ILLNESS PERCEPTION AND ITS INFLUENCE IN OUTCOME AND DISABILITY IN PATIENTS WITH TREATMENT RESISTANT DEPRESSION RECEIVING rTMS TREATMENT

by

Renata Barbosa Menezes

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The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, a thesis entitled:

Illness perception and its influence in outcome and disability in patients with treatment resistant depression receiving rTMS treatment

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Examining Committee:

Fidel Vila-Rodriguez, Department of Psychiatry, UBC

Supervisor

David Kealy, Department of Psychiatry (Psychotherapy), UBC

Supervisory Committee Member

Joelle LeMoult, Department of Psychology, UBC

Supervisory Committee Member

Daniel Cox, Educational and Counselling Psychology, and Special Education, UBC

Additional Examiner

Abstract

Background: Depressive disorders are a significant burden to patients and society, possibly leading to catastrophic damage to one's life. Unfortunately, many of these patients become resistant to treatment. Therefore, identifying possible aspects that can influence treatment responsiveness and return to life activities has become essential. Illness perceptions have been associated with many different conditions, including depression, treatment adherence, functionality, and coping behaviours.

Objectives: The objectives of this study were to describe illness perceptions in a sample of patients with treatment-resistant depression (TRD) undergoing repetitive transcranial magnetic stimulation (rTMS) treatment; to evaluate its correlation with changes in the level of disability and changes in depression symptoms after treatment; to identify the possible influence of treatment on illness perceptions changes over time.

Methods: Participants with a history of treatment-resistant depression were referred from primary and secondary care to receive treatment with rTMS. Measurements were done at baseline and after treatment using BIPQ, HRSD-17, and Sheehan Disability Scale (SDS). Patients were followed for a total of 16 to 18 weeks.

Results: The sample consisted of 62 participants. The majority were female with severe depression. Identity, consequences, concern, and emotional representations were very high before treatment and strongly associated with one another. Life stressors, genetics, and trauma were the most perceived causes of depression. There was an indication that identity and other dimensions could explain some of the variances in HRSD-17 scores after rTMS, and perceived identity could also explain the variance in work/school, social, and family/home scores. rTMS appeared to be correlated with changes in illness dimensions after treatment.

Conclusions: Depression takes over a patient's perception and life experience affecting social, professional, and personal life aspects. Most illness perceptions in TRD patients are severe and can mildly explain changes in symptoms and functioning over time. Changes in illness perception are part of the common-sense model's dynamic feedback and could partially be attributed to treatment in this sample.

Lay Summary

Depression is a medical condition where patients suffer from low mood and lack of interest in life, which can interfere significantly in their relationships, work, sometimes making them take their own lives. Different treatments exist, but a large number of individuals do not present improvements. The way a person sees their condition can interfere with how they respond to treatment and how they can function in their daily lives. This study's objectives were to identify how patients resistant to depression's treatment see their depression and how this could affect their symptoms and their ability to live regular lives. We noticed that these patients had a robust and negative perception of their depression and partially explained some improvements in symptoms and functioning.

Preface

This research is ultimately based on the apparatus and data of the randomized controlled trial of conventional vs. theta burst rTMS, a sizeable national collaboration registered on clinicaltrials.gov under the inscription NCT01887782. The text of this thesis was not previously published.

I wrote the thesis under the supervision of dr. Fidel Vila-Rodriguez, revised by supervisory committee members dr. David Kealy and dr. Joelle LeMoult and external examiner dr. Daniel Cox. The non-invasive neurostimulation therapies (NINET) laboratory team did the data collection.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

BIPQ	Brief Illness Perception Questionnaire
FDA	Food and Drug Administration
GAD	Generalized Anxiety Disorder
HRSD-17	Hamilton Rating Scale for Depression (17-item version)
IPQ	Illness Perception Questionnaire
IPQ-R	Illness Perception Questionnaire Revised
iTBS	Intermittent Theta-Burst Stimulation
MDD	Major Depressive Disorder
PTSD	Post-traumatic Stress Disorder
rTMS	Repetitive Transcranial Magnetic Stimulation
SDS	Sheehan Disability Scale
SD	Standard Deviation
TMS	Transcranial Magnetic Stimulation
TRD	Treatment Resistant Depression
UK	United Kingdom
US	United States

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I offer my abiding gratitude to the faculty, staff, and colleagues at the UBC, who have inspired me to be better. I owe particular thanks to Dr. Fidel Vila-Rodriguez, who has believed in my potential and consistently provided helpful resources for continuous growth. I thank Dr. LeMoult and Dr. Kealy for providing enlightening insights into my questions.

I owe special thanks to my mother, husband, and son, whose support has always encouraged me to go further.

Dedication

To my father

Chapter 1: Background – The Relevance of Self-Regulatory Concept in Depression

1.1 Major Depressive Disorder

1.1.1 Definition and Importance

Major Depressive Disorder (MDD) is characterized by sustained low mood, most days for at least two weeks, associated with anhedonia and symptoms like sleep, appetite, weight, sexual drive, and psychomotor changes, as well as the difficulty to concentrate and presence of pervasive guilty or thoughts of worthlessness. These symptoms can impair a patient's daily functioning and can evolve to fatal outcomes due to persistent suicidal thoughts (Sadock et al., 2017; DSM-5, American Psychiatric Association, 2013).

Depression is considered a heterogeneous illness. The monoamine hypothesis, dysfunction of the hypothalamic-pituitary-adrenal axis, neuroplasticity disturbance, cytokine theory, and genetic association with environmental factors were associated with its pathophysiology (Jesulola et al., 2018; Ressler & Nemeroff, 2000; Sadock, 2015).

Other components implicated in depression development are growth hormone imbalance, increased immunologic factors, increased corticotropin-releasing factor, thyroid dysfunction, abnormalities of second messengers' systems, and neurogenesis disturbance (Jesulola et al., 2018; Sadock, 2015). Psychological, genetic, and environmental factors potentially act on the hypothalamic-pituitary-adrenal axis,

stimulating the corticotropin-releasing factor secretion, which results in hypercortisolemia (Jesulola et al., 2018; Sadock et al., 2015). Despite these findings, there is no united hypothesis that would explain all symptomatology of MDD (Jesulola et al., 2018; Ressler & Nemeroff, 2000).

Literature suggests an average age of onset around 40 years for single episodes. However, recurrent episodes tend to present five to ten years prior, which could be associated with an increased incidence among individuals younger than 20 years of age. Commonly associated comorbidities are alcohol abuse or dependence, panic disorder, social anxiety, and obsessive-compulsive disorders. The association with anxiety illnesses or substance use increases the risk of suicide, as in bipolar disorders (Sadock et al., 2017).

There is an estimate that about half of the patients who have presented one episode of depression will have another, meeting criteria for major depression, recurrent. Depressive disorders became the third leading cause of all-age years lived with disability in 2007, remaining to the present day. These also are the most prevalent group of mental illnesses, affecting approximately 264 million individuals worldwide. Major depressive disorder solely accounts for about 163 million (James et al., 2018). It is a recognized burden for individuals and society. Patients with more severe presentations are inclined to have higher impairment work-related and use more health care resources (Chow et al., 2018). Depression is also considered a risk factor for other diseases like hypertension, diabetes, arthritis, and asthma (Jesulola et al., 2018).

In Canada, depressive disorders were the fourth most prevalent cause of disability in 2017. In 2012, about 11.3% of Canada's population had experienced a major depressive episode at any given point of life, reflecting more than three million individuals affected (Statistics Canada, 2013; Institute for Health Metrics and Evaluation, 2019). The lifetime prevalence in a cohort sample of Alberta, Canada, was calculated at 8.6% for both sexes in 1994 (Spaner et al., 1994). In 2002, the yearly risk of developing a depressive illness among British Columbians was about 4% (Goldner et al., 2002).

Adult Canadians experiencing recent episodes of MDD have a lower health-adjusted life expectancy than other medical conditions like obesity class 2, hypertension, and diabetes mellitus. (Steensma et al., 2016). A study in Ontario identified the annual per-capita total cost with MDD patients ranging from $2,413 and $4,008 without considering other expenses like costs with drugs, laboratory tests and non-physician emergencies, and overall hospital services (Chiu et al., 2017).

1.1.2 Treatment-Resistant Depression

Despite the large variety of therapies available for MDD, data shows that most patients do not remit and, between 40% to 60%, do not respond to first line therapies (Rush et al., 2006), having to live with symptoms indefinitely. There are different proposed models to classify and stage treatment-resistant depression (TRD). Thase and Rush (1997) proposed a model where the resistance's severity is measured by the number of drugs and classes to which an individual did not respond. Souery (1999) proposed another model where the number and duration of antidepressants evaluated the levels.

Fava (2003), on the other hand, suggested yet another based on a continuous variable to establish resistance.

Much controversy about what an adequate trial means and how many would be necessary to acknowledge this condition exists; nonetheless, those who do not respond to at least one antidepressant trial with sufficient dose and duration are considered resistant to treatment. Reduction in 50% in symptoms severity defines responsiveness in this group, whereas remission is equivalent to having residual to no symptoms left (Gaynes et al., 2008; Mrazek et al., 2014; Tundo et al., 2015).

Besides being a challenge to patients and physicians, productivity costs tend to be more than double for patients with treatment-resistant depression when compared with those that are responsive to therapy (Ivanova et al., 2010). According to studies, TRD patients have only a 20% chance of remission during the treatment course, a 17% lifetime prevalence of suicide attempts. Such a burden is higher in teenagers. They also experience a much lower quality of life when compared to the ones that remit and three times more medical visits than the general population, which increases the health system's costs (Jaffe et al., 2019; Mrazek et al., 2014). It is also frequently associated with comorbidities (Peréez-Wehbea et al., 2014).

1.1.3 Repetitive Transcranial Magnetic Stimulation and Depression

There are currently various therapies available for MDD, characterized by efficacy or level of evidence. The Canadian Psychiatric Association (CANMET, 2016) divides treatments into psychological, pharmacological, neurostimulation, complementary and

alternative medicine. The selection of specific therapy is based on clinical presentation (symptoms and severity), age, comorbidities, previous response to a particular treatment, patient's preferences, tolerability, cost and availability, and potential interaction with other medications. There is repetitive transcranial magnetic stimulation (rTMS) among the neuromodulation options, which acts most likely by modulating functional connectivity in different brain networks involving long-term plasticity mechanisms (Liston et al., 2014).

Initial studies involving transcranial magnetic stimulation (TMS) started in 1985 (Barker et al., 1985), evolving to the use of repetitive pulses (Pascual-Leone et al., 1999) in the following decade with current many different delivery methods and applications, including in the psychiatric field (Aleman, 2013; Guo et al., 2017). Health Canada approved the technique in 2002, Food and Drug Administration (FDA) in 2008, and it is currently one of the options of patients suffering from TRD (Gaynes et al., 2014; Somani and Kar, 2019). Literature reviews and meta-analysis showed a good antidepressant response to low and high-frequency stimulation of the dorsolateral prefrontal cortex as monotherapy or augmentation (Berlim et al., 2013; Berlim et al., 2014; Bulteau et al., 2017; Blumberger et a.l, 2018).

1.2 Depression and Illness Perception

Studies regarding illness perception in patients with depression have increased over the years, some of which tried to structure specific tools to evaluate beliefs while others used broader-use questionnaires (Lynch, 2006; Manber, 2003; Addis, 1995;

Fortune, 2004). The majority of these studies opted for cross-sectional designs that do not allow proper causality association but have enlightened other correlation levels.

A study in a group of Israeli Arabs with minor and major depression found that negative cognitive (identity, consequences, cure/control, and timeline) and emotional depression representations were associated with low quality of life (Abo-Rass, 2020). Baines and Wittkowski (2013), in a systematic review, found that many studies described participants as having a high number of symptoms (identity) that would severely affect their lives (consequences), cyclical or not, but susceptible to be controlled. Chronic depression with adverse but controllable effects was associated with more effective coping mechanisms.

In many Hispanics, individuals with depression perceived their condition as severe and debilitating and chronic or cyclical. (Cabassa, 2008; Zayas, 2011). Also, participants who saw depression as chronic did not believe they could control it by personal effort or medication (Cabassa, 2008). Similar findings were observed in a group of women in the UK (Fortune, 2004). However, a group of patients from primary care practices in the US perceived their illness as more cyclical, controllable, and only half identified it as a severe condition (Brown, 2007).

A study comparing a group of black African and white British women in London showed that the former would see their depression as less severe, with short duration and fewer symptoms than the latter (Brown, 2011), explaining the cultural influence over illness perceptions.

Patients' reasons for their depressive state can also be crucial to treatment success; however, causes can become more independent of an individual's mood with longer episodes of depression (Addis, 1995). Despite this, the most commonly described causes of depression by patients were stress, hereditary, other physical comorbidities, relationships, and personal behavior (Baines, 2013). Another study reported stress and interpersonal relationships as leading causes (Brown, 2007). Bann et al. (2004), evaluating a group of participants in a Hypericum Perforatum (St. John's Wort) in an MDD trial, found that most individuals gave psychological reasons instead of biological or alternative to their depression. Internal locus options were not associated with change over time in MDD severity, but external locus was associated with more severe depression at baseline, less improvement, and previous use of antidepressants. In another study, participants who believed 'interpersonal conflict' to be the reason for their depression were more prone to have work and social/leisure functioning affected (Addis, 1995).

When comparing different perspectives among sexes, Read et al. (2015) identified in their sample that men were more likely to report work-related stress as a cause of their depression, whereas women were more prone to correlate to family-related pressure. However, most participants had chemical imbalance as the primary causal attribution.

A Canadian study evaluating causes for depression in a sample of 10 South Asian women in Toronto found a personal socio-cultural model for its etiology, including family, relationships, culture, migration, and socioeconomic status (Ekanayake, 2012). In a

Swedish study (Hansson, 2010), a sample of participants with MDD stated stress associated first with work and then with family as the leading causes for their depression, followed by personality. As Read and colleagues (2015) mentioned, family affairs were more endorsed by women and work stress by males. Biological causes were seldom mentioned (Hansson, 2010).

Illness perception of patients presenting bipolar disorder has been studied in an attempt to understand its correlation to and influence over patient's adherence to treatment since the lack of proper treatment adherence has been reported as one primary concern associated with increased risk of recurrence and hospitalization (Gianfrancesco et al., 2009).

A French study (Averous et al., 2018) analyzing 38 patients with bipolar disorders and major depressive disorder found that participants that perceived themselves as having a coherent understanding of their condition were more likely to adhere to the treatment proposed, and that emotional representation and perceived control by the treatment would work as predictors of this adherence. This study also identified three categories of causal attributions labeled environmental factors as stress, trauma, death, and family problems; biological functioning (chemical imbalance); and psychological functioning, including thinking process, personality, and own behavior. The first group was considered less adherent.

As expected, researchers evolved their questions related to illness beliefs and investigated the relationship between these representations and outcomes. Lobban and colleagues (2013) studied a UK sample of 91 patients, mainly with bipolar type I not during

an active episode, to understand their perception regarding their mood swings and their association with clinical outcomes in a few longitudinal studies in this area. They found that severe consequences and low personal control were linked to higher levels of depression and increased severity of these symptoms over time.

In an English population of patients with schizophrenia, researchers found that perceived high identity, a chronic timeline, severe consequences, and a sense of lack of control over symptoms were associated with increased levels of depression, anxiety, and low self-esteem. The most common attributable cause, state of mind, showed a correlation with anxiety, while stress was associated with lower self-esteem (Watson et al., 2006).

Researchers investigated the relation between perception with psychosocial adaptation in a sample of 98 Spanish females with different eating disorders (Marcos, 2007). Most patients with anorexia nervosa would see their illness as controllable and treatable but highly distressful, causing many life consequences and lasting an extended period. Patients with bulimia nervosa saw their symptoms as being more cyclical when compared to AN's patients. Participants that would see their condition as more controllable would also believe in the bigger chances of cure, similar to the previous study (Holliday et al., 2005). In the same year, another study (Stockford et al., 2007) also addressing patients with these same conditions in the UK found results suggestive that depression in these populations was associated with perceived severe consequences, not treatable or low personal control, again congruent with previous findings (Holliday et al., 2005).

When comparing the presence of depression in two groups of subjects with rheumatoid arthritis and how their illness perception would differ, Murphy et al. (1999) found that depressed patients saw that their condition affected more seriously their lives (consequences), they were less able to control their symptoms and saw it as not curable. Overall, higher scores on the Hospital Anxiety and Depression questionnaire were associated with more negative rheumatoid arthritis views. Sharpe and colleagues (2000) performed a longitudinal study comparing patients that were recently diagnosed with the same condition and received different treatments with follow-ups for 21 months. Overall, disability, pain, anxiety, identity, and Ritchie Articular Index scores were associated with mood. Articular scores improved over time, but not the mood, suggesting a dissociation between physical and mental parameters.

According to a study evaluating illness perceptions and worry in a population of patients with psoriasis, the most common attributed causes were stress, genetics, and patient's state of mind. Worry was strongly related to high consequences, intense emotional representations, and an increased number of symptoms in a chronic setting with recurring episodes. Pathological fear was higher in the female representatives of this sample and correlated to more severe consequences and causes, associated by participants with emotional weakness (Fortune et al., 2000).

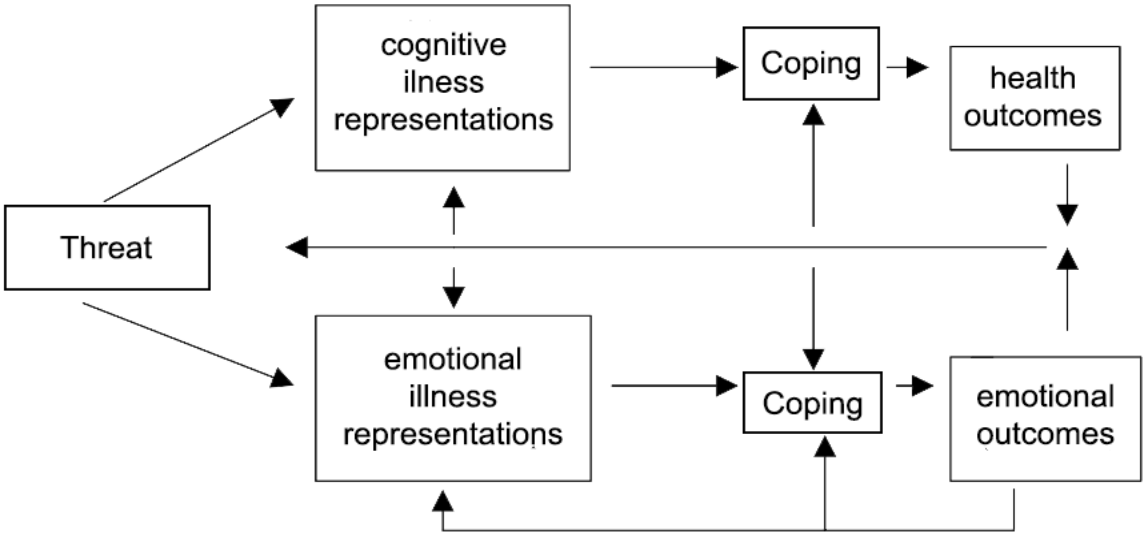
Patients with chronic fatigue syndrome presented with high identity and consequences profiles, and both dimensions were predictors of fatigue levels. In this sample, high identity, severe consequences, chronic duration, and emotional attribution were associated with depression and anxiety, although his sample had less than one-

third of participants scoring for both illnesses when applying the Hospital Anxiety and Depression scale (Edwards, 2001). Currently, to our knowledge, there are no studies of illness perception in TRD patients correlating beliefs to depression scores or disability levels.

1.3 Self-Regulation Models and Illness Perception

In the last forty years, many have discussed beliefs and perception, and ultimately how they influence a patient's behavior toward an illness. Over time, different models emerged to explain the basic structure of how emotional responses can relate to and act in motivational systems. The central concept of some of these models is based on parallel processing, in which problem-focused goals occur in parallel to emotion-focused ones to solve an objective health problem or emotional distress. Some of these models embrace a more general behavior approach, like the stress-coping model (Lazarus and Folkman, 1984), the hierarchical organization of goals (Carver and Scheier, 1998), the self-discrepancy theory (Higgins, 1987), and the regulatory focus theory (Higgins, 1998) which uses the self-regulatory system. Like the Common-Sense Model (Leventhal, 1980), others define a point of view that is specific to illness perception and how it regulates behavior (figure 1). Independent of the model, all work to understand that an individual ultimately aims at desired outcomes and avoids undesired ones (Higgins, 1998).

Figure 1. Levental's Common-Sense Model (1980)



Self-regulation models most likely will entail the dynamic elements of feedback, motivation, and goal pursuit (Cameron and Leventhal, 2003). One of the most straightforward definitions of "self" is found in the Merriam-Webster dictionary, "the conjunction of emotions, thoughts, body, and sensations that compose a person's identity." Cantor and Kihlstrom (1987) added to this concept that each individual has many interconnected self-representations that fuse to generate strategies to achieve goals, positive reference values. The most primitive goals are survival and coherence. Ultimately, humans need to establish ways to survive daily threats. They also need to understand and create logical pathways to ensure continuity (Cameron and Leventhal, 2003); illness experiences can threaten both. The elaboration of these goals moves from

a conceptual to a practical level where the latter is more emotionally evocative and can strongly influence behavior (Brownlee et al., 2000). Abstract goals are broad (e.g., be healthy), while experimental goals are more specific (e.g., eat vegetables daily) than these, and both are necessary to the individual's success. More concrete goals are critical in elaborating a palpable representation of the illness and establishing a feasible action plan. It is only until a goal has a personal meaning that it can alter behavior (Kuhl, 2000) (Sheier and Carver, 2003). This personal meaning could be designed by the fear or distress generated by the threat, leading to the need to manage the emotions and control the danger (Leventhal, 1970).

It is essential to understand that patients are active participants in understanding and regulating their medical situation, even though there can be a significant difference between perception and ability to plan and cope with the threat. Good preparation while experiencing a distressful situation like an illness depends, in part, on the patient's ability to interpret the cues and establish good coping strategies (Leventhal et al., 1980). Perhaps a patient who, for example, has experienced trauma during infancy (while not formally prepared for that situation) may elicit different perceptions and different coping mechanisms or even responsiveness to treatment. Although early life experiences have heavyweight in these scenarios, other conditions could be characterized as trauma by someone at any point of life (considering the readiness or not of an individual to a particular occurrence). Patients tend to elaborate their illness theory based on their body experience (signs and symptoms), associating this with information from the social environment and past personal experiences. Researchers suggested that depression

would be generated from a weak motivational response towards goals representing their ideal self (Strauman, 1992).

Illness representation can change with time or procedures for preventing and moderating the disease; additionally, it is highly influenced by social interactions. It is noticeable that the longer one lives with a condition, the more likely they are to find a symptom to represent and label their illness. Time has also played different roles within patients' representations and could vary from acute to cyclic to chronic manifestation. There is a tendency to associate acute episodes to more specific symptoms and situations, whereas cyclic episodes are related to random or repetitive symptoms and a chronic manifestation with long-term symptoms and attributional causes like heritage and age (Leventhal, 1980).

Besides identifying the label/identity of illnesses, Penrod (1980) also defined three other domains: consequences/severity, timeline/duration, and cause. Bishop (1991) added cure/controllability to the list. Leventhal et al. (2003) also mentioned that these representations serve as a guide to elaborating goals for self-management and feedback procedures for response evaluation.

Identity refers to symptoms that patients experience and that are used to label the disease from their perspective. For example, patient M. has depression and feels like low mood represents his condition, whereas psychomotor retardation is not so much. Patient D., however, feels exactly the opposite. Both patients have the same illness, but they experience symptoms differently. Consequences point to the perception patients have of how much these symptoms interfere in their lives. Timeline corresponds to their feeling

of duration, which can be, as mentioned above, acute, cyclical, or chronic. Causes entail identifying possible reasons for the illness, which do not necessarily have a scientific base. Cure/control, on the other hand, involves the sense of action over the condition and can be directed towards the own individual or their treatment plan.

1.3.1 Instruments for the Evaluation of the Common-Sense Model

During the development of a self-regulation model, Leventhal and colleagues used semi-structured interviews to analyze different groups of patients, which can be time-consuming and strenuous, generating a more considerable variability between answers, making it difficult to measure them (Leventhal et al., 1980). Other authors (Broadbent et al., 2006; Lobban et al., 2005; Lynch et al., 2011; Manber et al., 2003; Moss-Morris et al., 2002; Weinman et al., 1996) developed questionnaires in an attempt to objectify the relations between perceived dimensions and clinical illnesses characteristics.

The first of this series of instruments, the illness perception questionnaire (IPQ), was based on seven different groups of patients with distinct diseases (diabetes mellitus, rheumatoid arthritis, renal insufficiency, asthma, chronic fatigue syndrome, chronic pain, myocardial infarction). The scale assessed identity, cause, timeline, consequences, and control/cure. Identity items could be adjusted according to the disease being appraised, considering that they reflect symptoms patients identify with their illness. Items would vary from "strongly agree" to "strongly disagree", ranging from one to five. Two dimensions, 'consequences' and 'cure/control', had higher test-retest reliability levels compared with 'identity' and 'timeline', as expected by the authors. An excellent initial internal consistency

and test-retest reliability were achieved, although establishing psychometric status and providing normative data to different populations, more information was necessary (Weinman et al., 1996).

Some remodeling was necessary, especially regarding cure/control and timeline sub-scales, which had lower internal consistency. Also, emotional representation needed to be addressed since only cognitive dimensions had been appraised so far (Moss-Morris et al., 2002). The Illness Perception Questionnaire was then revised to gauge and improve the aspects mentioned above. Eight groups of New Zealand and the United Kingdom participants comprehending distinct diseases were assessed (asthma, diabetes, rheumatoid arthritis, chronic and acute pain, myocardial infarction, multiple sclerosis, and HIV totaling 711 participants).

The Illness Perception Questionnaire-Revised (IPQ-R) was elaborated and currently consists of identity, consequences, timeline acute/chronic, timeline cyclical, coherence, emotional representation, and causal attribution sub-scales rated in a 5-point Likert type (strongly disagree, disagree, neither agree nor disagree, agree and strongly agree). The last one, causal attributions, was divided into psychological, risk factors, immunity, and accident/change attributions (Moss-Morris et al., 2002). This questionnaire demonstrated good internal reliability, which was analyzed using two principal component analyses for most scales and paired sample t-test for the identity part. Overall, the inter-correlation between dimensions showed that identity was positively associated with psychological and immune attributions, personal and treatment control, and coherence. Timeline and coherence were both negatively related to individual and treatment control.

Beliefs that the illness presentation was severe were associated with a chronic than cyclical timeline. Risk factors were associated with a sense of understanding, opposite to chance attributions. Test-retest reliability showed consistent results over 3-week and 6-month periods, with attributional beliefs being the most consistent. Discriminant validity was assessed by correlating dimensions and the Positive and Negative Affective Schedule expressing low to moderate responses. The authors also compared chronic and acute groups retrieving different and compelling results for all measurements (Moss-Morris et al., 2002).

Despite being a reliable tool to address illness beliefs based on Leventhal's self-regulatory model, the length of the questionnaire, with over 80 items, was not practical in situations where there was limited time to answer the questions or too many other assessments to be done. Having this in mind, Broadbent and colleagues (2006) proposed a shorter version, the Brief Illness Perception Questionnaire (BIPQ).

The BIPQ consists of 9 items contemplating the following dimensions: identity, consequences, concern, timeline, emotional representation, causes, treatment control, personal control, and coherence. The first five items range from 0 to 10, increasing with severity, whereas the final three decreases with intensity. They are anchored on the extremes of range with words like "not at all" and "extremely". The item "causes" is a subjective component, where participants are asked to rank the three most important causes of their illness. The psychometric properties were studied in six illness groups (renal disease, type 2 diabetes, asthma, minor diseases like allergies, colds or headaches, and a group of patients with chest pain during stress-exercise testing) totaling

just above one thousand participants from New Zealand and the United Kingdom. The test-retest reliability was studied with participants from the renal disease group, which had follow-ups after 3 or 6 weeks, with good reliability for both periods. The concurrent validity was assessed comparing BIPQ and IPQ-R answers by participants from the renal, diabetes, and asthma groups. Personal and treatment control showed low correlations, requiring further assessment, which was done by comparing the BIPQ results to self-efficacy scales, HbA1c (this last one on the diabetes sample), and asthma morbidity and beliefs about medications, then obtaining favorable results. In terms of predictive capability, higher identity scores anticipated presence in rehabilitation classes after discharge in patients with MI, while more profound concern and treatment control perceptions were associated with a slower return to work. The discriminant validity was attested by significant differences between the study groups (Broadbent et al., 2006).

Adaptations and new questionnaires assessed the perception of specific conditions like schizophrenia (Lobban et al., 2005) and depression, but none was as objective as BIPQ. In 2011, Lynch and colleagues developed a tool called the Beliefs about Depression Questionnaire, consisting of fifty-one items addressing the original five CMS dimensions. Manber and colleagues (2003) developed a questionnaire based on Leventhal's SRM called the Perception of Depressive Illness Questionnaire. The questionnaire was divided into three lists totaling 63 items rated on a four-point scale ("not at all", "somewhat", "quite a bit", "very much so"). Items from the Perception of Depressive Illness Questionnaire had good test-retest reliability; however, they could not add significant variance to predict treatment response. Despite this, the authors highlighted

the use of the scale relative to treatment preference and adherence, as well as patient's expectations (Manber et al., 2003).

1.4 Aims

1. To characterize perception of the severity of symptoms (identity) and life interference (consequences) in a sample of patients with treatment-resistant depression and compare to depression in patients with other chronic conditions and previous reports on patients with primary depression.

2. To characterize illness perception changes over time in TRD patients receiving rTMS.

3. To explore the relationship between illness perceptions, symptoms, and level of functioning.

1.5 Hypotheses

1. Patients with treatment-resistant depression will show more negative identity and consequences perception than patients with depression and not resistant to treatment and patients with other chronic conditions.

2. rTMS treatment will not be associated to changes in illness perception

3. TRD patients who have higher negative illness perception will be less likely to improve in symptoms and functioning.

1.6 Thesis Organization

The thesis is organized as follows: Chapter 1 introduces the background of depression, its correlation with illness perception and self-regulatory models. Chapter 2 entails the methodology for collecting, processing and analyzing research data. Chapter 3 demonstrates the results and chapter 4 discusses the highlights and limitations of our study, besides the conclusion and future recommendations.

Chapter 2: Data and Methods

2.1 Introduction of the study

This analysis was derived from a non-inferiority randomized trial (Blumberger et al., 2018) which compared the efficacy of intermittent theta-burst stimulation (iTBS) with conventional repetitive transcranial magnetic stimulation (rTMS) in a sample of patients with treatment-resistant depression. Patients had their diagnosis initially confirmed by psychiatrists before receiving an offer to participate in the study. Once the clinical raters assessed all inclusion and exclusion criteria, participants were ready to continue to baseline, randomization, and treatment. Clinical outcome measures, among them illness perceptions, were assessed at baseline, weekly during the acute treatment phase, and after finishing treatment at weeks 1, 4, and 12. Demographic data consisting of age, sex, marital status, the highest level of education, employment status was also collected during screening.

The projects were registered on www.clinicaltrials.gov (identifier NCT01887782 and NCT02800226 and approved by the Clinical Research Ethics Board of the University of British Columbia and Vancouver Coastal Health Authority. Participants were requested to sign an informed consent form at the screening.

2.2 Methods

2.2.1 Participants and experimental procedures

Participants were outpatients between 18 and 65 years who had not achieved good responsiveness to at least one adequate antidepressant trial. They also had no contraindication to receive rTMS. Minimal scores on the Hamilton rating scale for depression (HRSD-17) were 18. The patient needed to adhere to the treatment schedule, and if in use of psychiatric drugs, doses had to be stable for the four weeks previous to rTMS treatment to be included in the trial.

They would not be accepted if: they had any lifetime history of bipolar or schizophrenic spectrum disorders, active psychotic symptoms, unstable medical condition, any other psychiatric condition that would be more prominent than depression, active suicidal intent, were pregnant, had failed electroconvulsive therapy or more than three adequate antidepressant trials in the current depressive episode, were taking more than 2mg daily of lorazepam or any correspondent anxiolytic, had engaged in psychotherapy in the last three months or had not a stable course of it, had any safety concerns regarding rTMS or magnetic resonance imaging.

There were three groups: one receiving 37.5 minutes excitatory, 10 Hz stimulation (conventional) rTMS, another receiving 3 minutes iTBS, both on the left dorsolateral prefrontal cortex for 4 to 6 weeks, and the third group to control for demographic information.

2.2.2 Clinical Outcome Measures

Measurements used in this thesis were retrieved at baseline, before the start of treatment, and after rTMS treatment. Clinical raters were blinded to treatment allocation.

Brief Illness Perception Questionnaire (BIPQ)

As mentioned in chapter 1, BIPQ is a self-reported questionnaire with eight objective items assessing these dimensions: identity (severity of experienced symptoms), consequences (how symptoms have affected their lives), timeline (how long they believe their symptoms will last), understanding/coherence (how much they feel patients understand their depression), personal and treatment control (how much they believe they and the treatment can control their symptoms), concern (how preoccupied they are about their illness) and emotions (how depression has affected them emotionally). Items range from 0 to 10 and are anchored at the extremes by words like 'not at all' and 'extremely'. One more item elicits the three leading perceived causes of the illness in a ranked order.

Hamilton Rating Scale for Depression (HRSD-17)

HRSD-17 is a 17-item scale ranging from 0 to 52 points divided into five categories: no depression (0-7 scores), mild depression (8-13 scores), moderate depression (14-18 scores), severe depression (19-22 scores) and very severe (>=23 scores) (Rush et al., 2009; Hamilton, 1960). Participants needed to present with at least a moderate depressive episode. Those who achieved at least a 30% decrease in depressive symptoms assessed by HRSD-17 at week four were considered initial responders and

were rendered additional two weeks of treatment. Subjects with at least a 50% decrease in HRSD-17 scores by the end of 6 weeks of treatment were considered final responders, while those with score ≤ seven scores were classified as remitters.

During data analysis, factors previously established in the literature (Shafer, 2006) were used to correlate similar symptoms with dimensions. They were labeled here as 'depression' (depressed mood, suicide, guilt, retardation, work, and interests), 'anxiety' (anxiety, psychic agitation, anxiety somatic, hypochondriasis, loss of insight), 'insomnia' (insomnia middle, initial and delayed) and 'somatic' (gastrointestinal, general somatic, lost weight and libido loss).

Sheehan Disability Scale

Sheehan Disability Scale (SDS), also known as discretized analog disability scale, is a short cost-effective measurement developed to assess functional impairment in patients with psychiatric conditions (Sheehan, 1983). It can be patient-rated or clinician-rated, but it was used as a self-assessment tool in this study.

It contains five questions, three regarding disruption of social life, work or school activities, family life or home responsibilities by the presence of symptoms, and two concerning the number of days in the last thirty that the person missed school/work or daily activities and a second one for the individuals that went but were not able to function as before (Sheehan et al., 1996). For the first set of questions, answers were structured from 0 to 10 and anchored by groups of three except for the extremes. There is no cut-

off score, but scores above five in any of these questions are associated with high functional impairment.

2.3 Statistical Analysis

2.3.1 Analyses of Illness Perceptions Characteristics

A descriptive analysis of demographic information, BIPQ dimensions, HRSD-17, and SDS scores were executed to create a participants' profile.

Pearson's and Spearman's correlations were selected to evaluate the associations between beliefs dimensions. The choice of statistic test used was based on the sample distribution of the variables.

Qualitative data were analyzed using a clustered function of NVIVO® software, which categorizes variables by word similarity. Each participant's response was added as a new variable and clustered. After NVIVO® generated the groups, two researchers verified them. Most of the clustered answers had one word in common; however, some presented in different contexts. Because of this, some were reorganized manually. Also, words that formed smaller clusters due to low similarity with other groups were evaluated individually and added to larger groups according to its definition. Later, these larger groups were divided into two categories of answers, intrinsic, when associated with responses within the individual, or extrinsic, when the cause was external. Attributed causes were also evaluated, comparing groups divided by sex and responsiveness to rTMS treatment.

2.3.2 Analyses of Illness Perceptions Modification After Treatment

Two-sample T-tests were computed to interrogate differences in perceptions by types of treatments. Paired T-tests were used to compare changes in illness perceptions over time overall, in responders and in non-responders individually. Rainclouds were used to visualize individual trajectories when comparing changes in perceptions of responders and non-responders over time.

Treatment response was defined as 50% or more decrease in HRSD-17 depression scores as per standard criterion used in clinical trials for depression (Rush et al., 2006; Blumberger et al. 2018).

2.3.3 Analyses of the Interaction Between Illness Perceptions, Depressive Symptoms and Functioning

Correlation analyses between illness perception, HRSD-17 and SDS scores were computed to investigate the degree of collinearity between instruments and construct validity.

Changes in HRSD-17 were computed as follows ($HRDS_{baseline}$ – $HRDS_{follow\ up}$ = Change in symptoms; positive values indicate improvement). Changes in SDS scores were computed as follows ($SDS_{baseline}$ – $SDS_{follow\ up}$ = Change in functioning; positive values indicate improvement). These deltas were used as dependent variables in their correspondent regression models.

Pearson's and Spearman's correlations were used to evaluate associations between changes in HRSD-17 total scores, its factors, SDS subitems, and other

variables, including BIPQ dimensions. Statistically significant correlations were added to a regression model. Variance in HRSD-17 and SDS scores was considered outcomes while BIPQ dimensions, among the other variables that presented a significant correlation level previously, were used as independent variables.

Two-sample T-tests were applied to verify differences in HRSD-17 scores and SDS scores in responders and non-responders, males and females, by types of treatments, marital status, employment status, presence of comorbidity, and attributable causes (intrinsic or extrinsic) to evaluate the importance of these variables on the regression model. Bonferroni and Holm corrections calculation were considered to adjust multiple T-tests.

Multiple linear regressions were administered to analyze if illness perception could even partially explain the changes in depression and disability scores. Stepwise fitting model or sequential replacement, an automatic procedure executed by R software that uses a combination of forwarding and backward selections, was chosen.

Quantitative data were therefore analyzed using R statistical software® (Foundation for Statistical Computing, Vienna, Austria).

Chapter 3: Tables, Figures, Illustrations and Graphics

3.1 Characterizing Illness Perception in TRD Patients

3.1.1 Demographic and Clinical Characteristics of the Sample

Sixty-two patients passed screening and were assessed at baseline. From these, two did not provide BIPQ responses at that point and were excluded, leaving an initial sample of 60 participants. During treatment, five individuals withdrew participation totaling 55 individuals by the end of this period. The majority of this group was composed of middle-aged white females, single, divorced or separated. Almost half of the sample was working at that point, while the other 51.7% could not (table 1).

Table.1 Demographics

Total number of patients	n= 60
Age (years), Mean (SD)	43.1 (12.2)
Female, n (%)	34 (56.7)
Marital Status, n (%)	
Single	24 (40.0)
Divorced or Separated	12 (20.0)
Married or in a Domestic partnership	24 (40.0)
Employment Status, n (%)	
Working/Studying	27 (45.0)
Not Working (disabled, temporary laid off, unemployed, retired, on assistance)	31 (51.7)
Unknown	2 (3.3)

Ethnicity, n (%)	
White	43 (71.7)
Chinese	3 (5.0)
South Asian	2 (3.3)
East Asian	1 (1.7)
Black	1 (1.7)
Jewish	1 (1.7)
Other	7 (11.7)
Prefer not to answer	1 (1.7)
Unknown	1 (1.7)

The average onset of MDD in this sample was around the mid-'20s, and the time they had been experiencing depression reaching almost twenty years, with the current episode lasting approximately two years. Almost half of the participants listed at least one comorbidity with anxiety disorders accounting for most of these. Other conditions listed were dysthymia, post-traumatic stress disorder (PTSD), alcohol/substance abuse, personality traits, bulimia, fibromyalgia, and restless leg syndrome.

At baseline, the HRSD-17 score average was 22.1, which is classified as severe depression. By the end of treatment, the mean score was 9.9, shifting to mild depression instead; above half of the participants achieved at least 30% of improvement after receiving rTMS, while 43.1% ended treatment with minimal to no symptoms. Disability scores at baseline were higher at baseline and presented a significant drop after 18 weeks (table 2).

Table 2. Clinical Characteristics

Duration of Illness, Mean (SD)	17.6 (11.7)
Age of Onset, Mean (SD)	25.7 (12.4)
Duration of Current Episode - Months, Median (Range)	24 (8, 240)
Presence of Psychiatric Comorbidities n (%)	29 (48.3)
Listed Comorbidities (n)	
GAD/ Panic Disorder/Social Anxiety Disorder	20
Dysthymia	5
PTSD	4
Personality Traits	3
Alcohol or Substance Abuse Disorder	3
Bulimia	2
Fibromyalgia	1
Restless Leg Syndrome	1
HRSD-17[a] *at* Baseline, Mean (SD)	22.2 (4.0)
HRSD-17 After rTMS, Mean (SD)	9.9 (6.7)
Responder [b], n (%)	32 (53.3)
Remitter [c], n (%)	25 (41.7)
SDS at Baseline and After 18 Weeks	
Impaired Social Life, Mean (SD)	8.1 (1.7) / 4.7 (2.9)
Impaired Family Life, Mean (SD)	7.4 (2.1) / 4.7 (3.1)
Impaired Work/School Life, Mean (SD)	7.8 (2.6) / 4.9 (3.6)
Days Missed of Work/School, Mean (SD)	13.5 (12.5) / 9.2 (12.3)
Days with Reduced Productivity, Mean (SD)	18.3(11.0) / 9.2 (12.1)

[a] Total of 18 or above on the Hamilton Rating Scale for Depression 17-item at baseline was required to enter the study
[b] 50% decrease at end of TMS compared to baseline
[c] Total of 7 or below at end of TMS

3.1.2 Cognitive and Emotional Dimensions' Profile in Treatment-Resistant Depression

Patients presenting with treatment-resistant depression in this sample expressed beliefs that symptoms were very much present and bothersome, generating a great disturbance in their life and their emotions, which would cause great concern. They also reported that the depression would last for a long time, if not forever, as demonstrated in figure 2. As represented by the histograms, all participants graded their concern, emotions, consequences, timeline, and identity above the midline, with the majority above score 7, placing their beliefs in a very high category. However, personal control had significant variance, not being able to establish a harmonic distribution. Most patients were unsure of the efficacy of treatment, although tending to a more positive approach, similar to their ability to understand their symptoms.

Overall, most correlations were positive with almost no negative associations. The most robust connections found were between identity and consequences (0.71), consequences and concern (0.58), emotions and consequences (0.58), and concern and identity (0.48). These suggest that participants perceiving more symptoms also sensed severe consequences in their lives, more emotions affected, and more concern about their depression (Table 3).

Figure 2. Illness Perceptions' Distributions in Patients with Treatment Resistant Depression

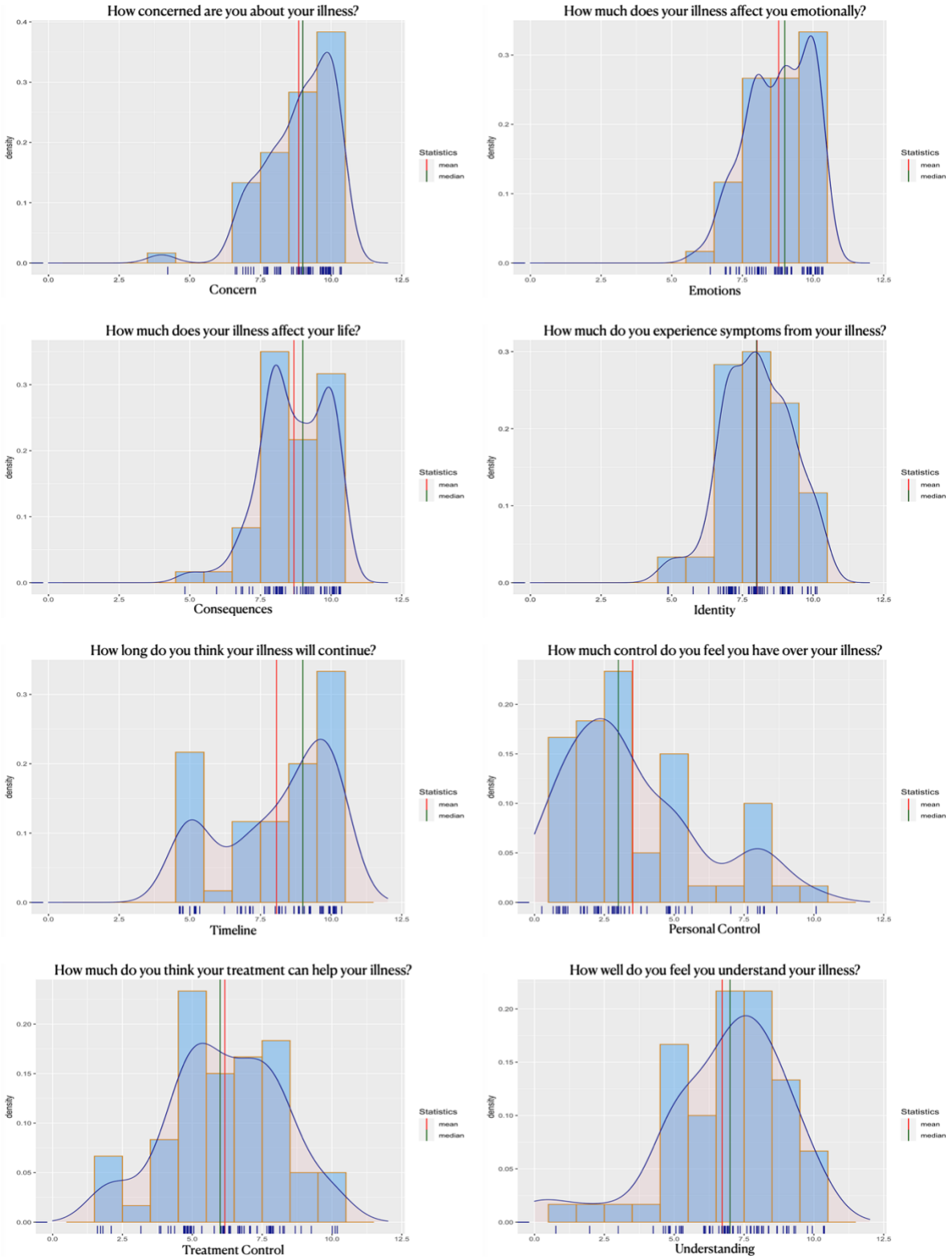


Table 3. Matrix Correlation Between BIPQ Dimensions at Baseline

	1	2	3	4	5	6	7	8
1 Emotions	1	**0.49*** **	**0.58*** **	**0.33***	**0.37****	-0.02	-0.10	-0.01
2 Identity		1	**0.71*** **	**0.48*** **	**0.30***	0.13	-0.02	0.03
3 Consequences			1	**0.58*** **	**0.33***	-0.05	0.06	-0.07
4 Concern				1	0.23	0.04	0.08	0.00
5 Timeline					1	0.05	0.05	0.00
6 Treatment Control						1	**0.28***	0.06
7 Personal Control							1	-0.10
8 Understanding								1

* < .05 ** < .01 *** < .001

3.1.3 Causal Attributions of Depression in Treatment-Resistant Depression

BIPQ requested to participants three perceived causes of depression, which were to be ranked according to the level of importance given by them. As mentioned in chapter 2, participants' answers were classified by word similarity and clustered by NVIVO® software. These clustered categories were then rearranged by two of the researchers into smaller groups generating subcategories. Since groups created by this classification were too small to participate in quantitative analyses, a division into two more comprising categories: 'intrinsic' for causes within the patient and 'extrinsic' for the external ones, was executed. Perceived causes dichotomic classification was used to calculate causes associations with other variables.

All 60 participants provided at least one answer to the BIPQ question. Fifty-five of them contributed with all three ranked causes, five listed only two, and five others only

one, totaling 164 answers. Eleven categories emerged: 'life stressors', 'genetic', 'trauma', 'existential concerns', 'chemical imbalance', 'personality', 'cognitive process', 'other biological factors', 'behaviour' and 'unknown'. While most categories were established in a very linear way, the latest to be labeled, 'pathological process', was chosen when answers did not fit any other group and would contain characteristics of depression itself. Examples of the answers given by a sample of the participants can be found in table 4.

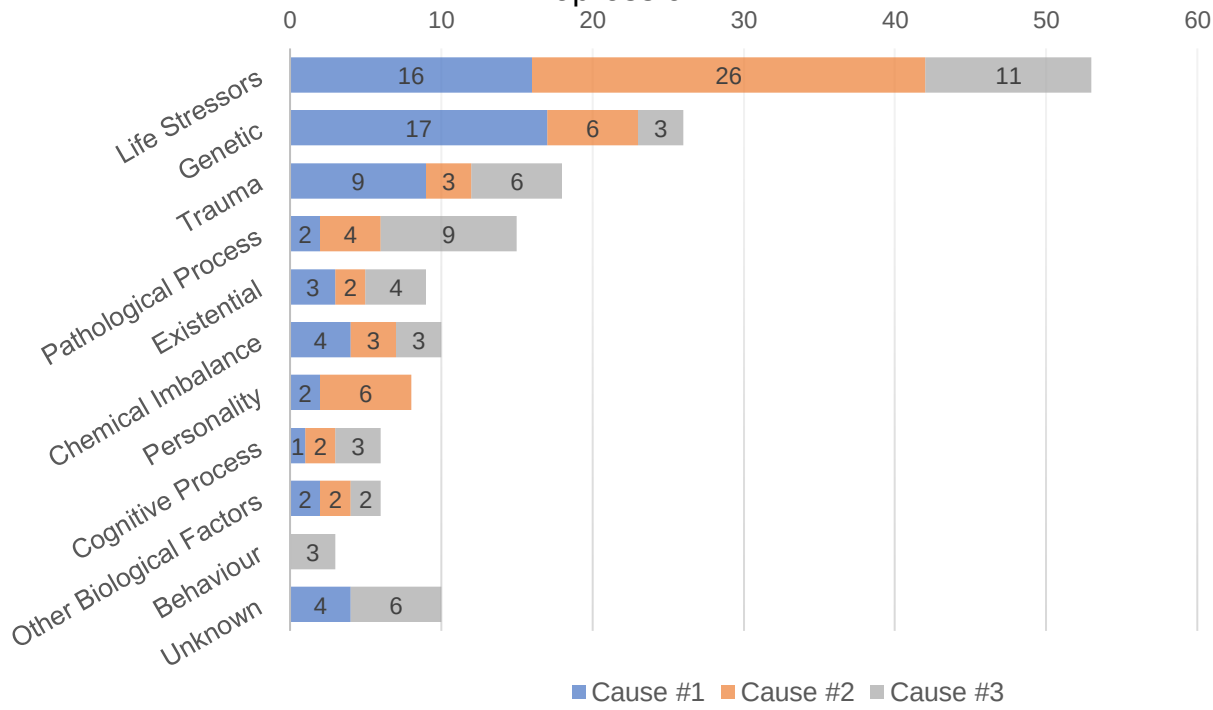
Table 4. Perceived Causes of Depression and Clusters

Example of Answers	**Classification**	
Divorce Job loss Death of a parent Relationship issues Financial setbacks	Life Stressors	Extrinsic
Being sexually abused as a child Emotional trauma in childhood & adolescence Emotionally abusive relationships	Trauma	
Fate I feel different from others Isolation and loneliness	Existential	Intrinsic
Genetics Hereditary	Genetic	
Sense of failure Poor life skills Loss of identity and self-worth I feel hopeless	Pathological Process	
Cognitive processes/thinking Fears	Cognitive Process	
Lack of symptom treatment Late treatment Chemical imbalance	Chemical imbalance	

Other physical issues General health Menopause	Other Biological Factors	
Low self-esteem Lack of Confidence Perfectionism	Personality	
lifestyle factors (diet, nutrition, exercise, sleep, self-isolating) Choices	Behavior	

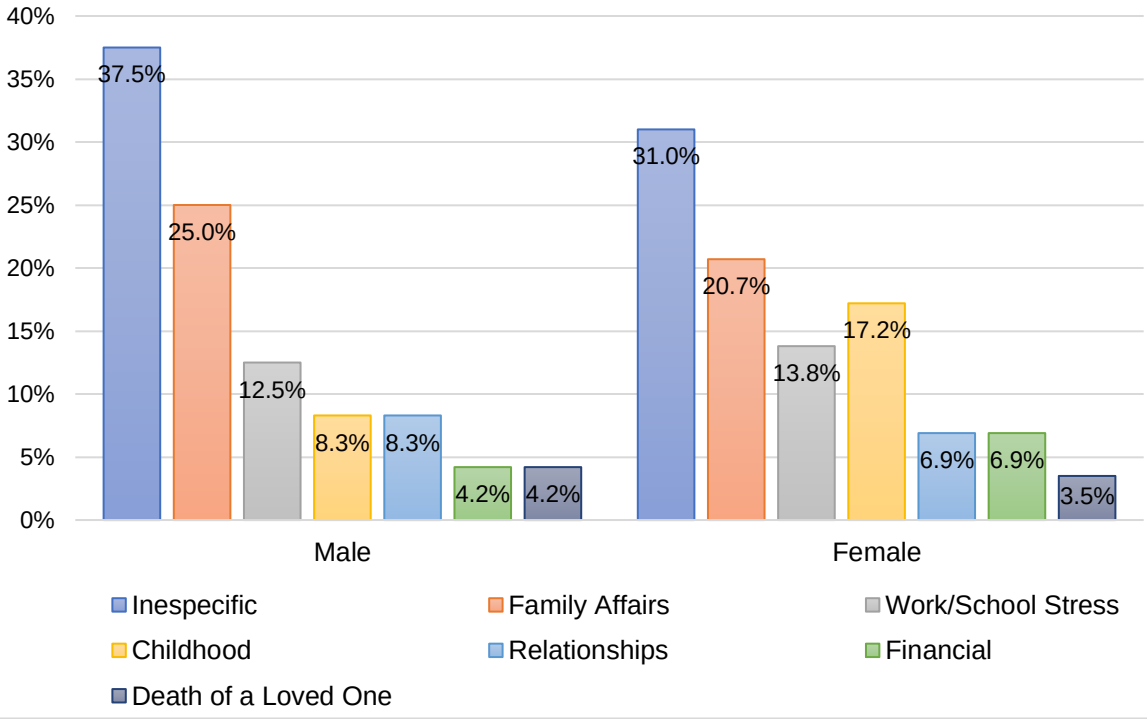
While 'life stressors', 'genetic' and 'trauma' were the leading perceived causes, 'cognitive process', 'other biological factors' and 'behavior' were listed the least. 'Life stressors' answers predominated, corresponding to 32.3% of all answers, which was more than double of the following group 'genetic' 15.9% (Figure 3).

Figure 3. Ranked Attributional Causes to Treatment Resistant Depression



Since 'life stressors' was the largest group, further stratification was carried out considering males and females. The majority of men chose general answers like 'life circumstances' to express themselves, similar to women. 'Family affairs' were second labeled life stressor by both sexes, but while for men work or school-related stress was the third more common life stressor associated with depression, for women childhood-related stress instead occupied the equivalent position, with more than double the frequency referred by men (Figure 4).

Figure 4. Types of Perceived Life Stressors Categorized by Sex

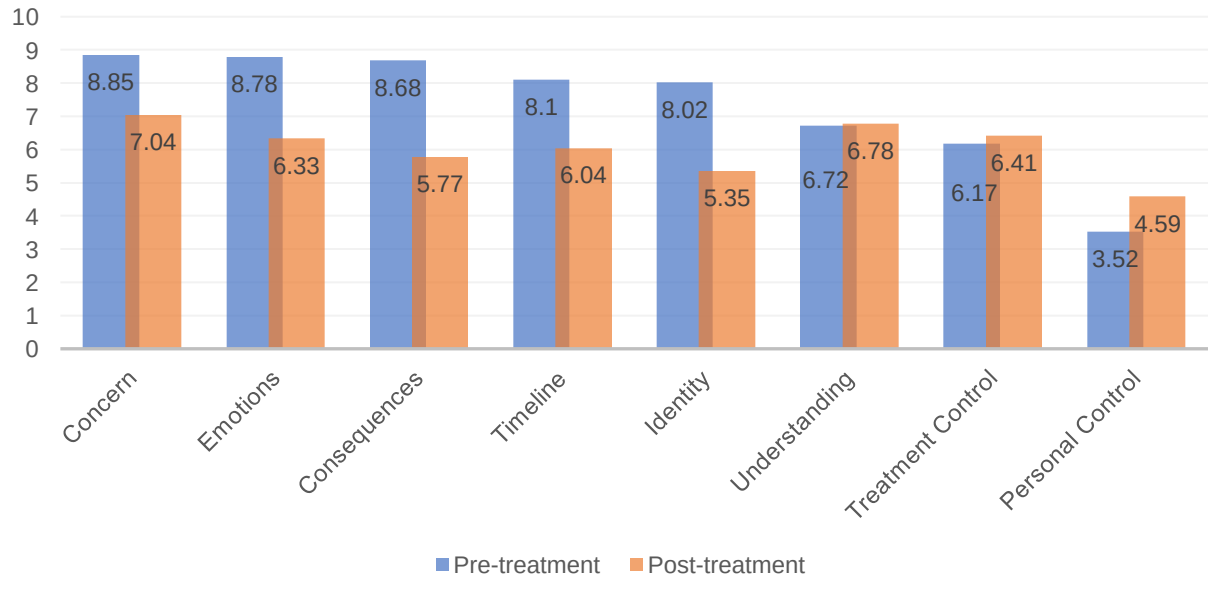


3.2 Modifications in Depression's Perceptions After Treatment

Dimensions averages and standard deviations (SD) at baseline and after treatment were compared and results showed that, before receiving rTMS, the majority of patients had a severe perception of their disease, with high mean scores for most of the dimensions, which indicated that they were experiencing a high number of symptoms that were concerning, affecting their lives and emotions bringing a feeling that these would not go away. Treatment control, personal control and understanding did not reach high scores, with most patients believing they had a moderate understanding of their depression but were not able to control it or were not sure if treatment would be helpful.

All dimensions presented with changes after treatment, although a paired T-test used to compare them could not initially identify differences between understanding and

Figure 5. Perceptions of Depression at Baseline and After Treatment



treatment control, resulting in an understanding that participants were perceiving fewer symptoms which were interfering less in their daily lives and mood, generating less concern and easing the perception of the duration of the depression (figure 5).

To further comprehend the influence of treatment on illness perception, patients were divided in responders and non-responders and compared inside groups. Almost all dimensions presented with change if the individual responded to rTMS, with the exception of treatment control. On the other hand, there was no evident change in non-responders for the majority of the beliefs, except for consequences and treatment control as demonstrated by the results in table 5. Individual trajectories of these changes divided by responsiveness can be visualized in figures 6.1, 6.2, 6.3 and 6.4. When analyzing information provided in these, it is clear that those who do not respond to rTMS also felt that symptoms were interfering somewhat less in their lives, but perception regarding the helpfulness of treatment had worsened when compared to previous beliefs.

Table 5. Difference Between in Dimensions Changes After Treatment in Responders and Non-Responders

	Responders			
	Mean of Differences	CI	T	P-value
Concern	2.44	1.57 - 3.30	5.76	**2.46e-06**
Emotions	2.81	1.83 - 3.79	5.86	**1.85e-06**
Consequences	3.34	2.25 - 4.44	6.24	**6.28e-07**
Timeline	2.41	1.32 - 3.49	4.53	**8.19e-05**
Identity	3.47	2.55 - 4.38	7.73	**1.03e-08**
Personal Control	-1.25	-2.36 - -0.14	-2.30	**0.029**
Treatment Control	-0.88	-1.89 - 0.14	-1.76	0.088
Understanding	-0.94	-1.69 - 0.19	-2.55	**0.016**
	Non-Responders			
	Mean of Differences	CI	T	P-value
Concern	0.63	-0.56 - 1.83	1.11	0.280
Emotions	0.58	-0.31 - 1.46	1.38	0.190
Consequences	1.63	0.65 - 2.61	3.50	**0.003**
Timeline	1.28	-0.18 - 2.73	1.85	0.081
Identity	0.79	-0.10 - 1.68	1.87	0.078
Personal Control	-0.63	-2.06 - 0.79	-0.93	0.363
Treatment Control	1.32	0.50 - 2.14	3.37	**0.003**
Understanding	0.00	-0.94 - 0.94	0.00	1.000

Figure 6.1 Changes in Concern and Emotions Over Time Distributed by Responsiveness

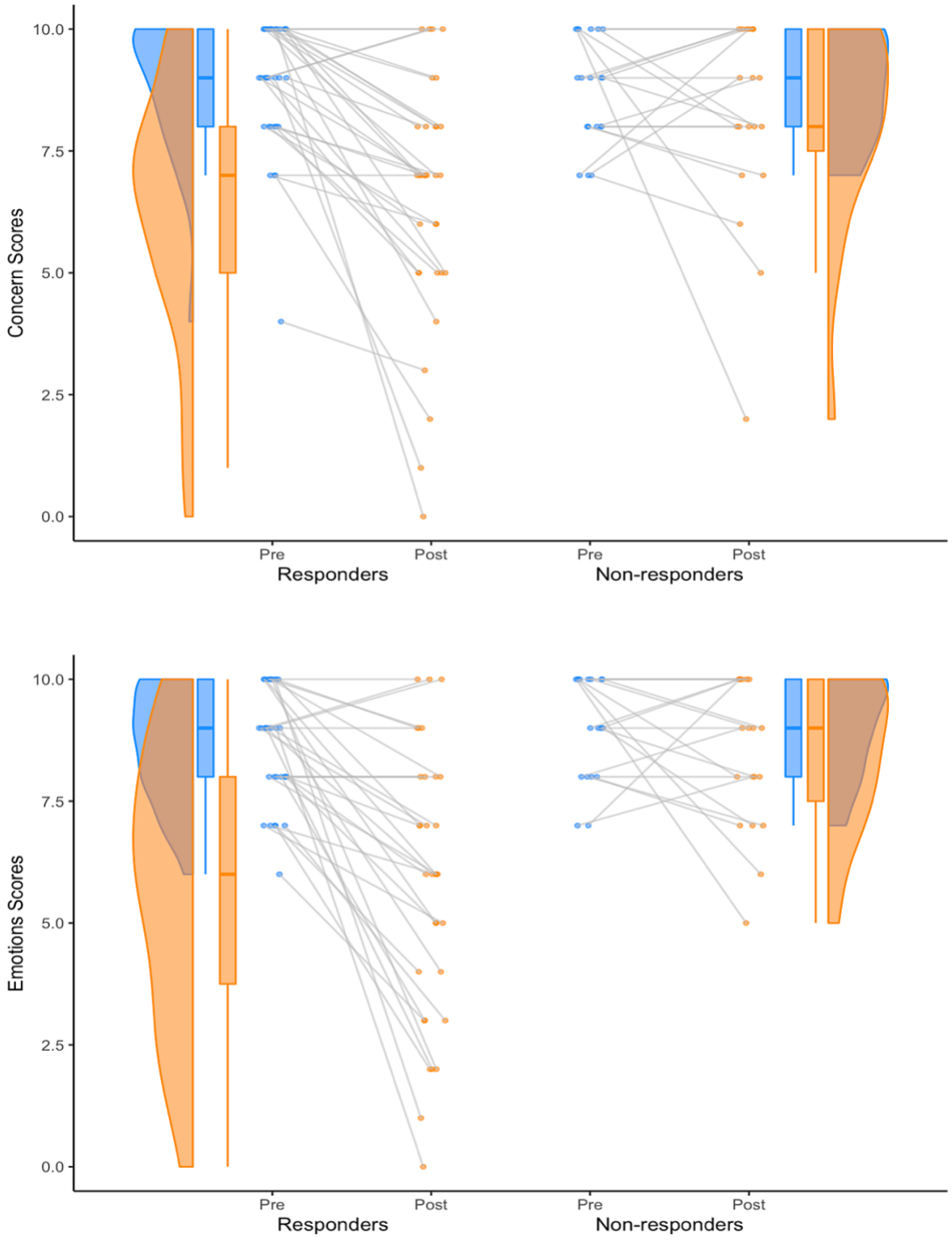
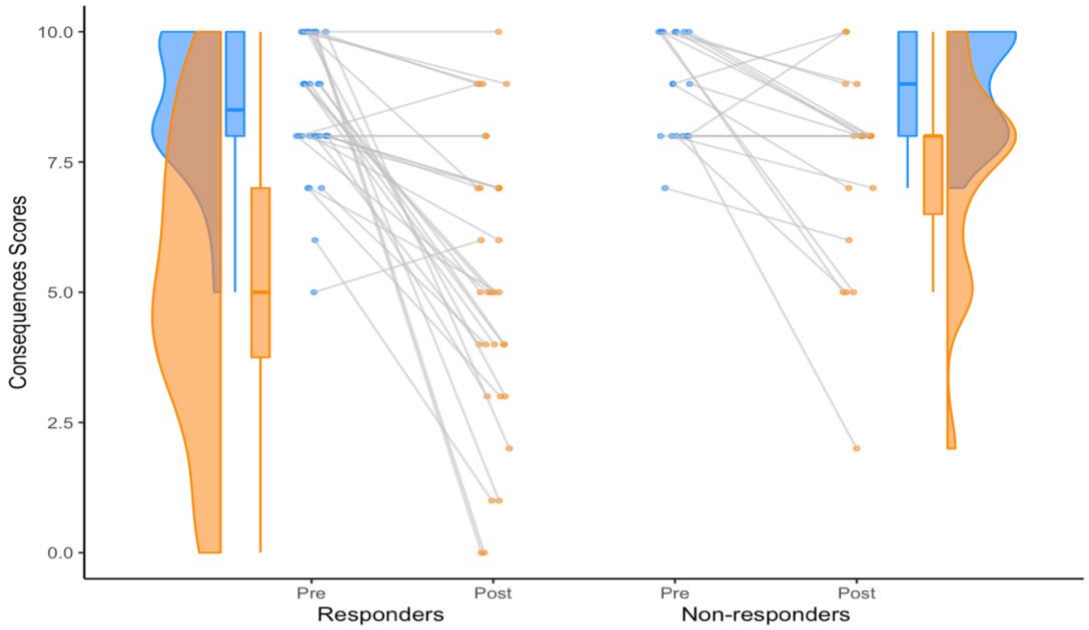


Figure 6.2 Changes in Consequences and Timeline Over Time Distributed by Responsiveness



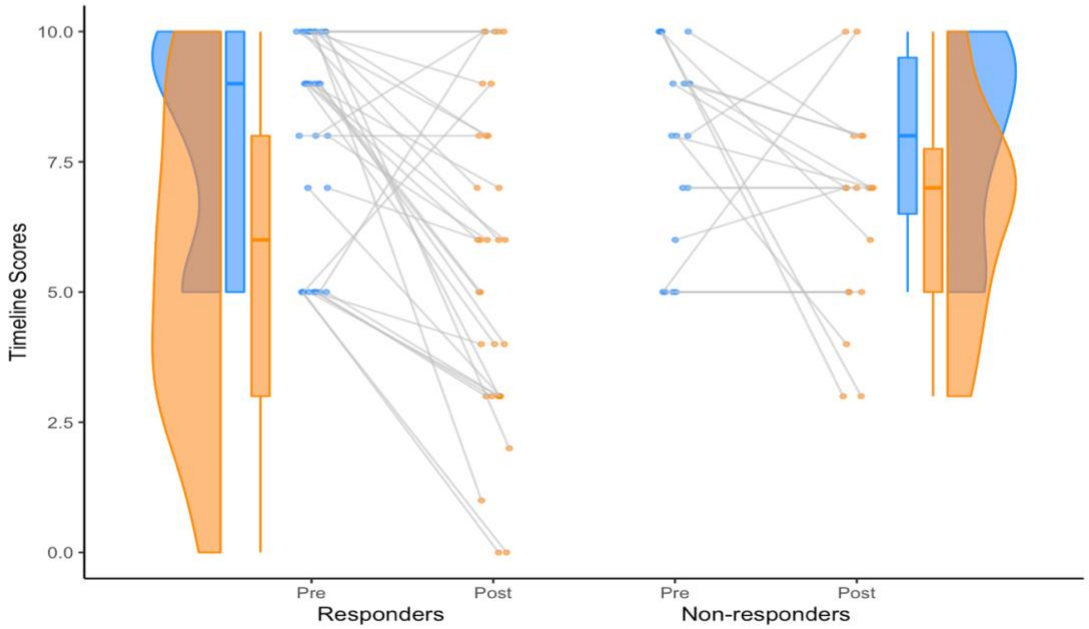


Figure 6.3 Changes in Identity and Personal Control Over Time Distributed by Responsiveness

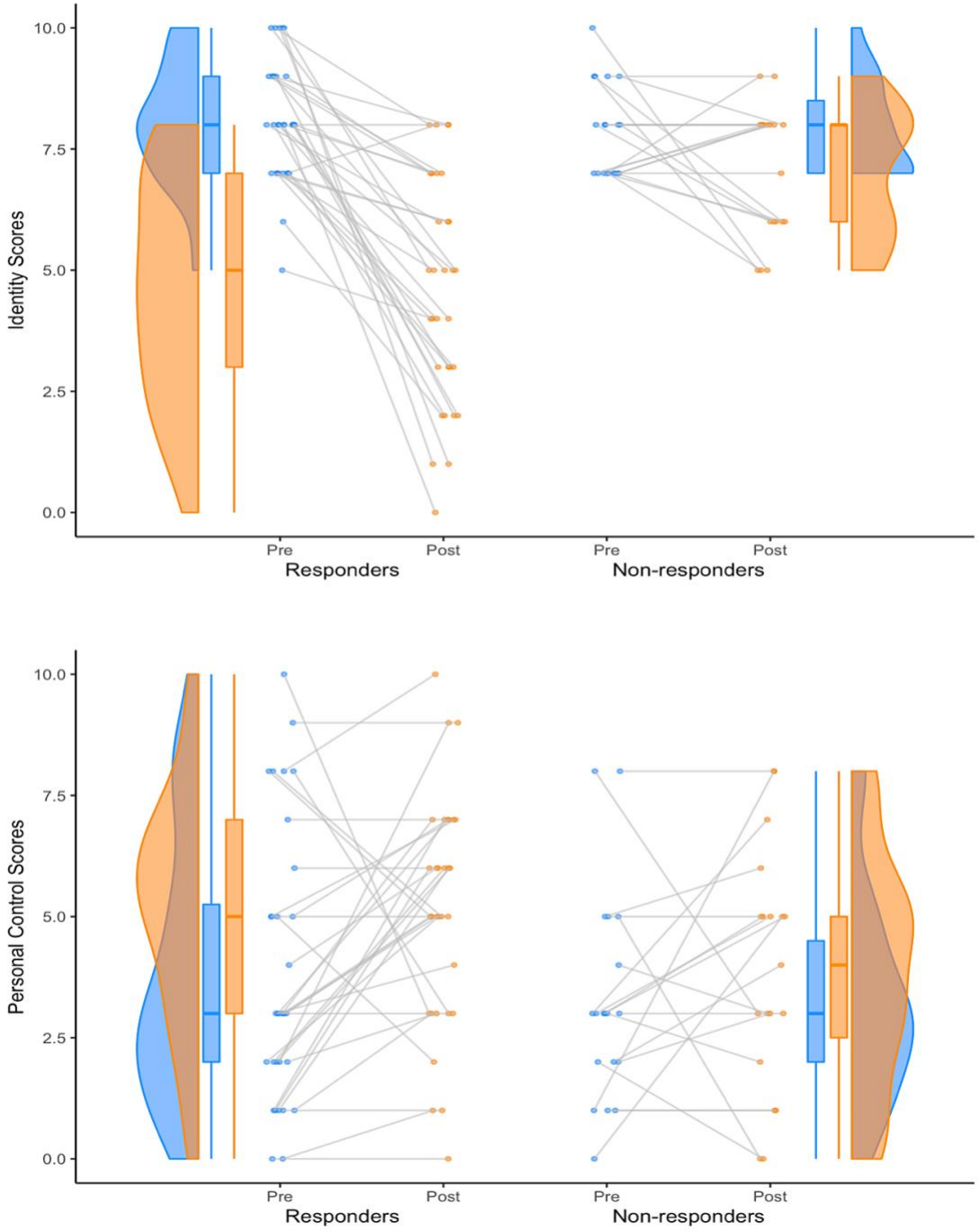
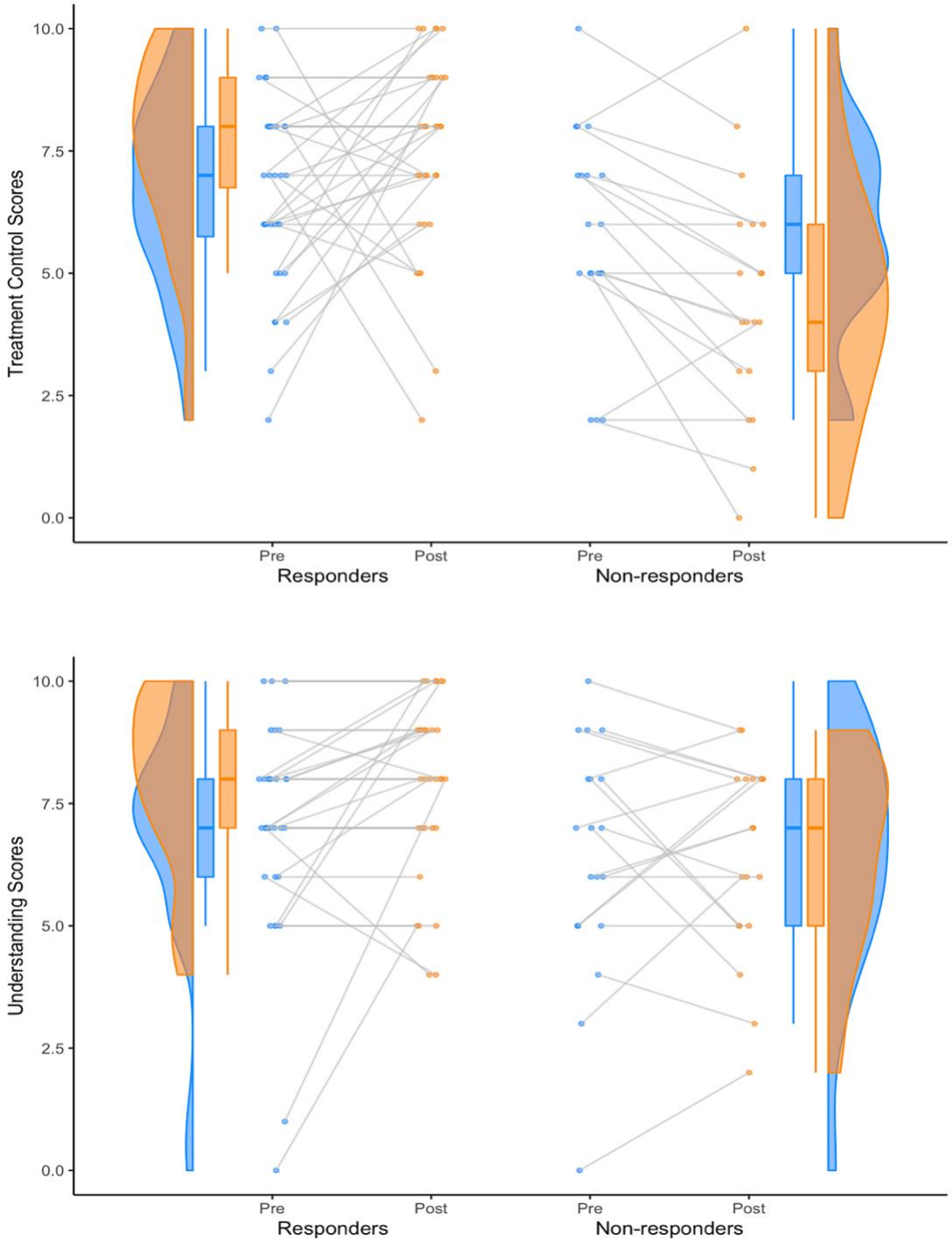


Figure 6.4 Changes in Treatment Control and Understanding Over Time Distributed by Responsiveness



3.3 Illness Perception, Depression and Disability Scores

As mentioned in chapter 2, HRSD-17 was divided into subcategories following Shafer's model (2006) to understand the association with specific sets of symptoms experienced by participants. The subgroups generated were labeled 'depression', 'anxiety', 'insomnia', and 'somatic'.

Considering that from baseline to end of treatment, one participant reported worsening of scores compared to baseline records, more significant changes after rTMS are viewed as better scores and improvement in symptomatology. However, it is essential to notice that despite the large number of participants improving, they were not necessarily responders since it was necessary an improvement of at least 50% from baseline HRSD-17 scores to be included in this category.

3.3.1 Associations Between Perceptions and HRSD-17 scores

Correlation between illness perceptions and HRSD-17 scores at baseline was used to identify the level of correspondence between perception and symptoms in this TRD sample, how much overlapping would exist between these and if participants were able to distinguish the particular purpose of each tool.

Identity, consequences, and emotions were moderately associated with HRSD-17 total scores, particularly identity (0.42), while concern presented a low association. The correlation between identity and HRSD-17 appeared to be significantly influenced by ‘depression’ and ‘somatic’ subscales. Similar results were found regarding

consequences. Emotions, however, were notably linked to the ‘somatic’ subscale (table 6).

Table 6. Correlation Between Illness Perceptions and HRSD-17 Scores at Baseline

	HRSD-17	Depression	Anxiety	Insomnia	Somatic
Identity	**0.42*** **	**0.25***	0.19	0.15	**0.33****
Consequences	**0.34****	**0.37****	0.01	0.05	**0.29***
Concern	**0.26***	0.21	0.19	0.00	0.16
Emotions	**0.37****	0.23	0.10	0.17	**0.35****
Timeline	0.10	0.18	0.00	-0.10	0.12
Personal Control	-0.18	-0.06	-0.06	-0.10	-0.20
Treatment Control	0.05	0.01	0.03	0.03	0.03
Understanding	-0.04	-0.12	-0.17	0.22	0.04

* < .05 ** < .01 *** < .001

Changes in depression scores after rTMS treatment were moderately correlated with perceived treatment control and presence of symptoms (identity) at baseline, particularly with the 'depression' subscale. Concern also presented a low association with the 'depression' subscale but not with total scores.

Results suggested that participants who believed to be experiencing more symptoms and that treatment could be helpful had more remarkable changes in scores after treatment. Moreover, those were mainly associated with improvement on the 'depression' subscale scores, which encompass depressed mood, guilt, suicidality, anhedonia, and psychomotor retardation. (Table 7).

HRSD-17 scores at baseline were weakly to moderately associated with changes in HRSD scores after treatment, especially with the 'insomnia' subgroup, similar to reduced productivity perception at baseline. Besides these, scores of work/school

disruption at baseline were weakly to moderately correlated with changes in insomnia and somatic scores, indicating that more significant disruption in work and school activities caused by symptoms before treatment appeared to be related to improved scores in 'insomnia' and 'somatic' subscales, the latter including loss of appetite, fatigue and tiredness, sexual interest and loss of weight (see appendix B)

Table 7. Correlation Between BIPQ Dimensions at Baseline and Changes in HRSD-17 and its Factor Structures After Treatment

	HRSD Delta	Depression Delta	Anxiety Delta	Insomnia Delta	Somatic Delta
Concern	0.21	**0.25***	0.15	0.23	0.05
Emotions	-0.04	-0.10	-0.02	0.14	-0.11
Consequences	0.01	0.11	0.00	-0.13	0.09
Timeline	-0.02	0.20	-0.04	-0.11	0.07
Identity	**0.26***	**0.27***	0.23	0.23	0.21
Personal Control	0.11	0.04	0.03	-0.12	0.10
Treatment Control	**0.30***	**0.29***	0.13	0.12	0.06
Understanding	0.24	0.08	0.03	0.24	0.04

Non-parametric distribution was assessed by Spearman Correlation and Normal distributed variables were assessed by Pearson's Correlation
* < .05 ** < .01 *** < .001

Student's T-tests were used to identify any differences in HRSD-17 delta when compared by sex, marital status, employment status, presence of comorbidity, or attributable causes. Unfortunately, there was no significant difference found. (see appendix C).

Multiple regression was later executed in two steps. All illness perception dimensions were added to step 1. Other variables that presented an essential correlation

with changes in HRSD-17 scores were inserted in step 2. The stepwise fitting method was used, as mentioned in chapter 2. The regression model of HRSD-17 scores change was significant F= 3.43, p = 0.02, and explained 12% of the variability. Treatment control, identity, and consequences participated in the final equation, accounting for 12% of the total variance, along with HRSD-17 scores at baseline (see table 8).

Table 8. Regression Analysis for Changes in HRSD-17

HRSD-17 Delta 1	***B***	***Adj. r^2***
Identity Baseline	2.04*	0.12*
Treatment Control Baseline	0.95	
Consequences Baseline	-1.75	

*** p<.05

3.3.2 Association Between SDS Scores, Perceptions and Other Variables

Disability was assessed by Sheehan Disability Scale in two different moments, as explained in chapter 2. Five variables measure how much patients feel symptoms are interfering in their school or work, family life or home activities, social life, and how many days in the last month they have missed school or work due to their illness or how much the productivity went down.

Correlations between perceptions and disability scores at baseline assessed the degree of association between these scales' items. Moderate to high correlations were found between identity and disruption in work/school activities, identity, consequences,

and emotions and disruption in social activities by symptoms as demonstrated in table 9, along with results from other dimensions and SDS subitems.

Table 9. Correlation Between Illness Perceptions and SDS Scores at Baseline

	Work/ School	Family/ Home	Social	Missed Work/School	Reduced Productivity
Identity	**0.57*** **	**0.40** **	**0.52*** **	**0.27***	**0.37** **
Consequences	**0.47*** **	**0.27***	**0.63*** **	0.18	**0.31** **
Concern	**0.27***	**0.40** **	**0.45*** **	0.15	0.17
Emotions	**0.34** **	0.18	**0.50*** **	0.08	0.10
Timeline	0.21	0.18	**0.31** **	0.00	-0.08
Personal Control	-0.08	-0.21	-0.09	-0.18	0.01
Treatment Control	0.05	0.00	-0.03	0.17	-0.03
Understanding	-0.16	-0.04	-0.02	0.05	0.00

* < .05 ** < .01 *** < .001

The mean change of the domains analyzed by SDS varied from 3.11 to 3.89. Change in the number of days of missed school averaged 5.93 days, whereas the mean of days with poor productivity was 9.98. Change over time (from baseline to end of follow-ups) in SDS scores was later correlated with illness perception, and results showed weak to moderate associations between consequences and change in work/school disruption, timeline, and delta of work/school and social life. Identity was the dimension associated with more disability variables, excluding only change in the reduction of productivity.

Hence, results suggest that when patients with TRD believed that symptoms were interfering severely in their lives before receiving treatment as rTMS, work/school activities showed some tendency to improve after a few months, similar to those who

believed that depression was never going to end. These were also more prone to present improvement in social life. Besides this, participants who experienced more symptoms at baseline had improved all three life aspects but not in reducing productivity (see table 10).

Correlations involving changes in SDS scores and age, duration of current episode, age of onset, and HRSD-17 scores at baseline were addressed; only minimal associations were found, with the highest being a weak negative association of 26% among duration of the current episode at baseline and changes in disruption and missed days of work/school (see appendix D).

Table 10. Correlation Between BIPQ Dimensions at Baseline and Change of Sheehan Disability Scale Items 4 Months After Baseline

	Change in Disruption of Work/School	Change in Disruption of Social Life	Change in Disruption of Family Life	Change in Missed Work/School	Change in Reduction of Productivity
Concern	0.04	0.04	0.12	-0.05	0.09
Emotions	0.15	0.21	0.13	0.06	0.00
Consequences	**0.26***	0.25	0.22	0.16	0.19
Timeline	**0.27***	**0.26***	0.22	0.25	0.13
Identity	**0.37****	**0.34***	**0.34***	**0.27***	0.23
Personal Control	-0.02	0.00	-0.20	-0.22	0.07
Treatment Control	0.03	0.05	0.04	0.00	-0.09
Understanding	0.06	0.08	0.05	0.17	0.17

Non-parametric distribution was assessed by Spearman Correlation and Normal distributed variables were assessed by Pearson's Correlation
* < .05 ** < .01 *** < .001

However, when correlating changes in SDS scores with changes in HRSD-17 scores from baseline to after treatment, many moderate associations were found. The only item with minimal correlations was the change in missed days of school/work activities. Change in symptoms affecting all three life aspects (work/school, social, and family life) was associated with changes in delta one of HRSD-17 total scores and its factors except for 'insomnia'. Changes in productivity reduction were related to HRSD-17 total scores, 'depression' and 'somatic' subscales (see appendix E).

Similar to previous analyses, differences by sex, marital status, employment status, presence of comorbidity, and causal attribution could not be identified without excluding chance (see appendix F).

Stepwise fitting regressions were performed to identify if illness dimensions could be used to predict or explain some of the changes in disability over time in patients with TRD who were treated with rTMS. Overall, perception of how much symptoms were present (identity) before treatment, as well as the duration of illness (timeline), and the perception that treatment could be helpful, appeared to be correlated with changes in disability in the different life domains addressed in Sheehan Disability Scale, explaining some of the variability along with changes in different aspects of HRSD-17 by the end of treatment and after four months of baseline.

Baseline identity and changes in HRSD-17 total scores explained 20% of the variability in disruption by symptoms in work/school activities and 18% of changes in how symptoms disrupted family and home activities. Change of disturbance by symptoms in social activities was influenced by timeline and identity at baseline, explaining 18%

variance before the addition of other variables (table 11). Identity and treatment control, alongside with changes in HRSD-17 scores could explain 17% of the variance of days with reduced productivity. Dimensions could not explain variability in missed days of school or work.

Table 11. Regression Analysis for Changes in Disability

Disrupted Work/School Delta	***B***	***Adj. r^2***
Identity Baseline	1.61***	0.20**
HRSD-17 Delta	0.17*	
Disrupted Family/Home Delta		
Identity Baseline	1.20**	0.18**
HRSD-17 Delta	0.15*	
Disrupted Social Delta		
Timeline Baseline	0.33	0.28**
Identity Baseline	1.05**	
HRSD-17 Delta	0.19**	
Reduced Productivity Delta		
Treatment Control Baseline	-1.45	0.17**
Identity Baseline	3.42*	
HRSD-17 Delta	0.87**	

*** p<.05, **** p<.01, ***** p<.001

Chapter 4: Discussion and Conclusion

4.1 Profile of Depression Perceptions and Comparison with Previous Literature Findings

4.1.1 Demographic and Clinical Characteristics

Depression is a non-discriminatory illness affecting all ages and sex groups, although females have a twofold higher prevalence than males. The mean age of onset for recurrent unipolar major depressive episodes is in the 4th decade of life, and it is more frequently seen in divorced or separated people, although being single can also be a risk factor for depression. Individuals with depression are more prone to develop comorbidities, especially anxiety and alcohol consumption (Sadock, 2017). As per previous literature reports, females prevailed over males, but only by a small difference. Participants' mean age was 43.1 years, and age of onset was 25.7 years, indicating that most participants were living with this condition for approximately twenty years. Age of onset was lower than found in the literature; however, this could be justified as a particular sample characteristic, or it could indicate that treatment-resistant depression tends to develop in patients presenting earlier onset.

Only 20% of the sample claimed to be divorced or separated against 40% single, totaling 60%. Many single individuals in this sample could be associated with the lower age of onset of the group since depression has a significant social component, with potential interference in the beginning or sustaining a personal relationship.

More than half of participants were not working, which included being disabled, being laid off, unemployed, retired, or in some assistance, reflecting a high level of dysfunction and burden in this population already indicated in literature (Jaffe et al., 2019; Mrazek et al., 2014). SDS scores at baseline were also an indication of high interference of depressive symptoms in daily life.

Almost half of our sample presented with one or more associated psychiatric comorbidities, with the majority being categorized as a generalized anxiety disorder (GAD), panic or social anxiety disorder, and only 10% of alcohol or substance abuse disorder, unlike suggested by the literature, where the latter would also be predominant among patients with MDD (Sadock et al., 2017). One explanation for this could be the fact that one of the exclusion criteria was a recent history of alcohol/substance abuse or dependence (last three months), which may have incurred in selection bias; or TRD patients could be less prone to this comorbidity and more likely to present anxiety disorders, as suggested by Mrazek and colleagues (2014).

MDD scores before treatment were classified as severe, similar to previous findings (Mrazek et al., 2014), and responsiveness to rTMS treatment was 53.3%, congruent with previous literature (Bakker et al., 2015; Duprat et al., 2016; Gaynes et al., 2014). However, sample selection required at least 18 points on HRSD-17, making it unlikely to identify TRD patients with lower scores.

4.1.2 Cognitive and Emotional Representations in Treatment-Resistant Depression

Individuals with treatment-resistant depression participating in this study had, before treatment, strong negative beliefs of their condition with moderate to high understanding of their depressive symptoms and a moderate to low perception that they could control these, although with moderate to a high perception that treatment could be helpful.

Negative perceptions are congruent with previous findings in a study of patients with rheumatoid arthritis and depression where those with depressive mood were more likely to present more negative views of their primary condition (Murphy, 1999), also in agreement with a sample of patients with schizophrenia where these would be more likely to develop depression, anxiety and low self-esteem (Watson et al., 2006). Patients with chronic fatigue syndrome (Moss-Morris & Chalder, 2003; Edwards, 2001) and bipolar disorder (Lobban et al., 2013) also negatively saw their conditions. Patients with eating disorders with similar profiles were found, although most perceived their conditions in a more amenable and treatable way (Marcos et al., 2007). When associated with depression, though, consequences were perceived as more severe, not treatable, or controllable (Holliday, 2005). Samples of patients with MDD also identified participants with very negative views of their illness (Baines and Wittkowski, 2013; Cabassa et al., 2008; Zayas et al., 2011; Fortune et al., 2004).

Similar to Kaptein and colleagues (2010), who found that sociodemographic characteristics of patients with asthma were not associated with self-management

(personal control), our dataset indicated no association of demographic and clinical variables like sex, marital status, employment status, presence of comorbidity and the already mentioned responsiveness with personal control nor any other dimension.

The level of concordance, moderate to high, between dimensions like consequences and identity (71%), consequences and concern (58%), emotions and consequences (58%), and identity and concern (48%) was coherent with a similar level of severity and uniformity of the answers given by the participants as exemplified in figure 2. Furthermore, the correlation between identity and consequences could explain that both measures very close parameters. While one assesses the intensity of symptoms, the other evaluates the level of interference in ones' life, which can be very intertwined in depression. Baines and Wittkowski (2013) even mentioned that analyzing dimensions in patients with mental illnesses, especially depression, could generate a possible entanglement of negative thinking with dimensions like identity, consequences, and timeline, which in reality would lead to a co-dependence of one another, not being able to distinguish them. However, the degree of correlation showed in this sample, despite high, did not reflect this idea.

Moreover, patients with other conditions presented similar results, and not only but studies also showed that high presence of symptoms, substantial consequences in one's life, and chronic duration were associated with worse functioning in a sample of rheumatoid arthritis, chronic obstructive pulmonary disease, and psoriasis (Scharloo et a.l, 1998). In a sample of patients with chronic fatigue syndrome, high identity and consequences were predictors of fatigue (Edwards, 2001). A study with a bipolar sample

presented that consequences and lack of personal control were associated with increased severity of symptoms over time (Lobban et al., 2013).

A weak but relevant association was found between personal and treatment control, indicating that patients that perceived low personal control were more likely to believe that treatment would also not be helpful. Similar results were found in patients with eating disorders (Holliday et al., 2005; Stockford et al., 2007), medical conditions that also cause significant emotional distress and are, not seldom, associated with anxiety and depression (Sadock et al., 2017) as mentioned in chapter 1. In these patients, severe consequences were also associated with emotional distress, many symptoms, and perception of longer duration, but good understanding (Holliday et al., 2005; Marcos et al., 2007). Unlike another sample of patients with depression with a clear correlation between timeline and personal or treatment control (Cabassa et al., 2008), there was no evidence between control and duration of illness in this study.

4.1.3 Causal Attributions of Depression in Treatment-Resistant Depression

Much has been discussed about possible causes for depression with recent research leading towards a combination of factors, among them genetic predisposition (Boldrini et al., 2015; Sullivan, 2009; Muglia, 2010; Rietschel, 2010; Shadrina, 2018), hormonal, immunological (Leonard, 2020; Boldrini, 2015; Stefaniak, 2018; Jesulola, 2018; Shadrina, 2018) and neurochemical imbalance (Nemeroff, 1984; Banki, 1987; Carroll, 2007; Gillespie, 2005), and environmental exposure to stressors, especially in early life (Boldrini et al., 2015; Sadock et al., 2015).

Categories of attributional causes found in this TRD sample were very similar to those found in patients with bipolar disorders (Averous et al., 2018). Life stressors, genetic, and trauma were the main categories indicated in this sample as causes of depression, with the first corresponding to 32.3% of all answers, the second 15.9%, and the third 11%. While life stressors are frequently present among perceived causes of depression (Brown et al., 2013), high indices of genetics or heredity as a cause was only found in one other study (Brown et al., 2007), differing from reports with much lower rates (Hansson et al., 2010; Magaard et al., 2018). Ekanayake and colleagues (2012) included trauma in the same group as other life stressors, not specifying its proportion among their sample, while Hansson and colleagues (2010) mentioned a percentage of 5%. Other studies of illness perception and depression addressed other categories such as interpersonal relationships (Brown et al., 2013; Addis, 1995; Ekanayake et al., 2012) and socioeconomic status (Ekanayake et al., 2012) to their leading causes of depression. Interestingly, a sample of patients with psoriasis presented with similar views (stress, genetics, own behavior, state of mind) of possible causes to their condition (Fortune et al., 2000).

The examples of life stressors listed by TRD patients were more frequently generic, independent of sex, which could indicate more difficulty defining or associating situations that would have influenced their choice to label life stressors as potential causes of depression. This aspect is different from previous literature regarding depressive patients, where men were more inclined to answer work-related stress and women family-related stress (Read et al., 2015; Hansson et al., 2010).

Overall, attributional causes in TRD patients were congruent with views of other patients with depression regarding possible causes to their symptoms and are also compatible with scientific perspectives of the pathophysiology of depression. Nonetheless, the variety of answers could be explained by the lack of a unified theory for depression's occurrence. These attributional causes addressed here lead back to some aspects of the biopsychosocial model (Engel, 1977), where these three paths were endorsed to establish the pathophysiology of medical conditions. However, it is critical to realize that listing causes, even if ranked, may create delimitations or boundaries between these categories that do not exist. Depression is a complex illness with causes entangled in proportions that are different for each patient, and it is hard to create a pattern that could overflow to others equally.

4.2 Changes in Illness Perceptions After rTMS Treatment

After finishing rTMS sessions, participants' perceptions were overall less negative despite still presenting themselves with moderate to high scores. However, understanding and treatment control remained practically unchanged. Changes over time were previously observed in a group of patients with rheumatoid arthritis (Weinman et al., 1996). According to Leventhal's proposed model, perceptions are subjected to change since SRM is a dynamic model and counts with constant feedback between its components generated by constant adaptation to new situations, especially in more unstable conditions (Cameron and Leventhal, 2003). In terms of duration, these patient's depression could be considered stable since most of them lived with depression for about

twenty years or more and were experiencing the current episode for at least two years. However, they were inserted into a new treatment regime that required new daily activities and interactions (going to the laboratory to receive treatment and interact with the staff).

Regarding the dimensions that did not present significant changes by the end of treatment sessions, understanding was one. After years of living with an illness, it is expected that individuals acquire knowledge about it, which could justify moderate to firm beliefs of understanding about depression in the first place, even if they do not feel properly able to control it. It would be expected to be one of the dimensions with the least amount of change since all new information about the treatment, the one factor we are confident that has changed during the studies' period, was given before data collection. For treatment control, it is also coherent that if one willingly searches for a specific treatment to his/her condition, there is some level of hope that this trial could be helpful even if depressive symptoms were very intense and could interfere with this assumption. Changes over time were expected from the group responding to rTMS; however, the opposite took place.

In an attempt to comprehend further the treatment participation on these changes, responders and non-responders were segregated, and a new comparison was made. As mentioned in chapter 3, responders presented a compelling change in concern, emotions, consequences, timeline, and identity, same dimensions that had lower standard deviations at baseline, differently from non-responders, which had similar change trajectories, but not enough to present a statistical significance.

Personal control and understanding also significantly changed in this group, although lower than the previously mentioned dimensions. One possible reason for this could be the absence of associated interventions that would have worked on coping strategies to develop personal skills to change the perception of the illness and the self. Surprisingly results could not demonstrate a significant change in treatment control. When observing the individual trajectories in figure 6.4, scores improvement can be noticed, despite the statistical finding, which could reflect the level of caution TRD patients experience regarding treatments due to previous failed attempts.

Participants who did not respond to rTMS also did not present powerful changes regarding their beliefs, except for consequences and treatment control. Symptoms continued to affect their lives negatively, but a more precise statement that treatment could not help can be visualized in figures 6.2 and 6.4.

How much follow-ups or the fact that the participant needed to come for treatments daily and face people willing to help them getting better influenced the change in perception is unclear at this point. Also, a considerable number of participants also had to deal with anxiety disorders that could have interfered with their depression's representations. It is also difficult to account for other possible changes outside the treatment room during that time, like family and friends' relationships, other not controlled medical conditions, work status, or conflicts. Other factors not controlled for were personality traits and coping strategies, which could be essential parts of how people perceive life changes. Although anti-social personality disorder was excluded during screening with MINI and prominent personality disorders in initial assessments, there are

a myriad of other aspects to consider and that could have been addressed with personality and coping scales.

4.3 Illness Representations, Depressive Symptoms and Disability

4.3.1 Associations Between Dimensions and Depressive Symptoms

Initially, as mentioned in item 3.2, HRSD-17 was divided into subscales to evaluate possible correlation with a particular set of symptoms. Categories were labeled 'depression', 'anxiety', 'insomnia', and 'somatic'.

Some correlations were found between changes in HRSD-17 after treatment and dimensions. Patients who had more difficulty understanding their symptoms were less likely to present changes in 'insomnia'. Considering that understanding was one of the dimensions that did not present significant change over time, we can say that these patients maintained their level of uncertainty after treatment, which could be associated with the quality of their sleep. One possibility would be that patients that believed to have a good comprehension of depression would be more able to improve their sleeping patterns because that was not one of their concerns.

One other aspect that stood out was that lower change in 'depression' subscale scores was associated with belief at baseline that treatment was not so helpful. Lack of treatment control could reflect the failure of previous treatments as well as the intensity of hopelessness and how it could affect future treatments like rTMS since treatment control was also correlated with changes in overall HRSD-17 scores.

When identifying predictors of changes in scores after receiving rTMS, treatment control was one of the parameters, along with identity and consequences, suggesting that patients with a higher belief that treatment could be helpful associated with higher symptoms but with lower consequences in life were more likely to present changes in overall depressive symptoms after treatment. Broadbent et al. (2006) found, in a sample of patients with chronic fatigue syndrome, that patients with many symptoms and who believed that treatment could be helpful presented more active coping behaviours. On the other hand, those with a perception that symptoms severely affected their lives used more denial and negative coping strategies. Our results could suggest that patients' coping mechanism choices could deeply explain the findings mentioned above. Another study has highlighted treatment control participation in determining adherence to treatment, but in bipolar patients. (Averous et al., 2018).

Addis's (1995) findings suggested that extrinsic locus of causal attribution was associated with less improvement in patients with MDD; howbeit, our research could not identify a similar relationship.

4.3.2 Illness Perception and Disability

Weak correlations were found between illness perception dimensions and all levels of functionality measured by SDS scores. However, stronger correlations were found between identity and changes in disruption of school and work activities (37%), social life (34%), and family life (34%), showing that intense presence of symptoms before rTMS could be significative and influence how much patients' lives could be modified after

receiving this treatment. Differently, a study addressing perceptions in patients with rheumatoid arthritis, chronic obstructive pulmonary disease, and psoriasis found that beliefs about chronic duration and severe life consequences were indicative of worse outcomes (Scharloo et al.,1998). In a group with chronic fatigue syndrome, identity was considered a predictor of psychological adjustment (Moss-Morris et al., 1996). Our findings indicate that perceived identity could help predict changes in disability after receiving rTMS.

4.4 Limitations

4.4.1 Limitations of the tool

Leventhal mentioned that patients establish an idiosyncratic view of illness, which starts with labeling it. Unfortunately, the BIPQ fails to address which symptoms patients are considering when evaluating the 'identity' item of the scale. BIPQ authors parted from the assumption that all patients have the same label and are experiencing the same symptoms. It does not allow us to know more about the patients' experiences, as they see it, with the illness, only how intense it is.

Another point that may not be as relevant but also worth mentioning is that illness duration was initially divided into three categories: acute, cyclic, and chronic. Using a continuum (from 0 to 10) to determine the perception of duration can help differentiate between acute and chronic when the patient chooses the extremes of the values, but it eliminates the possibility of choosing the cyclic option.

4.4.2 Limitations of the study

The sample was restricted to one center. Despite Vancouver being a cosmopolitan city, it is difficult to extend the results to other populations of patients with treatment-resistant depression.

It is difficult to measure the participation of technicians, clinical raters, and the constant contact with people that want patients to improve or the constant contact with people at all since many patients have difficulty going out of their houses and socialize considering that this study did not have a sham group. Cameron and Leventhal (2003) emphasize the influence of social interactions on illness perception and say it can be transforming.

The study did not address personality types, which could be a vital factor in altering illness perception. As mentioned by Vitulić (2010), these traits seem to influence knowledge development and demonstrate how individuals behave towards adversity. Klein (2011) also reports a strong association between depression and personality, with three distinct possible correlations: having a common cause, a continuum relationship, or personality as a precursor of depression. Therefore, it would have been interesting to account for and correlate with the perception of depression in these patients.

4.5 Conclusion

4.5.1 Current State of the Field

Many studies have used illness perception to address different kinds of patients and their cognitive and emotional representations of experiences involving their illnesses

and health processes. Different factors can interfere and change such perceptions, being able to model them over time.

Illness beliefs are essential aspects of a whole and should be used more frequently to assess patients, including those with treatment-resistant depression. These patients appear to have beliefs about their condition as pessimistic compared to those who do not experience depression. If the depressive disorder is the primary condition or not, these representations seem to be very present in patient's lives, having the power to model their responsiveness to treatment and their ability to function afterward. Having depression that is resistant to treatment is one characteristic that adds up to this equation to make the illness perception even more harmful due to many previous failed cure/control attempts and usually long periods living in this context. Unfortunately, most studies involving depression and illness perception do not usually classify patients by the number of previous failed treatments. Regardless, the profile built here was equivalent to previous literature findings. This could signify that: there is no actual difference between illness perceptions of patients with depression that is or not resistant to treatment, or TRD is more common among participants of studies than we may realize. Further studies would be able to help to understand this situation.

Several instruments have been used to explore the common-sense model, among them the brief illness perception questionnaire. Despite not being a complete tool to approach depression's perceptions, it could still be advantageous in research, mostly due to its convenient size, characteristic that should be taken into consideration when addressing illness perceptions of patients that very frequently demonstrate cognitive

(memory or focus) difficulties or have several other tools to answer. In times that internet and different types of communication methods are available to reach patients, BIPQ seems to be an opportune feature to pre-assess patients that will have their first contact with a clinician or a psychologist, as well as a convenient tool to be used in follow-ups to understand the possible changes happening over time.

Changes in perception of patients with treatment-resistant depression after receiving rTMS were noticeable. They could be associated with different factors, many of which we could not account for, like the influence of weekly follow-ups and contemplation of emotional state regarding symptoms, since there was no control group. Notwithstanding, data indicated that being responsive to treatment, in this case, rTMS, was a significant factor in this change.

Some illness perceptions in TRD patients, in particular identity, were partially able to explain how patients' scores may change in response to treatment when receiving rTMS and how their level of functioning may change over time in these situations, indicating a possible use to the BIPQ in screenings involving these individuals. Other studies are, however, required to refine and confirm such findings.

This study helped shed some light on previous questions about the relevance of illness perceptions investigations in patients with depression and possible difficulties in disentangling perception from depressive symptoms. It addressed these questions in treatment-resistant depressive patients, who struggle with treatment and severe symptoms most of the time for long periods. Moreover, this study pointed out the possible participation of rTMS in short-time changes in perceptions regarding depression. TRD

patients' depression representations and causes can help clinicians target and intervene in particular aspects of their illness.

4.5.2 Future Recommendations

Vancouver area has a very mixed population, with different backgrounds. However, it would be relevant to have other studies with treatment-resistant depression patients from different locations or cultural backgrounds in order to be able to expand these findings to other populations. A larger sample would also help better understand the participation of causal attributions listed by our participants. Therefore, having more studies addressing illness perceptions in TRD patients, in particular with larger samples, would not only be validate the findings discussed here as would also increase power. Another important point would be to compare TRD with non-TRDs groups to assess particular characteristics of both populations. Having a placebo group would be very helpful to elucidate the influence of the external factors mentioned in the limitation section.

Another helpful addition would be a measurement of coping strategies and personality traits. There have been studies associating particular coping behaviours and personality traits with depression and also with illness perceptions.

In terms of tool, the recommendations would be to add a simple list of symptoms to BIPQ so patients could mark the most debilitating ones, and another item to address symptoms intermittence as there is in IPQ-R, since cyclic and chronic perceptions could be associated with different causes and symptoms of an illness (Leventhal, 1980).

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Appendices

A. Difference of Baseline Dimensions According to Sex, Marital, Employment Status, Presence of Comorbidity and Attributable Causes

	Sex	Marital Status	Employment Status	Presence of Comorbidity	Attributable Causes
Concern	-0.79	-0.23	1.18	-0.25	1.58
Emotions	1.25	1.43	0.27	-0.89	0.66
Consequences	1.01	1.71	1.65	-0.34	0.28
Timeline	1.11	1.25	0.14	-2.43	-0.15
Identity	2.43	0.80	2.12	0.47	-0.22
Personal Control	-0.21	0.26	0.66	0.07	-0.36
Treatment Control	1.31	1.39	0.75	-0.64	-0.17
Understanding	1.52	-0.85	-0.46	0.29	-1.76

Two-Sample T-test (t-statistic expressed in the table)
* < .05 ** < .01 *** < .001

B. Correlation Between Other Variables at Baseline and Changes in HRSD and its Factors After Treatment

	HRSD-17	Depression	Anxiety	Insomnia	Somatic
Age	0.14	0.20	-0.03	0.15	-0.05
Age of Onset	0.07	0.06	0.03	0.10	0.04
Current Episode Duration	0.06	-0.01	0.20	-0.08	0.04
Work/School Disruption	0.21	0.06	0.13	**0.29***	**0.26***
Social Life Disruption	0.09	0.13	0.04	0.14	-0.02
Family Life Disruption	0.09	0.25	0.00	0.20	-0.20
Missed Work/School	-0.04	-0.02	-0.14	0.15	-0.03
Reduced Productivity	0.16	0.11	-0.02	**0.27***	0.15

Non-parametric distribution was assessed by Spearman Correlation and Normal distributed variables were assessed by Pearson's Correlation
* < .05 ** < .01 *** < .001

C. Differences Between Variables at Baseline and Changes in HRSD and its Factors After Treatment

	HRSD -17	Depression	Anxiety	Insomnia	Somatic
Sex	0.72	0.57	0.14	0.66	0.59
Marital Status	-0.95	-0.21	-0.68	-1.24	-0.81
Employment Status	-0.70	-0.80	-0.71	-0.32	0.05
Presence of Comorbidity	-0.15	-0.62	0	-0.07	0.65
Attributable Causes	0.82	1.17	0.21	0.89	-0.37

T-test used (t-statistic expressed on the table)
* < .05 ** < .01 *** < .001

D. Correlation Between Other Variables at Baseline and Change of Sheehan Disability Scale Items 4 Months After Baseline

	Change in Disruption of Work/School	Change in Disruption of Social Life	Change in Disruption of Family Life	Change in Missed Work/School	Change in Reduction of Productivity
Age	-0.02	0.05	0.20	-0.01	-0.10
Age of Onset	-0.12	-0.05	-0.04	-0.09	-0.03
Current Episode Duration	-0.26	-0.17	-0.18	-0.26	-0.07
HRSD-17	0.09	0.09	0.13	0.16	-0.08

Non-parametric distribution was assessed by Spearman Correlation and Normal distributed variables were assessed by Pearson's Correlation
* < .05 ** < .01 *** < .001

E. Correlation Between Changes in HRSD-17 and Changes in Sheehan Disability Scale Scores After 4 Months of Baseline

	Change in Disruption of Work/School	Change in Disruption of Social Life	Change in Disruption of Family Life	Change in Missed Work/School	Change in Reduction of Productivity
HRSD-17	**0.35***	**0.42****	**0.36***	0.14	**0.37****
Depression	**0.27***	**0.35***	**0.34***	0.12	**0.30***
Anxiety	**0.28***	**0.36***	**0.26***	0.09	0.24
Insomnia	0.04	0.02	0.03	0.02	0.10
Somatic	**0.37****	**0.45****	**0.27***	0.14	**0.36***

Non-parametric distribution was assessed by Spearman Correlation and Normal distributed variables were assessed by Pearson's Correlation
* < .05 ** < .01 *** < .001

F. Comparing Nominal Variables at Baseline and Changes in SDS Items after 4 Months of Baseline

	Change in Disruption of Work/School	Change in Disruption of Social Life	Change in Disruption of Family Life	Change in Missed Work/School	Change in Reduction of Productivity
Sex	0.68	0.72	0.90	1.76	-1.04
Marital Status	0.14	-0.10	-0.56	0.18	0.42
Employment Status	0.16	0.16	0.60	2.78	-0.70
Presence of Comorbidity	0.44	0.42	0.61	0.56	0.94
Attributable Causes	-0.21	0.18	0.23	0.38	-1.33

T-test used (t-statistic expressed on the table)
* < .05 ** < .01 *** < .001