. There will be 20 consecutive sessions, one per day, except on weekends and holidays, totaling around 4 weeks. A day of stimulation with the same technique will be done in the 4th week, 6th week, 8th week and 12th week.

*Clinical variables:*

We will use the MINI questionnaire for the diagnosis of psychiatric disorders, applied by an experienced psychiatrist. It is translated and validated into the Portuguese language [39]. The demographic and clinical profile of the patients will be evaluated by: gender, age, schooling, socioeconomic status, clinical comorbidities, use and dose of antidepressants and other psychoactive drugs.

The main outcome will be measured using the HDRS scale. The primary evaluation will be done at the end of 6 weeks from the start of the first day of TBS. As secondary outcomes we will use the Hamilton Depression Rating Scale (HDRS), GDS (Geriatric Depression Scale), Cumulative Illness Rating Scale (CIRS) and the global clinical impression scale (CGI). All scales have already been translated and validated into Portuguese [40]. Outcomes will be measured on 8 occasions: baseline after 1, 2, 4, 6, 8 and 12 weeks of study entry. The presence of adverse effects and the Young mania (YMRS) questionnaire will also be evaluated to detect manic and / or hypomanic cycling.

*Biomarkers:*

BDNF (brain-derived neurotrophic factor) is implicated in the pathophysiology of depression. Recent meta-analyzes have shown that depressed patients have lower serum levels of BDNF than normal subjects [41] [42]. Recently, a pilot study reported that the low increase in serum BDNF levels in response to antidepressants at the beginning of treatment would be a predictor of treatment failure [43]. The samples of BDNF, IL-6 and IL-18 will be collected in dry tubes, centrifuged within two hours after collection, then separate the serum and refrigerate it in eppendorfs at -70oC in liquid nitrogen. The samples will therefore be stored in a cryogenic bank. They will be collected at the beginning of the survey and in the 6th week.

Cerebrospinal fluid (CSF) samples will be collected by means of lumbar puncture during the evaluation procedures, before the intervention begins. They will be used for the investigation of Alzheimer's disease (AD)

cerebrospinal fluid biomarkers, investigating the presence of beta-amyloid peptide ($A\beta^{1-42}$) and Tau protein (total and phosphorylated). This procedure is performed routinely in the Laboratory of Neurosciences (LIM-27) as part of a protocol dedicated to the evaluation of cognitive complaints in the elderly, including in this sample individuals with geriatric depression [44]. These determinations will not be included among the clinical outcome variables, but will allow the analysis of the interaction between the presence of AD pathology (as indicated by the biomarkers) and the therapeutic response to the TBS intervention.

Evaluation of sensitivity thresholds according to the Quantitative Sensitivity Test (TQS): This assessment is made by the psychophysical method that quantifies the positive and negative phenomena of exteroceptive sensitivity transmitted by the thin or thick fibers of the peripheral nervous system. It makes it possible to determine the thresholds for detecting general sensitivities and pain, and generates painful stimuli that make it possible to diagnose the occurrence of hyperalgesia or hyperpathy. The TQS device was developed by Fruhstorfer et al. (1976) and Dyck et al. (1978), in order to quantify the sensitivity exams in clinical practice. At the beginning of the test, the stimulator temperature (thermode) is maintained in the thermal adaptation range (31 (C to 36˚C). The perception of the hot or cold stimulus and the pain of hot or cold stimuli is determined by increasing or decreasing the temperature of the thermometer. The cutaneous receptors, that is, the free nerve endings, which, in turn, trigger action potentials in the thin myelinated A-delta and / or unmyelinated C fibers, which are transmitted to the long tracts of the spinal cord.

Diffuse Nociceptive Inhibitory Control (CIND) or Conditioned Pain Modulation (MCD): CIND is a term used to demonstrate a reduction in pain, in response to the application of painful stimuli outside the area of pain. In general, heterotopic painful stimuli tend to decrease the pain induced by harmful stimulation, applied extra-segmentally. Studies show that the application of harmful heat to a part of the body, such as the arm, ends up resulting in a decreased response to stimuli painful in a heterotopic region, using the legs as an example. CIND was developed and formulated describing a specific inhibitory mechanism mediated by the brain stem. Researches based on human beings, using a pain that inhibits other pain, admitted to adopting the term CIND, extending it to the psychophysical domain, and describing patterns of behavior that may belong to various neural mechanisms. The volunteers will be submitted to the same test stimulus: heat pain evoked by a suprathreshold stimulus with a thermode (30x30, Medoc) for five seconds on the thigh, on the right and left leg, with a maximum temperature of 49 ° C. The thermode is placed on the right thigh and then on the left thigh of the volunteer, instructed to press the mouse button when the temperature reached causes the onset of a hot pain. To verify the supra-painful stimulus, the temperature found as the LdorQ of the volunteer and the previous LdorQ is added by 2 ° C, in the Medoc machine we select the suprathershold stimulus and set it so that the stimulus lasts 5s, and is at a temperature of 2 ° above the LdorQ , the volunteer is then invited to describe his pain to the respective stimulus with a VAS scale> 70/100 mm, if the VAS reported by the volunteer is less than 70, we repeat the stimulus gradually increasing the temperature by 1 in 1 ° C, until he reports a VAS of at least 70/100 millimeters. The tests will be done before starting the TBS sessions and in the 4th week.

Actigraphy*:* Actigraphy consists of a wrist device equipped with an accelerometer, a microprocessor and an internal memory, which are capable of detecting and storing the movement record. Actigraphy is used in the

evaluation of sleep disorders such as diseases of circadian rhythm, insomnia and excessive daytime sleepiness. This method has some advantages in relation to polysomnography, such as the longer evaluation period, simplicity in use and interpretation and low cost. This study aims to validate the ActTrust actigraph in the assessment of sleep and wakefulness by comparing it with polysomnography. We will use the actigraphy on the left wrist of the volunteers 1 week before the beginning of the research and for another 4 weeks after the study. The device is very similar to a watch and should be worn for 24 hours during the test and has no side effects, just the inconvenience of using it, just like a wristwatch. The objective is to assess sleep changes associated with the clinical response to magnetic stimulation.

Pupil Examination (PLR): The participant will do a test lasting about 20 minutes in which a camera phone will record the size of your pupil during this period while you will hear some sounds. The exam is painless and without side effects.

*Sample size calculation:*

Based on the clinical trial of Li [45], which demonstrated an efficacy favoring bilateral TBS in depression of 52.5% for the active group and 17.4% for the sham group, for a two-tailed p 0.05 and a power of 90%, the total sample size Is 86 subjects. Considering a rate of friction of approximately 25%, we estimated the final sample size in 108 patients.

*Statistical analysis:*

Statistical analysis will be performed with the Stata 12 SE program for Mac OS X. All analyzes will be made on the intention to treat principle (ie the data of all participants will be included in the analysis) in which lost data will be allocated according to with the last observation carried forward principle and/or mixed data. Analyzes will be considered significant at $p < 0.05$. We will use parametric tests to analyze the main outcomes, which are allowed by the sample size. Number of previous admissions, presence of clinical comorbidities, refractoriness (measured by the Massachusetts General Hospital scale - MGH-S) [46] will be analyzed as ordinal data. For the main outcome we will use a repeated measures analysis, having HDRS scores as Dependent variable and TBS as independent variable at week 8. Secondary analyzes of the other scales and biomarkers will be performed in the same way, replacing HDRS as a dependent variable.

*Study Flow Chart:*

We show below the flowchart for each patient throughout the study. It is worth remembering that TBS will be applied 23 times: 20 consecutive sessions (week 0 through week 4), 6th week, 8th week and 12th week. Still, patients who receive *sham* stimulation and who are still depressed may receive active stimulation at the end of the study.

**Table 1.** Study schedule

| | **Triage** | **Baseline** | **Week** |
|---|---|---|---|

| | | | 1 | 2 | 3 | 4 | 6 | 8 | 12 |
|---|---|---|---|---|---|---|---|---|---|
| Assessment of eligibility | X | | | | | | | | |
| Structured interview (MINI) | X | | | | | | | | |
| Consent form | X | | | | | | | | |
| Theta-burst stimulation (active/sham) | | | D | D | D | D | W | W | W |
| Clinical interviews | X | | X | X | | X | X | X | X |
| Adverse effects | | | X | X | | X | X | X | X |
| Blood collection for serum biomarkers | | X | | | | | X | | |
| Neuropsychological evaluation | | X | | | | | X | | X |
| Cerebrospinal fluid collection | | X | | | | | | | |

*Ethical aspects and safety:*

The rTMS is very safe when used properly and has few adverse effects, and as mentioned above, the most common is headache. Applications will always be made in a hospital setting with a physician present. We will evaluate patients 23 times over 12 weeks - so that we can quickly identify any worsening of the clinical picture and perform early intervention.

Data collection will only begin after approval of the project by the Research Ethics Committee and, for each volunteer, after signing the free and informed consent form. The study will also be prospectively registered on clinicaltrials.gov. All the procedures described present minimal risk. If a volunteer presents a risk of major suicide, the same will be excluded from the study, adopting the standard procedure for the management of this type of patient (ie, if the outpatient management is possible, we will refer the patient, with a relative, for treatment - if this If it is not possible to perform the outpatient treatment and there is a need for an evaluation of hospitalization, we will contact the psychiatric reference emergency of the region for such cases). Participants may have access to their data and may leave the study at any time, without prejudice to any treatment they may perform within the institution. The data will be collected, analyzed and published in order to preserve the anonymity of the individual. In addition, the study will be conducted in accordance with all requirements of the Research Ethics Committee and also based on the recommendations established in the Declaration of Helsinki (1964), as amended in Tokyo (1975), Venice (1983) and Hong Kong (1989). As a

benefit, participants will be able to participate in a clinical trial to treat their clinical condition. This will be possible even if they receive sham stimulation, as they may receive active stimulation at the end of the study if they still have severe depressive symptoms.

**f. Bugdet:**

| | Quantity | 1st year | 2nd year | 3rd year | Total |
|---|---|---|---|---|---|
| *Execution costs :* | | | | | |
| TT III scholarship | 2 | 27273,60 | 27273,60 | 27273,60 | 81820,80 |
| Computer | 2 | 2350,00 | 2350,00 | | 4700,00 |
| Neuropsychological testing | 140 | 7500,00 | 7500,00 | 6000,00 | 21000,00 |
| Statistican | 1 | | | 5000,00 | 5000,00 |
| Datalogger | 1 | 1600,00 | 1600,00 | 1600,00 | 4800,00 |
| Data Manager (RedCap) | 1 | 2500,00 | 2500,00 | 2410,20 | 7410,20 |
| Applicator of scales | 350 | 8750,00 | 8750,00 | 7000,00 | 24500,00 |
| Electrodes | | 325,00 | 325,00 | 1750,00 | 2400,00 |
| Transport | 140 | 3614,44 | 3614,44 | 2879,24 | 10108,12 |
| *Overhead:* | | | | | |
| Complementary benefits | | 8000,00 | 8000,00 | 8000,00 | 24000,00 |
| Technical reserve | | 8086,96 | 8086,96 | 8086,96 | 24260,88 |
| Total | | 70000,00 | 70000,00 | 70000,00 | 210000,00 |

**g. Cronogram:**

| Months | 01 to 03 | 04 to 06 | 07 to 09 | 10 to 12 | 13 to 15 | 16 to 18 | 19 to 28 | 28 to 36 |
|---|---|---|---|---|---|---|---|---|
| Purchase of fixed and consumption materials | | | | | | | | |
| Team training / qualification | | | | | | | | |
| Data collect | | | | | | | | |
| Entering data | | | | | | | | |
| Statistical analysis of data | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Elaboration of reports and scientific publications derived from research data | | | | | | | | |

**h. Identification of all project participants:**

The following researchers will participate in the project: Leandro da Costa Lane Valiengo, psychiatrist, doctor of medical sciences, having already participated in several clinical trials and several with neuromodulation; André Brunoni, psychiatrist, doctor in neuroscience and behavior and head of the Interdisciplinary Neuromodulation Service at IPq and at the University Hospital and Drs. Universidade São Paulo and head of the Psychogeriatrics Group at the Neuroscience Laboratory (LIM-27). In addition to these, doctoral students (Julia Cunha Loureiro, Kalian Almeida Pereira Marinho, Leonardo Afonso dos Santos, Paulo Jeng Chian Suen, Pedro Subrack Oliveira, Rafael Garcia Benatti, Renata Aparecida Rocha Vaughan) and master´s (Luara Cristina Tort) and other professionals interested in the research (Bianca Silva Pinto, Bruna Bariari Teixeira, Cristiane Siqueira Miranda, Henriette Baena Cardeal). A nurse (Valquíria Aparecida da Silva) with experience in applying EMTR for clinical trials will also participate.

**Effective availability of infrastructure and technical support for project development:**

The Institute of Psychiatry at the University of São Paulo Medical School (IPq-HCFMUSP) has a structure and previous experience in EMT research, with rooms available for attendance and data analyzes, secretaries, intercurrent care and participation of interested parties. Graduate students and residents. One of the psychotherapeutic services of this institution, linked to the Laboratory of Neurosciences (LIM-27), has a multidisciplinary team and offers assistance to the elderly population with psychic and cognitive disorders of the catchment area of the Hospital das Clínicas of FMUSP. It is organized in the form of specialized outpatient clinics, with emphasis on care and research applied to cognitive disorders (mild cognitive impairment, Alzheimer's disease and other dementias) and mood disorders (depression and bipolar disorder) in the elderly.

**i. Requests for TA scholarships must be submitted:**

One TA will participate in the data collection and of biomarkers collection and storage. The other TA will be responsible for the daily application of TBS in patients for the purpose of ensuring study blinding.

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