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Allostatic load as a predictor of response to repetitive transcranial magnetic stimulation in treatment resistant depression: Research protocol and hypotheses

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A B S T R A C T

Treatment resistant depression is challenging because patients who fail their initial treatments often do not respond to subsequent trials and their course of illness is frequently marked by chronic depression. Repetitive transcranial magnetic stimulation (rTMS) is a well-established treatment alternative, but there are several limitations that decreases accessibility. Identifying biomarkers that can help clinicians to reliably predict response to rTMS is therefore necessary. Allostatic load (AL), which represents the 'wear and tear' on the body and brain which accumulates as an individual is exposed to chronic stress could be an interesting staging model for TRD and help predict rTMS treatment response. We propose an open study which aims to test whether patients with a lower pre-treatment AL will have a stronger antidepressant response to 4 week-rTMS treatment. We will also assess the relation between healthy lifestyle behaviors, AL, and rTMS treatment response. Blood samples for AL parameters will be collected before the treatment. The AL indices will summarize neuroendocrine (cortisol, Dehydroepiandrosterone), immune (CRP, fibrinogen, ferritin), metabolic (glycosylated hemoglobin, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, uric acid, body mass index, waist circumference), and cardiovascular (heart rate, systolic and diastolic blood pressure) functioning. Mood assessment (Montgomery-Åsberg Depression Rating Scale and Inventory of Depressive symptomatology) will be measured before the treatment and at two-week intervals up to 4 weeks. With the help of different lifestyle questionnaires, a healthy lifestyle index (i.e., a single score based on lifestyle factors) will be created. We will use linear and logistic regressions to assess AL in relation to changes in mood score. Hierarchical regression will be done in order to assess the association between AL, healthy lifestyle index and mood score. Long-lasting and unsuccessful antidepressant trials may increase the chance of not responding to future trials of antidepressants and it can therefore increase treatment resistance. It is essential to identify reliable biomarkers that can predict treatment responses.

1. Introduction

Despite an extensive range of treatment options, many patients with major depressive and bipolar disorder develop treatment-resistant depression (TRD) [1,2]. TRD is challenging because patients who fail their initial treatments often do not respond to subsequent trials and their course of illness is frequently marked by chronic depression [3]. Up to a third of patients do not respond to first-line approaches, such as antidepressant medication and psychotherapy [4]. In that context, refined treatment options are needed.

Repetitive transcranial magnetic stimulation (rTMS) is a well-established treatment alternative for TRD [5,6]. rTMS is a noninvasive procedure that uses magnetic fields to stimulate neurobiological circuits in the brain with the aim of improving symptoms of depression [7]. With an advantageous side effect profile over medication, response rates have been estimated to be as high as 25–35% [5,8]. Unfortunately, rTMS is burdened by several limitations that decreases accessibility, such as high equipment costs, complexity of technical operation, and the need for daily sessions over several weeks [9]. This reinforces the need for careful patient selection to maximize treatment outcomes and avoid futile treatment courses. Identifying biomarkers that can help clinicians to reliably predict response to rTMS treatment is therefore greatly needed.

Clinical staging in depression builds on strong epidemiological evidence indicating that what we regard as TRD often evolve over time in terms of treatment resistance and severity [3]. Many models exist in the staging of TRD which are often based on course, treatment failure and severity of the illness. Ultimate endpoints vary from single self-limiting episodes to a chronic duration of illness with highly recurrent episodes

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[10]. A second perspective to TRD provides a staging model with more specific prognostic variables or biomarkers, analogous to other medical specialty such as oncology where higher stages are related to worse prognosis [11].

The allostatic load (AL) model [12], which represents the 'wear and tear' on the body and brain that accumulates as the individual attempts to re-establish homeostasis after multiple stressors [13] could be an interesting way to assess TRD through biomarkers. More stressors, depressive episodes, and engagement in unhealthy behaviors provoke further adaptations that further increase AL over time [14]. This can generate a potential 'vicious cycle' which can further impact brain circuits required for mood regulation and cognition [15] and amplify treatment resistance [16].

Though the relationship between AL and depressive symptoms has been established [17,18], the relationship between AL and treatment resistance is not well studied. Some authors have demonstrated that higher AL is associated with poorer selective serotonin reuptake inhibitors (SSRIs) - treatment response [19], but no studies have used AL in the evaluation and prediction of response to rTMS.

Furthermore, evidence is growing that lifestyle choices, especially exercise, nutrition, and sleep, play a role in the onset, treatment, and progression of depression [20,21] and also impact AL [14]. However, the research remains limited on the association between lifestyle factors, depression and AL and evaluating their associations in psychiatric treatment setting will be a nice addition to the literature. The goal of this protocol paper is to outline an open feasibility study that tests if AL can predict rTMS treatment response. In addition, we will explore lifestyle behaviors in association with AL and rTMS treatment response.

2. Hypotheses

In the proposed study, we will conduct an open study protocol which aims to test two hypotheses:

1) Patients with lower pretreatment AL will have better antidepressant response to rTMS treatment.
2) Lifestyle risk factors (sedentary and lack of physical activity, consumption of unhealthy foods, tobacco use, alcohol and substance abuse, and sleep deprivation) will modulate the association between AL and rTMS treatment response.

3. Methods

3.1. Design of the proposed trial

This feasibility study will involve 35 patients with TRD referred by psychiatrists in the Montreal community. We will conduct an open trial that will assess the association between pretreatment AL and rTMS treatment response changes in mood after a 4-week treatment protocol.

3.2. Clinical implication and pertinence of the study

To maximize the clinical utility of the AL concept, we need to have more studies with better ecological validity, so that the findings can be generalized to real-life settings. Researchers have traditionally conducted experiments on AL in specialized research settings. Whether laboratory-based experiments permit the generalization of the results in clinical setting is an open question [22].

This feasibility study aims in part to explore if the AL concept is useful in clinical context and can be integrated in psychiatric clinics without significant change in the usual clinical care. All the biomarkers were chosen have great potential for translational application into clinical practice. Indeed, they are noninvasive, simple and are part of the panel of biomarkers frequently used by clinicians. Moreover, most have been previously incorporated in the AL literature [23,24].

The ultimate goal of this project is to orient future randomized controlled trials that assess the relationship between AL and rTMS treatment response in relation to different stimulation parameters. This study will help to gather preliminary data for power calculation for future larger clinical trials. With regards to this aspect, some authors have recommended an overall sample size around 30 [25,26]. If data findings of our study direct us to the fact that it could lack power (type II errors), we will use method of statistical inference in which Bayes' theorem would be used to update the probability for a positive result as more evidence or information becomes available. This will allow us to assess the real absence of association and the relevance of doing other studies on this subject.

3.3. Participants

3.3.1. Inclusion and exclusion criteria

Inclusion criteria: a) patient diagnosed by the study psychiatrist with major depressive disorder or bipolar disorder based on DSM-5 criteria and confirmed by the international neuropsychiatric mini-interview (MINI); b) patient had to meet the selection criterion of treatment resistance, defined as a partial response or no response to at least two antidepressant medications, either as a monotherapy or in combination, at minimum adequate dose and duration; c) stable pharmacological and psychotherapeutic treatment 8 weeks prior the trial and for its entire duration; d) the patient has a score of 14 or more on the Montgomery Äsberg (MADRS) scale; and e) the patient is between 18 and 65 years of age.

Exclusion criteria: a) unstable medical disease defined as any disease whose treatment was not well controlled with standard drugs; b) severe psychiatric comorbidities (for example, acute psychosis, acute hypomania/mania, unstable personality disorder) and defined as any psychiatric disorder requiring immediate treatment c) suicidal people who require immediate treatment such as hospitalization; d) active treatment with a benzodiazepine or a psychostimulant.

3.3.2. Planning the intervention

rTMS treatment will be delivered through MagPro R30/X100 stimulators equipped with B70 coils (MagVenture, Farum, Denmark). Resting motor threshold (rMT) will be determined according to standard techniques [27]. Treatment will consist of 2 daily sessions of rTMS spaced by at least 50 min, 5 days a week (Monday through Friday) over 4 weeks, for a total of 40 sessions. Each rTMS session will consist of a high-frequency (HF) 20 Hz protocol delivered over a 10 min period (5 s ON, 15 s OFF, 3000 pulses per session) at 120% of rMT over the left dorsolateral prefrontal cortex, localized according to a previously published heuristic [28].

3.3.3. Medication(s)/treatment(s) allowed and not allowed before and/or during the trial

Medication that may interact with rTMS response such as benzodiazepines and psychostimulants will not be allowed during the study. We will collect the patient's pharmacological history, but no additional supplementary analysis is intended. No previous research demonstrates that some antidepressants or other medication (other than benzodiazepines and psychostimulants) might influence rTMS response [29]. Therefore, patients will remain stable on their treatment 8 weeks prior to treatment and during the entire protocol.

3.3.4. Suggested outcomes

Questionnaires will be completed by participants by computer or smart device via Qualtrics, a highly secure internet platform. Qualtrics is a Software-as-a-Service that provides a platform for creating and distributing online surveys and other research services, referred to as the XM Platform. The questionnaires will gather information regarding demographics, health risk behaviors, and a variety of psychosocial constructs (see Table 1). The baseline survey takes between 30 and 45 min on average to complete while the follow-up mood assessment takes

Table 1
Clinical characteristics of patients.

Demographics
Age
Sex and gender
Bem masculine gender-roles
Bem feminine gender-roles
Kinsey sexual attractions
Socioeconomic
Working hours per week
Education, years schooling
Occupational status
Civil status
Single
In a relationship
Married
Separated or divorced
Coupled, binary coded
Parenthood, number of children
Parents with children living at home
Health behaviours
Physical activity
Sedentary
Sleep
Alcohol consumption
Smoking
Illicit drug use
Nutrition
Mindfulness
Physical health condition(s)
Medication(s) prescribed
Psychotropic(s) prescribed

between 10 and 15 min.

3.3.5. Sociodemographics

Sociodemographic variables (e.g., education, income, family support, civil status, age, race/ethnicity) will also be assessed via the screening questionnaire.

3.3.6. Sexual orientation and gender roles

Because sexual orientation and gender role modulate endocrine stress physiology [30] and AL [31,32], we will also assess these variables as potential covariates. The questionnaire will include items that measure birth-assigned sex, current gender identity, and current lived gender. The Sex Role Identity Scale will assess how masculine and/or feminine a person believes they are, as well as how masculine and/or feminine a person believes they are perceived by others [33]. Every item is coded on a 5-point scale ranging from "not at all" to "extremely", and two scores are then calculated. A high score on masculinity, for example, means that the participant considers that they are and appear to others as very masculine. The original validation of this scale showed strong internal consistency, with the three masculine identity items inter-correlating positively for men ($r = 0.66$, $p < .001$) and for women ($r = 0.68$, $p < .001$) and the three feminine identity items inter-correlating positively for men ($r = 0.80$, $p < .001$) and for women ($r = 0.70$, $p < .001$; [33]).

The Heterosexual-Homosexual Rating Scale, more commonly known as the Kinsey Scale, will be used to assess sexual orientation [34]. Data gathered as part of thousands of interviews led by Kinsey and his team revealed that the three most commonly used categories of sexual orientation (heterosexual, bisexual and homosexual) did not accurately reflect people's sexual histories and experiences. This measure therefore uses a 7-point scale to assess how participants identify with regard to their sexual orientation, ranging from "exclusively heterosexual" to "exclusively homosexual" along a continuum. Participants scoring in between heterosexual and homosexual extremes report varying levels of sexual behavior and attraction toward either sex. The item also includes an "asexual or non sexual" option.

3.3.7. Lifestyle risk behaviors

Because lifestyle risk factors influence both AL and depression trajectories, we will assess these factors. For physical activity, we will use the Simple Physical Activity Questionnaire (SIMPAQ), which has been validated to evaluate physical activity, exercise and sedentary behaviors in people with mental disorders [35]. For sleep evaluation, we will use the Pittsburgh Sleep Quality Index (PSQI), which assesses sleep quality over a 1-month interval [36]. The questionnaire has been used in many settings and is considered to be a reliable and a valid tool in the assessment of sleep problems. For mindfulness, we will use the Mindful Attention Awareness Scale (MAAS), which is a scale designed to assess core characteristics of dispositional mindfulness.

Maladaptive time perspective has been associated with AL [37] and the MAAS score will allow us to assess self-regulation and various areas of well-being [38]. It is also an indirect way to measure the willingness and practices of mindfulness. For tobacco smoking, drug, and alcohol consumption, we will use surveys used by Statistics Canada to assess past and present behaviors. Statistics Canada is Canada national statistical office that uses many reliable and valid set of questionnaires for diverse health behaviors [39]. A Mediterranean diet questionnaire will be used, and a higher score will be given for better compliance to a traditional Mediterranean diet [40]. The Mediterranean diet has received increasing attention as an important lifestyle factor that influences health outcomes.

3.3.8. Healthy lifestyle index (HLI)

Multiple studies have investigated the combined effects of multiple lifestyle risk factors on health [41]. Accumulating evidence suggests the importance of constructing a healthy lifestyle index (i.e., a single score based on lifestyle risk factors that people adopt) as it captures the combined effects of multiple health-related lifestyles known to co-exist [42]. An HLI will be constructed from the sum of seven lifestyle risk factors component scores, by assigning a 5-category score (0–4) to each category (nutrition, physical activity, sleep quality, smoking, alcohol abuse, illicit drug use and mindfulness). The score for every lifestyle factor will be generated by categorizing the values of total questionnaire score for the participants into five quintiles. This means that the highest 20% of answers will be assigned with the highest score, four, and the lowest 20% answers with the lowest score, zero. The HLI will be generated by adding the number of dichotomous risky or non-risky lifestyle factors. It will range from 0 to 28, with higher values indicating adherence to a greater number of healthy lifestyle factors. The creation of this index will be useful in the evaluation of how lifestyle risk factors modulate the association between AL and treatment response.

3.3.9. Depressive symptoms

The Montgomery-Åsberg Depression Rating Scale (MADRS) is a 10-item scale with a maximum score of 60 that measures the severity of depression and is recognized to be sensitive to treatment and has excellent psychometric properties [43]. Reliability analyses confirm that the MADRS scale is able to detect changes during treatment [44]. Research indicates a reliability of 0.95 and an excellent internal consistency with Cronbach's Alpha (α) of 0.90 [43]. At present, this scale is among the most commonly used tools to assess depression in medical research.

Most research on rTMS treatment has included the MADRS scale in their analyses. Responders will be determined by a reduction of 50% in MADRS score, and patients in remission will be determined based on $\leq$10 scores. A 50% reduction and a score of $\leq$10 in MADRS are operational criteria internationally recognized in the field of research for treatment response and remission in MDD [45].

In addition to the MADRS, the 30 item Inventory of Depressive Symptomatology (IDS) will also be used to assess the severity of depressive symptoms [46]. The IDS questionnaires are available in the clinician (IDS-C) and self-rated versions (IDS-SR). Complete assessment of depression should include both clinician-rated scales and

self-reported measures [47]. Furthermore, the MADRS assesses all the criteria symptom domains designated by DSM-5, but do not encompass anxious, atypical, or melancholic features or other commonly associated depressive symptoms such as pain or gastrointestinal disturbances. These symptoms relevant to melancholic, or atypical depression are included within the IDS. Although the MADRS might not perfectly encompass all depressive features, it has demonstrated greater sensitivity to change [48]. The use of both questionnaires (i.e., MADRS and IDS) will give a more interesting valid picture of depression. We will operationalize the IDS score as following: IDS-C total score $\leq$14 and $\geq$ 50% reduction from baseline on IDS-C total score.

3.3.10. Individual biomarkers

Blood samples for AL parameters will be collected one week before the beginning of treatment at the tests center of the CHUM. The Centre Hospitalier de l'Université de Montréal (CHUM) laboratory will assay biomarkers. Immune/inflammatory, metabolic and hormonal markers will be analyzed using standard hospital techniques. We will assay a wide variety of blood biomarkers that are commonly used in the AL literature [23] that are incidentally also useful in clinical practice: Dehydroepiandrosterone, morning cortisol, hemoglobin A1c, fibrinogen, C-reactive protein, ferritin, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, and uric acid. See Table 2 for the function of specific markers.

Systolic blood pressure, diastolic blood pressure, and heart rate will also be measured by registered nurses. We will use the mean of two recordings measured with an electronic sphygmomanometer (A&D Medical: Model UA-631 V). Anthropometric measures will be measured by the research coordinator to calculate body mass index (BMI) and waist circumference.

Baseline standard 12-lead electrocardiogram (ECG) will be assessed by a certified cardiac technician. The ECG will be done at the cardiac electrophysiology clinic of the CHUM when patients are at rest in the examination room. Electrocardiogram measurements include heart rate, PR interval, and presence of Q waves and T wave. 25 Marquette 12SL ECG Analysis Program from GE Healthcare will be used to assist in measuring and interpreting resting 12-lead EGGs for rhythm and contour information by providing an initial automated interpretation. Bazett correction formulas (QTc = QTHR/60) will be used for calculating the corrected Q-T.

3.3.11. Allostatic load

Our selection of biomarkers is based on an array commonly employed biomarkers in the AL literature [23]. AL represents the sum of biomarkers attaining critical cut-offs that are ascribed a score of "1" while those in a healthy range are ascribed a score of "0" based on the sample's distribution of biomarkers or based on clinical reference ranges [23,49]. The 75th percentile will be used for all biomarkers, except high-density lipoprotein where the 25th percentile denotes risk. For cortisol, both the 12.5th and 87.5th percentiles will be used since hypo- and hyper-active functioning can be damaging [49,50].

As suggest by literature on AL index formulations, we will also use an alternative "sex-specific" AL index with cut-offs tailored to birth-assigned men and women separately [51]. The distribution for our biomarkers will be based on our sample of patients; however, we will also be able to assess another alternative formulation based on clinical cut-offs and sex-specific formulations as mentioned above [49]. We are deliberately exploring various AL formulations to best account for variation in this rare sample in the hopes of identifying the most clinically meaningful version.

3.3.12. The psychosocial index (PSI)

A clinimetric approach will also be used in conceptualizing AL. Although AL is typically operationalized and measured using several biomarkers, the PSI is a short clinimetric index, tailored for use in busy clinical settings, for the assessment of stress and related psychological

Table 2
Biomarkers in allostatic load with a brief overview of their functions.

Biomarker	Function and rationale
Cortisol	Glucocorticoid produced by the adrenal glands. Functions include the conversion of stored fats and proteins into carbohydrates, anti-inflammatory and immunosuppressive effects, increased blood pressure and heart rate, suppression of digestive, growth, and reproductive activities, and modulation of limbic and prefrontal regions upon traversing the blood–brain barrier. Primary mediators of allostatic load because of its immediate correlation with adrenal function.
Dehydroepiandrosterone	Androgen produced by the adrenal glands. Known functions include its role as a HPA-axis antagonist and its ability to convert into androgens and estrogens. It also suppresses inflammatory cytokines, improves lipid metabolism and lean muscle mass, decreases insulin resistance, and reduces oxidative brain damage. Primary mediators of allostatic load because of its immediate correlation with adrenal function.
C-reactive protein	Protein synthesized in the liver. Functions by enhancing phagocytosis during acute phase reactions that promote inflammation. Secondary outcomes of AL because of its immediate correlation with immune function and inflammation
Fibrinogen	Protein that synthesizes into fibrin in the liver. Upon synthesis, functions as a blood clothing factor that promotes coagulation but when excessive increases risk of thrombosis. Secondary outcomes of AL because of their immediate correlation with inflammation
Ferritin	Ferritin is a protein that stores iron. High level of serum ferritin is also a well-known inflammatory marker. Secondary outcomes of AL because of their immediate correlation with inflammation
BMI	Measure of weight and height that is then calculated into an index by dividing weight by height. Represents a proxy measure of an individual's relative body fat percentage ranging from severely underweight, underweight, normal, overweight, to three different classifications of obesity.
Waist circumference	The waist circumference is the narrowest part of the waist. It is a good indicator of visceral fat. Higher levels represent greater adipose fat distribution of concern for obese individuals.
Triglycerides	Glyceride formed from glycerol and three-chain fatty acids. Functions as an important source of energy and as transporter of dietary fat.
High density lipoprotein	Lipoprotein synthesized in the liver. Transports cholesterol from tissues to the liver. Commonly referred to as ''good cholesterol'', as its high protein/low cholesterol form is more easily removed by blood in the liver and excreted in bile.
Low density lipoprotein	Lipoprotein synthesized in the liver. Transports cholesterol to tissues that synthesize cell membrane and secretions. Commonly referred as ''bad cholesterol, as its low protein/high cholesterol from is more likely to be deposited in the walls of blood vessels and contribute to atherosclerosis.
Uric Acid	Molecule resulting from the degradation and excretion of purines. Uric acid is considered a contributory causal factor of metabolic syndrome.
Systolic blood pressure	Measured using a sphygmomanometer. Represents the maximal force exerted by blood against the blood vessel walls when the left ventricle is contracting during systole.
Diastolic blood pressure	Measured using a sphygmomanometer. Represents the minimal force exerted by blood against the blood vessel walls when the left ventricle is relaxed during diastole.
Heart rate	Measured at sites where arterial pulsation can be felt. Represents the number of palpations made by the heart within a period of time.

distress [52]. It offers a synthesis of previously validated instruments. The integration of biological parameters and clinimetric approach gives a more comprehensive assessment of AL beyond biomarkers.

4. Strategy for measurements

The following describes the general organization of the study.

4.1. Screening

All patients referred to the neuromodulation clinic of the CHUM for TRD will be offered the opportunity to meet the research coordinator. Patients are normally referred from psychiatrists practicing in the greater Montreal area and the surrounding region. The diagnosis of major depressive episode (MDE) will be confirmed by the international neuropsychiatric mini-interview (MINI) of the DSM-5. The MINI is a structured diagnostic interview, developed to assess the diagnoses of psychiatric patients according to DSM-5. It will be administered by a mental health professional familiar with the classification and the DSM-5 diagnostic criteria. The MINI ensures that the main diagnostics of DSM-5 are systematically evaluated. It ensures that all patients have symptoms that meet the DSM-5 criterias for MDE and that all patients with other severe mental health disorders are excluded. The diagnosis of TRD will be confirmed by the study's psychiatrist.

Psychiatric rating scales will be administered to patients and only patients with a MADRS score $\geq$14 will be included into the study. Patients will respond to a questionnaire that provides their sociodemographic and lifestyle risk factors characteristics. They will also be asked about their treatment history (both psychotherapeutic and pharmacological) as well as their physical health. Table 1 lists the sample's descriptive statistics for sociodemographics, gender and sexual orientation, and lifestyle-risk factors. In order to participate in the study, eligible patients will be required to sign a consent form previously approved by the CHUM Ethics Committee.

4.2. In-person follow-up visits (weeks 1–4)

From admission into the study, visits will take place at the outpatient neuromodulation clinic at the CHUM over a period of 4 weeks (see Fig. 1). The primary tests should occur on the week before the start of the treatment. We will then proceed to the basic medical evaluation including physical examination including vital signs and anthropometric measurements. The blood test will then be conducted. As mentioned earlier, treatment will consist of 2 daily sessions of rTMS spaced by at least 50 min, 5 days a week (Monday through Friday) over 4 weeks, for a total of 40 sessions.

In addition to their involvement in the selection of participants, the physicians will: a) perform medical assessments; b) provide general medical advice; and c) monitor patients' progress throughout the treatment. A physician will meet the patients at week 0 to confirm eligibility and 2 to determine if the protocol is appropriate and at week 4 to determine the appropriate study exit plan. Nursing and research staffs will provide psychosocial assessments (including symptoms assessment, physical examination, and vital signs measurements) and blood tests. A symptom assessment will also be done on at 4th week. Patients will receive supportive psychotherapy and psychoeducation from the clinical psychiatrist, which is the standard care offered by neuromodulation clinics.

5. Potential risks

Suicidal risk: Standard care offered at the neuromodulation clinic will be done for suicidal risk. The Columbia-Suicide Severity Rating Scale (C-SSRR) will be used to screen for suicidality at the beginning of the study and at the end of the study. The staff have a high level of expertise in the assessment of depression and suicide. Since patients will be at every working day at the clinic for a period of 1-month, suicidal behaviors are evaluated and managed clinically by the nurses and psychiatrists on a daily basis. In case of immediate suicidal danger, patients will be evaluated by the study psychiatrist and proper conduct will be determined according to the level of suicidality. Hospitalization could be suggested or imposed on the patient depending on the level of risk.

Potential risk of the project: This study is included in the usual clinical care of the CHUM's neuromodulation clinic without much change in the usual patient's journey. At the beginning of the study, patients will do a blood test, a structured diagnostic interview, and answer a 1-h survey. The 1 h survey is the only added time in the patient's journey since the blood test is part of the standard clinical care.

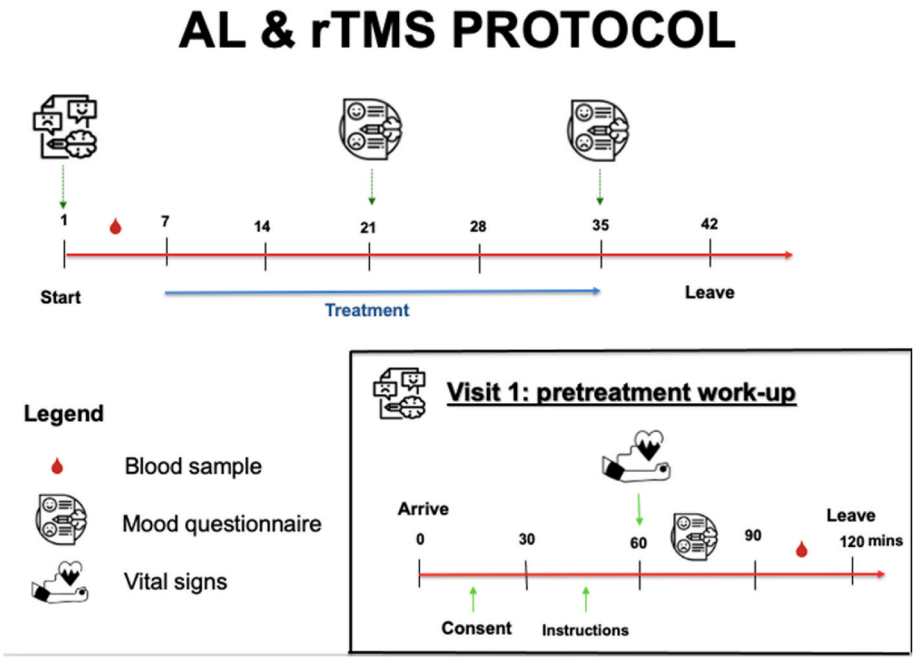

Fig. 1. Study protocol and timeline.

The survey can potentially induce fatigue especially since mood assessment is emotionally demanding. This is the reason why we intend on encouraging participants to take breaks between tasks to attenuate potential fatigue that they may experience.

Side effects: the most common rTMS side effects are scalp pain during stimulation (40%) and headache after stimulation (30%), two transient symptoms that normally decrease gradually during the course of treatment [8]. These headaches respond usually to analgesic treatments normally available as over-the-counter products. Patients will be informed of these side effects and analgesic treatments will be offered if these side effects do appear. Patients will be questioned daily about any side effects and the medical team will record treatment tolerability.

6. Ethical considerations

This study will be carried out in agreement with ethical standards from the Declaration of Helsinki, the standards of good Canadian and international clinical practices (Guidelines from Health Canada and the International Council for Harmonization), applicable provincial government laws and CRCHUM's institutional research policies. The study will be submitted to the CHUM's Ethics Committee for approval before being initiated.

6.1. Confidentiality of participants, data processing and record keeping

Several measures will be taken to protect the confidentiality of participants' data. The research staff will inform participants that all information gathered during the study will remain strictly confidential within the limits provided by the law and that no information that could make them identifiable will be revealed in any publication or research presentation. We will use the Qualtrics® Transport Layer Security encryption for all transmitted data. The use of secure online questionnaires is increasingly more common in scientific research [53–57] and are as valid as paper/pencil questionnaires [58,59]. Data will be fully stored in Canada and Qualtrics employees will not have access to any data, questionnaire, or information the research teams upload on the Platform, except when technical assistance is required. Well-validated questionnaires are available in English or French.

7. Expected recruitment rate

In total, 35 patients (birth-assigned males and females) will be recruited at the CHUM neuromodulation clinic. Data collected over 12 months in 2017–2018 indicates that 50 new patients were admitted to the program in a year. Patients will be systematically screened for depressive symptoms and TRD. This strategy should allow for rapid recruitment. We do not foresee any major difficulties in achieving the planned recruitment rate of 35 patients (4–5 patients per month).

7.1. Probable follow-up loss rate

The rate of loss of follow-up over 1 year at the psychiatric neuromodulation unit of the CHUM is below 10% (1 and 2 patients every year). Should we experience attrition in our study, we will report the patient characteristics to help inform future clinical research.

8. Type of analysis proposed

This is an open study protocol which aims to test two hypotheses: 1) Patients with decreased pretreatment AL will have stronger antidepressant response to rTMS treatment. 2) Lifestyle risk factors will modulate the association between AL and treatment response. All data analysis will be completed using the Statistical Package for the Social Science Version 25 (SPSS statistics 25) for Macintosh.

Descriptive statistics will include means and standard deviations for quantitative variables. Frequency distributions will be done for categorical variables. In order to examine the change in the average mood score, the intra-patient differences will be tested using complementary approaches: (i) a simple paired *t*-test will be used to determine significant differences in baseline demographics and characteristics between rTMS responders and non-responders (ii) logistic regressions will be used to assess pretreatment AL in relation to MADRS score (e.g., responders versus non-responders). (iii) linear regressions will be used to assess pretreatment AL in relation to MADRS score (continuous scores) (iv). Hierarchical regression will also be done in order to assess the association between AL, healthy lifestyle index and mood score. (v) Finally, post-hoc and exploratory secondary analysis will be done to investigate the association between specific lifestyle risk factors and response to rTMS treatment.

The different descriptive statistics (see Table 1) will be used as potential confounding factors (maximum of 3 factors (e.g., age, sex, HLI) based on sample size). The estimated adjusted differences will be reported with 95% confidence intervals based on the model with significance level $\alpha = 0.05$. The rate of loss of patients in the CHUM's Psychiatric Neuromodulation program is less than 10%. Missing data will then be imputed using the simple method of the last observation (last-observation-carried-forward (LOCF), that is, the data will be replaced by the last available value for the same patient. The biases of the approach LOCF are only minimal if the frequency of missing data is low.

8.1. Proposed frequency of analyses

Considering the total sample size and the relatively short duration of the open study, no interim analysis is planned. The data will be analyzed once the participants have completed the trial.

8.2. Expected results

The rTMS response rate at the CHUM's neuromodulation clinic is estimated at 46%. Thus, during our open-label trial, we expect a similar treatment response. We believe there will be a significant difference in pretreatment AL between responders and non-responders. Patients that will have lower AL will better respond to rTMS treatment. We believe the HLI will modulate the association between AL and rTMS response.

9. Conclusions and implications

The current approach to the treatment of TRD uses a strategy of trial and error that results in delay in response and remission [60]. Ineffective treatment prolongs suffering needlessly. In addition, long and unsuccessful antidepressant trials can reinforce negative cognitions and may increase the chances of not responding to future trials of antidepressants, thus increasing treatment resistance [61]. For these reasons, it is essential to identify reliable biomarkers that could help us in illness staging of depression and that can predict the response to treatment [62]. These can then be used to shorten or eliminate the long and inefficient trials. AL constitutes a very interesting battery of biomarkers that we expect will predict response to rTMS treatment. To our knowledge, no study has evaluated the relation between AL and response to rTMS treatment. If the results of our study convincingly suggest that there is a link between AL and response to rTMS, the next step would be to try to replicate these results in a larger, multi-site, double-blind, placebo-controlled clinical trial. This project could have unique medical value for patients and societies affected by depression.

Conflicts of interest

Authors have no disclosures to report.

Funding statement

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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