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FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM PSIQUIATRIA E CIÊNCIAS DO COMPORTAMENTO

TESE DE DOUTORADO

DEVELOPMENT OF AN EMOTIONAL MEMORY TEST AND ITS NOVEL USE IN PATIENTS WITH BIPOLAR DISORDER: IMPACT OF MULTIPLE MOOD EPISODES AND CHILDHOOD TRAUMA

ADAM FIJTMAN
Orientadora: Profa. Dra. Marcia Kauer-Sant'Anna

Porto Alegre, Brasil
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Tese apresentada ao Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento da Universidade Federal do Rio Grande do Sul como requisito parcial para a obtenção do título de Doutor em Psiquiatria.

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CIP - Catalogação na Publicação

Fijtman, Adam
DEVELOPMENT OF AN EMOTIONAL MEMORY TEST AND ITS NOVEL USE IN PATIENTS WITH BIPOLAR DISORDER: IMPACT OF MULTIPLE MOOD EPISODES AND CHILDHOOD TRAUMA / Adam Fijtman. -- 2019.
120 f.
Orientadora: Marcia Kauer-Sant'Anna.

Tese (Doutorado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento, Porto Alegre, BR-RS, 2019.

1. transtorno bipolar. 2. trauma na infância. 3. cognição. 4. emoções. 5. memória. I. Kauer-Sant'Anna, Marcia, orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

To the memories of my dad Denys Fijtman,

And my grandma Fany Fijtman,

Thank you for always being with me.

ACKNOWLEDGMENTS

I owe this thesis, my M.D/Ph.D. degree and every other accomplishment I ever made or will achieve in my life to my mother, Liana Renkovski Fijtman. Thank you for always providing me with all the conditions to pursue my dreams, to study, and to advance my career.

On April 30, 2012, at the end of my second month of medical school, aiming to start extracurricular activities as soon as possible, I went to the Research Secretary at the School of Medicine of the Universidade Federal do Rio Grande do Sul to ask about research opportunities for medical students. In the peak of knowledge of a first-year medical student, I said I would be happy with anything within Infectious Diseases, Oncology, or Psychiatry. I came back home with a list of projects and some emails. A couple of days later, I sent several emails saying "Hi, my name is Adam. I am interested in your project." I have never heard back from most of them, but my future advisor Marcia Kauer-Sant'Anna answered saying we could schedule a meeting. Thank you for being an inspiration, for sharing your knowledge with me and for giving me opportunities since my first naive email.

I joined the Laboratory of Molecular Psychiatry at the Hospital de Clínicas de Porto Alegre as a research student. There, I had several outstanding mentors, who are always aiming to teach, including Clarissa Severino Gama, Giovanni Abrahão Salum, Júlio César Walz, Keila Maria Mendes Cereser, Pedro Goi, and Raffael Massuda. Thank you for sharing with me your passion for research in psychiatry.

I also would like to thank my colleagues who were with me during my journey and with whom I had the pleasure of working with including Andrea Ruschel Trasel, André Goldani, Bárbara Tietbohl dos Santos, Daniel Prates Baldez, Felipe Cesar de Almeida Claudino, Helena Maldonado, Luciana Guerchmann, Monise Constanzi, and Ramiro Reckziegel.

Thank you to all the brilliant minds which allowed me to collaborate in their research projects, including Ana Claudia Umpierre Knackfuss, Carolina Gubert, Erico de Moura Silveira Junior, Gabriel Fries, Juliana Sartori, Kelen Burke, Mirela Vasconcelos Moreno, and Thaís Martini.

A special thanks to those people who helped me with the research presented in this thesis. Thanks to Joana Bücker, for sharing your expertise in emotional memory with me and for helping me during every step of the project. Thanks to Bryan Strange, for aiming to help a group in Brazil

to translate your test and apply it in patients with Bipolar Disorder. Thanks to Dayane Santos Martins for helping with the data bank. Thanks to Ives Cavalcante Passos for helping with the statistical analysis. Thanks to Ana Cláudia Mércio Loredo Souza, Mathias Hasse-Sousa, and Flavia Moreira Lima for working on the subjects inclusion and cognitive testing. Thanks to Letícia Sanguinetti Czepielewski for helping with study methodology. Thanks to Lakshmi Yatham for helping with the conceptualization of the study. Thanks to Flavio Kapczinski for collaborating with data interpretation, but mostly, for being an inspiration in terms of how to pursue cutting-edge research in psychiatry. It is impossible to research by yourself, and it is much easier when amazing people surround you.

I also would like to thank all my friends and family who support me and understand my absence while I am studying.

Finally, I would like to thank Paul Felder for his support and companionship in every aspect of my life.

CONTENTS

PRESENTATION - ABOUT THIS THESIS

The present thesis adds essential knowledge to the study of neurocognitive changes in individuals with bipolar disorder. The study author of this thesis joined the Laboratory of Molecular Psychiatry at the Hospital de Clínicas de Porto Alegre during his first semester of medical school. There, the young doctor-to-be, who barely knew what bipolar disorder was, but was extremely curious and aiming to work hard, was introduced to the fascinating world of psychiatric research, where the study of cognition and behavior meets molecular neurosciences. The student was able to collaborate on projects that investigated the progression of bipolar disorder associated with cognitive and behavioral alterations, changes in systemic inflammation and oxidative stress, and brain damage that are observed through neuroimaging studies.

At the laboratory of molecular psychiatry, the doctoral student learned the concept of emotional memory and how it is associated with amygdala function and is disrupted in patients with bipolar disorder. A previous study from the group concluded that patients with bipolar disorder tend to evaluate neutral items as more emotional and have altered memory for emotional events (Kauer-Sant'Anna et al., 2008). These results led to questions of whether these emotional memory changes were different between patients in different stages of the disorder and also in patients with previous exposure to trauma during childhood.

The laboratory contacted Dr. Bryan Strange from the Universidad Politécnica de Madrid, who developed a task to assess emotional memory which correlates with amygdala function (Strange and Dolan, 2004). Dr. Strange helped the group to develop a translation and cross-cultural adaptation of the test to Brazilian Portuguese and to apply it in patients with bipolar disorder further. This enriching exchange experience synthesizes how science has no borders, bringing people together from different parts of the world with the common objective of elucidating research questions.

The trajectory of the author of this thesis started as a research student and culminated with an M.D/Ph.D. scholarship (Programa de Bolsa Especial para Doutorado em Pesquisa Médica - The Brazilian Federal Agency for Support and Assessment of Post-graduate Education 62/2014) at the Postgraduate Program in Psychiatry and Behavioral Sciences at the Universidade Federal do Rio Grande do Sul. It resulted in two scientific papers and one psychometric test that will contribute to future studies in the field. The following papers will be presented in this thesis:

- Translation and cross-cultural adaptation of the Brazilian Portuguese version of the Emotional Memory Scale.
- Emotional Memory in Bipolar Disorder: Impact of Multiple Episodes and Childhood Trauma.

1. Kauer-Sant'Anna M, Yatham LN, Tramontina J, Weyne F, Cereser KM, Gazalle FK, et al. Emotional memory in bipolar disorder. Br J Psychiatry [Internet]. 2008 Jun 2;192(06):458–63. Available from: https://www.cambridge.org/core/product/identifier/S0007125000235241/type/journal_article
2. Strange BA, Hurlemann R, Dolan RJ. An emotion-induced retrograde amnesia in humans is amygdala- and -adrenergic-dependent. Proc Natl Acad Sci [Internet]. 2003 Nov 11;100(23):13626–31. Available from: http://www.pnas.org/cgi/doi/10.1073/pnas.1635116100

LIST OF ABBREVIATIONS

BD- bipolar disorder

BD-T- patients with bipolar disorder without previous exposure to trauma during childhood

BD+T- patients with bipolar disorder with previous exposure to trauma during childhood

CTQ- Childhood Trauma Questionnaire

DSM- Diagnostic and Statistical Manual of Mental Disorders

E- emotional word

E-1- word preceding the emotional word

E+1- word succeeding the emotional word

EM- emotional memory

fMRI- functional magnetic resonance imaging

FME- few mood episodes

GEE- generalized estimating equations

HAM-D- Hamilton Depression Rating Scale

HC- healthy controls

HC-T- healthy controls without previous exposure to trauma during childhood

HC+T- healthy controls with previous exposure to trauma during childhood

HPA- hypothalamus-pituitary-adrenal

IQR- interquartile range

MDD- major depressive disorder

MME- many mood episodes

P- perceptual word

P-1- word preceding the perceptual word

P+1- word succeeding the perceptual word

PTSD- post-traumatic stress disorder

SCID-I- Structured Clinical Interview for DSM-IV Axis I Disorders

SD- standard deviation

T- translator

YOE- years of education

YMRS- Young Mania Rating Scale

ABSTRACT

Emotional memory is an essential amygdala-dependant cognitive function characterized by an enhanced memory for emotional stimuli, which usually leads to retrograde amnesia for neutral events. Emotional memory and amygdala function are disrupted in neuropsychiatric conditions, including affective disorders. Previous studies indicate that patients with bipolar disorder tend to evaluate neutral stimuli as emotional and suggest a blunted emotional memory in these patients. This thesis aims to assess emotional memory in euthymic patients with bipolar disorder through an amygdala-dependant task and to investigate the influence of previous exposure to trauma and multiple mood episodes on emotional memory. We conducted the translation and cross-cultural adaptation of an emotional memory test to Brazilian Portuguese. This process was composed of five steps: translation, negative selection, positive selection, semantic selection, and semantic assessment. Furthermore, we assessed for the validation of this test in healthy controls. We investigated the differences in emotional memory results between patients with bipolar disorder and healthy controls. We also examined how emotional memory is affected by previous exposure to trauma during childhood in patients with bipolar disorder and healthy controls. Finally, we explored differences in emotional memory between patients with few and multiple mood episodes. This thesis resulted in a translated and cross-culturally adapted test to investigate emotional memory in the Brazilian Portuguese-speaking population. Our results indicate enhanced emotional memory in patients with bipolar disorder, particularly with a higher number of previous mood episodes in spite of previous exposure to trauma. Our findings also suggest an emotional memory augmentation in healthy controls who were exposed to trauma during childhood. Emotional memory enhancement seems to be a promising marker of progression in patients with bipolar disorder.

Keywords: bipolar disorder, childhood trauma, cognition, emotions, memory.

RESUMO

Memória emocional é uma importante função cognitiva dependente da amígdala, a qual é caracterizada por um aumento de memória para estímulos emocionais normalmente ligado a uma amnésia retrógrada para eventos neutros. Memória emocional e função da amígdala estão alteradas em doenças neuropsiquiátricas, incluindo transtornos de humor. Estudos anteriores indicam que pacientes com transtorno bipolar tendem a avaliar estímulos neutros como emocionais e sugerem uma memória emocional embotada nesses pacientes. O objetivo dessa tese é avaliar memória emocional em pacientes eutímicos com transtorno bipolar por meio de uma tarefa dependente da amígdala e investigar a influência de exposição prévia a trauma e estadiamento do transtorno bipolar na memória emocional. A tradução e adaptação trans-cultural de um teste de memória emocional para português brasileiro foi conduzida por meio de cinco etapas: tradução, seleção negativa, seleção positiva, seleção semântica e avaliação semântica. Logo após, foi avaliada a validação desse teste em controles saudáveis. Foram investigadas as diferenças dos resultados de memória emocional entre pacientes com transtorno bipolar e controles saudáveis. Além disso, avaliou-se como memória emocional é afetada por exposição prévia a trauma durante a infância em pacientes com transtorno bipolar e em controles saudáveis. Por fim, foram exploradas as diferenças de memória emocional entre pacintes com poucos e múltiplos episódios de humor prévios. Essa tese resultou em um teste traduzido e adaptado trans-culturalmente para investigar memória emocional na população falante de português brasileiro. Nossos resultados indicam memória emocional aumentada em paciente com transtorno bipolar, em especial naqueles com maior número prévio de episódios de humor independente da exposicao previa a trauma. Os resultados tambem sugerem um acrescimo de memória emocional em controles saudaveis expostos a eventos traumaticos durante a infancia. Aumento de memória emocional parece ser um marcador promissor de progressão em pacientes com transtorno bipolar.

Palavras-chave: transtorno bipolar, trauma na infância, cognição, emoções, memória.

1. Introduction

1.1 Emotional Memory

Emotional memory (EM) is defined as an enhanced memory for emotional stimuli, which usually associates with a decreased memory of neutral preceding events (Christianson S-Å, 1992). Individuals tend to have a higher recall of events which trigger emotions and sensations, and of facts which are considered emotionally negative by them (Bowen et al., 2018). Temporal lobe brain regions, particularly the amygdala, hippocampus, and prefrontal cortex, play a fundamental role during encoding and retrieval of emotional episodic memories (Dolcos et al., 2017).

Strange et al. (2003) published a study in which they assessed ten healthy controls with an emotional memory test. The test consisted of 8 lists of words. Each list with 19 semantically similar words, one of the words with a negative emotional valence (which the author called E), one with a perceptual difference due to a different font (which the author called P), the word preceding E (E-1), the word following E (E+1), the word preceding P (P-1), and the word following P (P+1). Also, there were neutral control nouns not within the first five words of the list and not preceding E, P, E-1, E+1, P-1, or P+1. Words were shown on a computer screen, lasting 3 seconds per word, with the words "new list" between each list. After each list, subjects were supposed to do a free recall: to remember as many of the previous words as they could.

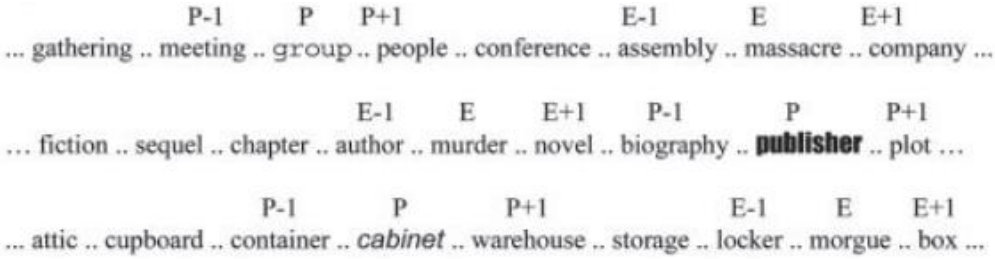

Figure 1. Emotional memory test. Extracted from Strange et al. 2003

The experiment showed, as seen in figure 2, enhanced memory for both emotional and perceptual items. The main finding of the experiment was on the preceding items. There was a negative recall of E-1, but not of P-1. In the graph, zero represents the recall of each category of

words equal to the recall of control nouns. An emotional induced retrograde amnesia can explain this finding.

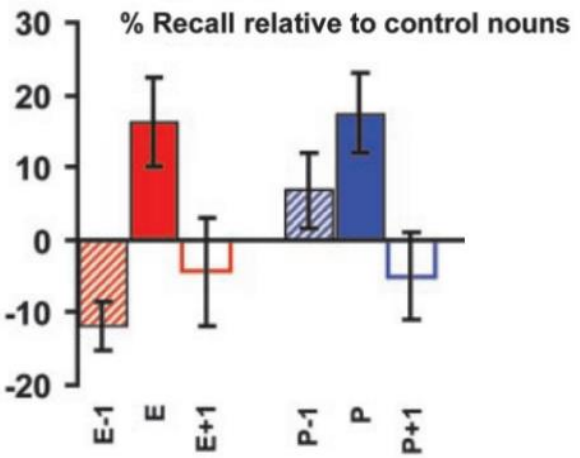

Figure 2. Emotional memory test results in healthy subjects. Adapted from Strange et al. 2003

In a second experiment, the authors wanted to test the effect of the beta-blocker propranolol in EM. They included subjects in two groups: one received propranolol, and the other received placebo before underwent a similar EM test. As seen in figure 3, placebo group presented with similar findings of the previous experiment. However, the propranolol group did not have an enhanced memory for the emotional stimuli. They more frequently recalled E-1 than E, while continued having an enhanced memory for perceptually different words.

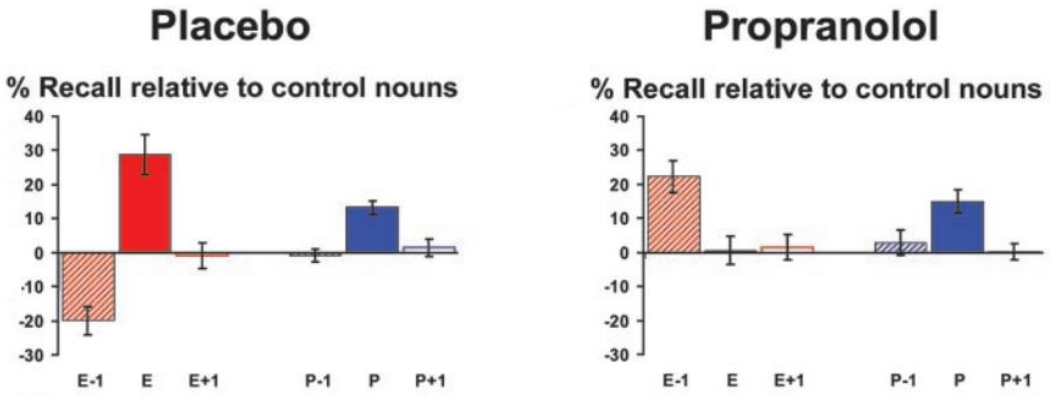

Figure 3. Emotional memory test results in healthy subjects that received propranolol and in healthy subjects that received a placebo. Adapted from Strange et al. 2003

In the third experiment, the authors wanted to assess the same test in a patient (AM) with Urbach-Wiethe disease, a type of lipoid proteinosis. This patient had selective bilateral amygdala damage, but regular attention and short-term memory. The patient was a German speaker. Therefore, the authors performed a translation of the EM test to German and inclusion of 12 native german-speakers healthy subjects. As seen in Figure 4, there was a similar pattern between German controls and English speaker controls. Interestingly, the patient with amygdala dysfunction had a recall pattern similar to subjects who received propranolol on the previous experiment, with no enhanced recall for E, but enhanced recall for P.

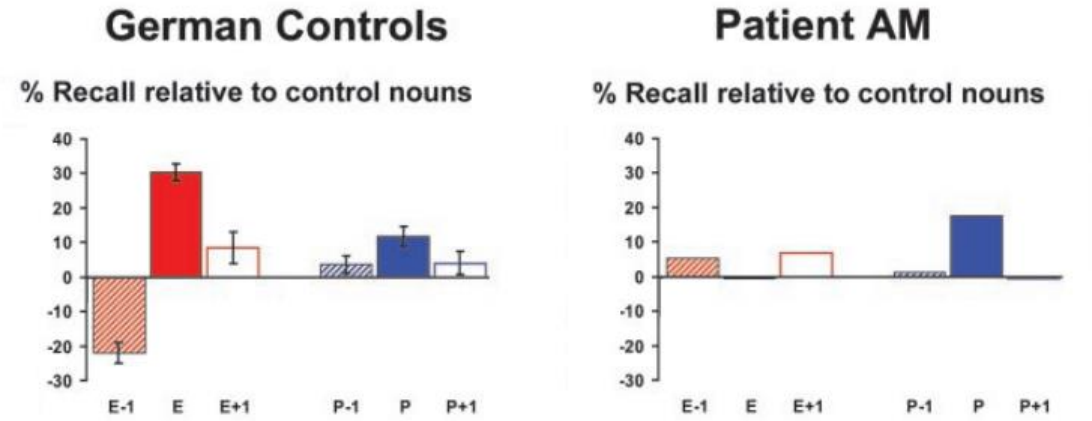

Figure 4. Emotional memory test results in healthy subjects and patient with selective bilateral amygdala damage. Adapted from Strange et al. 2003

Therefore, this study concluded that enhanced recall and amnesia associated with emotional stimuli are amygdala-dependent and influenced by beta-adrenergic modulation. Another study (Strange & Dolan, 2004) assessed for the correlations between emotional memory and functional magnetic resonance imaging (fMRI) findings in healthy controls. For that, subjects underwent an fMRI task, which consisted of encoding and recognition of neutral and emotional items. The authors' found that encoding of emotional items evokes increased human amygdala responses compared to when encoding neutral items. During recognition, those items that evoked greater amygdala activation at encoding led to a greater hippocampal response. Subjects that received propranolol had both effects diminished, indicating that EM is associated with a beta-adrenergic-dependant modulation of amygdala-hippocampal interactions.

Emotional memory is disrupted in neuropsychiatric disorders. Patients with post-traumatic stress disorder (PTSD) exhibit a higher false recall for trauma-related memories. They

also have reduced activity in the amygdala and hippocampus during recall of trauma-related events, and a negative correlation between hippocampal activation and PTSD symptoms (Hayes et al., 2011). Patients with major depressive disorder (MDD) perceive positive items as less positive and have higher false negative memories than healthy subjects (Yeh & Hua, 2009). Patients with schizophrenia have deficits in emotional memory modulation, mainly associated with long-term memory consolidation (Dieleman & Röder). Bipolar disorder (BD) is also associated with changes in structures associated with emotional processing (Kryza-Lacombe et al., 2019) and will be explored in further detail in this thesis.

1.2 Childhood Trauma

Childhood trauma is a complex multifactorial phenomenon. According to the World Health Organization (2006), it occurs in the form of physical and emotional mistreatment, sexual abuse, neglect and negligent treatment, and commercial or other exploitation. Twenty-five percent of adults report having been physically abused during childhood, including one in five women and one in thirteen men reported sexual abuse as a child (World Health Organization, 2016).

During the past few decades, a mutual effort of government, entities, and society contributed to a decline in childhood trauma. Despite the slight improvement, the prevalence of this phenomenon still raises concern. According to Child Trends (2018), in 2016, there were approximately 672,000 maltreated children in the United States, a rate of 9.1 per 1,000. Contrasting with 1994, the rate of maltreatment was 15 per 1,000. Trauma is more ubiquitous at young ages: in 2016, children age 3 or less had a maltreatment rate of 15 per 1,000, while children from 12 to 15 had a rate of 5 per 1,000. Neglect is the most common type of child maltreatment and is also the one that raises concern due to its increasing prevalence. Among all traumatized children, the proportion with reported neglect increased from 49 percent in 1990 to 75 percent in 2016. At the same time, those with reported sexual abuse declined from 17 to 9 percent, and those with reported physical abuse declined from 27 to 18 percent (Child Trends, 2018).

Childhood trauma leads to several consequences for individuals in terms of coping with stress, cognition and interpersonal relationships (Tiwari and Gonzalez, 2018). The amygdala,

prefrontal cortex and hippocampus undergo significant development during childhood, which makes them vulnerable to environmental effects, including trauma (Teicher and Samson, 2016). Individuals exposed to trauma present hypothalamus-pituitary-adrenal (HPA) axis dysfunction (Ladd et al., 1996). Childhood maltreatment is also associated with increased inflammatory markers, including c-reactive protein, fibrinogen, and proinflammatory cytokines, even when controlling for clinical comorbidities (Coelho et al., 2014; D'Elia et al., 2018). Telomere length shortening is seen in children and adolescents who underwent traumatic events (Xavier et al., 2018). Furthermore, individuals who underwent trauma during early life and have specific variants in the FKBP5 gene have an increased risk of aggressive behavior (Bevilacqua et al., 2012).

Psychiatric disorders are multifactorial and usually due to a combination of genetic and environmental factors. While their etiologies are heterogeneous and not completely understood, some factors, including exposure to traumatic events during childhood seem to develop a fundamental role. Individuals who suffered childhood maltreatment have a higher risk of developing PTSD (Berenz et al., 2018) and other psychiatric conditions, including psychosis (Fekih-Romdhane et al., 2019), major depressive disorder (Gomes Jardim et al., 2019), bipolar disorder (Xie et al., 2018), and suicide (Mohammadzadeh at al., 2019).

1.3 Bipolar Disorder

Bipolar disorder is a psychiatric condition characterized by the occurrence of episodes of mania, hypomania, and depression between periods of euthymia. It has a lifetime prevalence of 2.4 percent (Karam et al., 2014). BD is considered the 16th leading cause of years lost to disability (Ferrari et al., 2016) and the 46th highest cause of disability and mortality in the world (Murray et al., 2012). Symptoms usually appear at around twenty years old (Merikangas et al., 2011). BD has a greater impact on people younger than twenty-four years old, being the 6th cause of disability in this age range (Gore et al., 2011). The cost estimated per person with BD ranges from over two thousand to over thirty thousand dollars per year (Jin & McCrone, 2015). BD affects men and women in a similar lifetime prevalence (Seedat et al., 2009). Despite necessary improvements in the past century, a significant number of patients nowadays still never have a chance to receive treatment during their lives (Merikangas et al., 2011).

Symptoms and complications of BD are not exclusive to periods of elevated or depressed mood. Patients present significant cognitive impairment during euthymia. Bourne et al., (2013) published a meta-analysis that included 31 studies, with over 1,000 euthymic BD patients compared to controls in terms of cognitive measurements, including verbal memory, processing speed, executive functioning, and working memory. This review found significant impairment in all domains of cognition studied in euthymic patients with BD even after adjusting analyses for age, educational level, and gender.

1.3.1 Emotional Memory in Bipolar Disorder

Specific aspects of cognition, including emotional memory, are disrupted in patients with bipolar disorder. Neural pathways directly involved with mood changes also play a fundamental role in emotional control (Phillips, 2003). Memory for emotional events activates unique neuroanatomic areas, including the amygdala (Dere et al., 2010). In BD, the occurrence of manic and depressive episodes seems to be due more to an increased intensity of emotions than to different emotional states (Henry et al., 2003).

Despite being one of the most common psychotic disorders, few studies are assessing emotional memory on BD. Most of the studies evaluated facial recognition (Degabriele et al., 2011; Haldane et al., 2008; Malhi et al., 2007). Studies on emotional processing in BD have focused on recognition of emotional facial expressions and the reaction to emotional stimuli. Patients with BD have an impairment in emotional facial recognition and exacerbated reaction to emotions (Addington & Addington, 1998; Degabriele et al., 2011; Getz et al., 2003; Hoertnagl et al., 2011; Malhi et al., 2007; Rocca et al., 2009;). However, the perception of emotions and emotional memory involve different neural mechanisms (Brierley et al., 2004). Facial recognition is not supported primarily by the amygdala. Memory of emotional words correlates to amygdala function (Strange & Dolan, 2004).

Kauer-Sant'Anna et al. (2008) studied emotional memory in BD. Twenty patients with BD and twenty healthy controls (HC) underwent an emotional memory test. Half of the subjects watched a neutral story presentation, while half watched a similar presentation with an emotional story. One week later, subjects answered questions about the stories. The first result, as expected, showed that patients with BD had a worse general recall than HC, which is explained by the

cognitive deficits found in patients with BD. Subjects were also asked, at the end of the story, how emotional they thought the story was. Patients with BD evaluated the neutral story as having a more significant emotional valence than controls.

Further, the study assessed how much each group recalled from each part of the story. Controls had a higher recall for the emotional aspect, while patients did not present with this enhancement. In conclusion, patients with BD had a blunted emotional recall and a higher emotional perception of neutral stimuli when compared to HC.

The study (Kauer-Sant'Anna et al., 2008), despite its importance, left some gaps that justify further studies of this topic. The emotional memory task, due to its particularities, could not be repeated over time in order to assess the progression of this cognitive marker. Also, the authors did not investigate correlations between emotional memory and markers of severity of the disease, including the number of mood episodes. Finally, the study did not assess the influence of other factors that may contribute to emotional memory changes, including exposure to trauma during childhood.

1.3.2 Childhood Trauma in Bipolar Disorder

The incidence of childhood trauma is greater in patients with bipolar disorder and other affective disorders when compared to healthy controls (Etain et al., 2010; Fowke et al., 2012; Lu et al., 2008). Patients with BD who suffered maltreatment during childhood tend to have worse clinical outcomes (Lu et al., 2008). In addition to predisposing individuals to develop psychiatric conditions, including BD, childhood trauma also aggravates the disorder, worsens the progression of the disease, increases vulnerability, and exacerbates symptoms severity (Hammersley et al., 2003; Etain et al., 2008; Daruy-Filho et al., 2011). Patients with BD and previous history of trauma present with worse response to treatment (Marchand et al., 2005), a higher number of psychiatric hospitalizations (Carballo et al., 2008), worse premorbid functioning level and more frequent forensic history associated (Conus et al., 2010). These patients have a higher prevalence of a family history of affective disorder in first degree relatives (Carballo et al., 2008). Patients with BD who suffered maltreatment during childhood also have a higher prevalence of suicide than other patients with BD (Halfon et al., 2013; Dilsaver et al., 2007; Garno et al., 2005; Leverich and Post, 2006; Brown et al., 2005).

Childhood maltreatment is associated with an increased inflammatory state during adulthood (Coelho et al., 2014). Patients exposed to traumatic situations during early life show elevation of serum proinflammatory cytokines (Danese et al., 2009) and decreased serum levels of brain-derived neurotrophic factor (Kauer-Sant'Anna et al., 2007).

Childhood trauma is associated with changes in neuroanatomical structures, including decreased corpus callosum volume in patients with BD who suffered maltreatment at early ages when compared to patients with BD who did not suffer trauma during childhood (Bücker et al., 2014). In other mood disorders such as MDD, sexual abuse, mistreatment, and neglect during infancy alter amygdala function (Grant et al., 2011).

1.3.3 Trajectory of Bipolar Disorder

Bipolar disorder has a progressive and deteriorating trajectory (Fries et al., 2012). Clinical, cognitive, and neurobiological differences are seen between patients in the early and late stages of the disorder. Impairment in terms of inflammatory markers, level of neurotrophins, systemic oxidative stress and neuroanatomy are correlated to disease trajectory in BD (Andreazza et al., 2009; Kauer-Sant'Anna et al., 2009).

BD progression presents with cognitive decline, worse clinical outcomes, functional impairment, poor response to treatment, shortening of inter-episodic period, higher symptom recurrence, more frequent comorbidities, increased risk of suicide and more frequent hospitalizations (Berk et al., 2011; Hawton et al., 2005; Matza et al., 2005; Reinares et al., 2010; Rosa et al., 2012; Kessing and Andersen, 2004; Kapczinski et al., 2008). Progressive cognitive impairment involves mostly episodic memory, sustained attention, executive functioning, verbal fluency, and abstraction ability (Goodwin and Jamison 2007; Bora et al., 2009; Kessing and Andersen, 2004; Torres et al., 2007). No studies have assessed emotional memory in different stages of BD.

Staging models suggest BD as a continuum, progressing from a latent phase to a chronic phase. The latent phase is usually asymptomatic, while patients in chronic phases usually have severe impairments. Early-stage patients have a short duration of the disorder and few mood episodes; late-stage patients have multiple episodes and are more resistant to treatment (Kapczinski et al., 2009).

Stage	Clinical features	Cognition	Prognosis
Latent	At risk for developing BD	No impairment	Good when protected from pathogens
I	Well-defined periods of euthymia without overt psychiatric symptoms	No impairment	Good with careful prophylaxis
II	Symptoms in inter episodic periods related to comorbidities	Transient Impairment	Depends on how well comorbidities can be managed
III	Marked impairment in cognition and functioning	Severe cognitive Impairment	Reserved
IV	Unable to live autonomously owning to cognitive and functional impairment	Cognitive impairment prevents patients from living independently	Poor

Table 1. Clinical staging in Bipolar Disorder. Adapted from Kapczinski et al., 2009.

According to McEwen and Stellar (1993), allostasis is the process of achieving stability through behavioral or physiological changes. This skill relates to how each person deals with stressor events. Subjects are harmed when stressor events are extreme or when coping skills are inefficient. Allostatic load is the cumulative harm as a consequence of adaptation of a subject. Mood episodes are stressor events which increase the allostatic load (Kapczinski et al., 2010; Grande et al., 2011). Due to the successive occurrence of mood episodes and their cumulative effects (Magalhães et al., 2011), patients with BD are regularly exposed to activation of allostatic mechanisms. This activation leads to a cumulative allostatic load, responsible for consequences seen in BD trajectory and for differences seen in early versus late stages of BD. Higher allostatic load is associated with more significant recurrence of mood episodes (Kapczinski et al., 2008),

HPA dysregulation, and accelerated cellular aging (Vasconcelos-Moreno et al., 2017). Figure 5 shows how the burden of the disease (allostatic load) and the impairment in cognitive functioning tends to increase after multiple mood episodes.

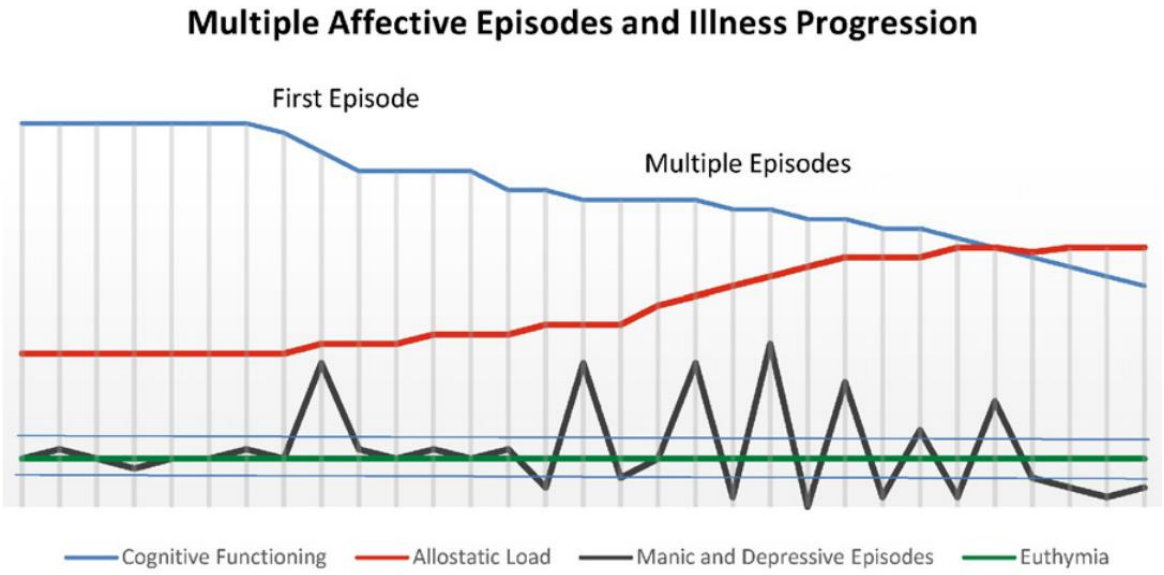

Figure 5. Cognitive impairment observed in patients with BD with few vs. multiple mood episodes. Extracted from Da Costa et al., 2016

1.3.4 Amygdala in Bipolar Disorder

The amygdala is a highly differentiated cluster of nuclei located deep and medially within the temporal lobes (Swanson and Petrovich, 1998). This limbic region is associated with emotion, motivation, fear and rewarding (Janak and Tye, 2015). It is associated with essential dimensions of the human personality related to adaptive and maladaptive socio-affective functioning (Frühholz et al., 2017). There are associations between how patients with cognitive impairment perceive their control over their lives and amygdala networks (Ren et al., 2017). The amygdala plays a fundamental role in judgment of facial trustworthiness, mostly during the processing of negative social (untrustworthy) faces (Santos et al., 2016). Perception of social support is associated with amygdala volume (Sato et al., 2016). Furthermore, the amygdala plays a crucial role in supporting memory for emotionally arousing experiences due to its connectivity with other areas of the brain, such as the hippocampus (Desmedt et al., 2015).

Bipolar disorder is involved with dysfunction of neural circuitry, including the prefrontal-hippocampal-amygdala axis. This circuitry is involved with characteristic behavioral

abnormalities associated with BD, including emotional lability, emotional dysregulation, and heightened reward sensitivity (Phillips and Swartz, 2014). Studies indicate variation of the amygdala volume in patients with BD: while adult patients and patients with multiple episodes have an increased amygdala volume, children and adolescents with BD and patients after their first mood episode have a decreased amygdala volume (Roda et al., 2015).

Findings from studies that assessed amygdala function in BD through fMRI are not universal. Amygdala activity seems to be more related with the nature of the stimuli to which the patient is exposed (i.e., stimuli causing fear or sadness) than to the state of the mood of the patient (euthymia, manic, or depression) (Townsend and Altshuler, 2012). Amygdala hyperactivation is associated with abnormal interactions between the amygdala and cortical brain regions and working memory impairment in BD (Stegmayer et al., 2015). Finally, patients with BD show enhanced activation of the amygdala, prefrontal, and ventral striatal area, while they have decreased hippocampal activity when executing neutral memory tasks (Benson et al., 2014).

2. AIMS

2.1 General aim

To study emotional memory in patients with bipolar disorder through an amygdala-dependant task and to investigate the impact of childhood trauma and disease trajectory on emotional memory.

2.2 Specific Aims

- To translate and cross-culturally adapt to Brazilian Portuguese the emotional memory test developed by Strange et al. (2003);
- To assess for the validation of the translated and cross-culturally adapted emotional memory test in healthy controls from the south of Brazil;
- To compare emotional memory differences between patients with bipolar disorder and paired healthy controls;
- To investigate the impact of previous exposure to trauma on emotional memory in patients with bipolar disorder and healthy controls;
- To investigate the influence of bipolar disorder and disease trajectory on emotional memory.

3. PAPERS

3.1 Paper 1 - Published in Trends in Psychiatry and Psychotherapy - vol.40 no.1 Jan./Mar. 2018

Translation and cross-cultural adaptation of the Brazilian Portuguese version of the Emotional Memory Scale

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Abstract

Background

Emotional memory is an important type of memory that is triggered by positive and negative emotions. It is characterized by an enhanced memory for emotional stimuli which is usually coupled with a decrease in memory of neutral preceding events. Emotional memory is strongly associated with amygdala function and therefore could be disrupted in neuropsychiatric disorders. To our knowledge, there is no translated and culturally adapted instrument for the Brazilian Portuguese speaking population to assess emotional memory.

Objective

To report the translation and cross-cultural adaptation of a Brazilian Portuguese version of the Emotional Memory Scale, originally published by Strange et al. in 2003.

Methods

The author of the original scale provided 36 lists with 16 words each. Translation was performed by three independent bilingual translators. Healthy subjects assessed how semantically related each word was within the list (0 to 10) and what the emotional valence of each word was (-6 to +6). Lists without negative words were excluded (negative selection), most positive and most unrelated words were excluded (positive and semantic selection, respectively), and lists with low semantic relationship were excluded (semantic assessment).

Results

Five lists were excluded during negative selection, four words from each list were excluded in positive and semantic selection, and 11 lists were excluded during semantic assessment. Finally, we reached 20 lists of semantically related words; each list had one negative word and 11 neutral words.

Conclusion

A scale is now available to evaluate emotional memory in the Brazilian population and requires further validation on its psychometrics properties.

Keywords Cross-cultural comparison; memory; emotions; amygdala

Introduction

Emotional memory (EM) is defined as an enhanced memory for emotional stimuli which is coupled with a decrease in memory for events preceding those stimuli.[1] In healthy subjects, EM has already been proven to be associated with amygdala function. In experiments involving lists of words (in which each list contained a word with a negative emotional valence, surrounded by emotionally neutral words), healthy controls tended to have a greater recall of words with a negative emotional valence and a decreased recall of words immediately preceding them. This feature was not seen in the same experiment with patients with amygdala lesions.[2]

The amygdala, a central nervous system structure that is classically associated with emotional control, may be responsible for mediating EM. Strange et al. showed that, in healthy controls, emotional items of a cognitive task are more likely to be recalled than neutral items. Additionally, neutral items that directly precede emotional stimuli are less likely to be recalled than other neutral items. Yet, when these same subjects received propranolol, a beta-blocker medication that acts in the amygdala, enhanced recall of emotional items and deficient recall of preceding items were diminished.[2] These data corroborate the hypothesis that amygdala lesions may impair a subject from distinguishing if an event has a neutral, positive or negative emotional valence.[3] Therefore, patients with amygdala dysfunction may attribute a negative emotion to an event that most individuals would consider emotionally neutral.

Neuropsychiatric disorders, specifically those with repercussions in amygdala function, may be associated with changes in EM. Studies have demonstrated EM changes in patients with bipolar disorder.[4] Amygdala function and EM may be important markers of neurological and psychiatric disorders. However, to the authors' knowledge, a scale to assess EM had so far not been translated to Brazilian Portuguese and culturally adapted.

Therefore, the objective of this study was to describe the creation of a Brazilian Portuguese translation and cross-cultural adaptation of the Emotional Memory Scale originally published by Strange et al.[3]

Methods

Permission to cross-culturally adapt the scale to Brazilian Portuguese was requested from the original author of the Emotional Memory Scale. We also asked for a full list of words used in his experiments. The author of the original scale sent us 36 lists, each with 16 words, in English. Words from each list were semantically related and each list contained a word with a negative valence. After obtaining permission and the lists, we began a five-step validation process: translation, negative selection, positive selection, semantic selection and semantic assessment.

Translation was done by two independent bilingual translators (T1 and T2) who had had no previous contact with the lists of words. Next, a third independent translator (T3) compared the translations and resolved differences.

A group of healthy controls were recruited from a population of volunteer blood donors at blood bank program of Hospital de Clínicas de Porto Alegre. Inclusion criteria were age 18-60 years, not fulfilling criteria for any psychiatric diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (checked with Structured Clinical Interview for DSM-IV Axis I Disorders – SCID-I), a negative history of psychiatric and neurological disorders, and a negative history of psychiatric disorders in first-degree relatives.

Each subject received two copies of the 36 lists of 16 words each. In the first copy, each subject was asked to assign a score to the emotional valence of the word, from -6 to +6 (-6 to -3 was considered negative, -2 to +2 was considered neutral, and +2 to +6 was considered positive). In the second copy, each subject had to assign a score from 0 to 10 on how semantically related each word was compared to other words from the list (0 = not semantically related, 10 = completely semantically related). After that, we calculated the mean emotional valence of each word, the mean semantic relationship of each word, and the mean semantic relationship of each list.

In the step of negative selection, lists that did not have any words with a mean negative emotional valence were excluded. In the step of positive selection, we excluded the two most positively ranked words from each list. Semantic selection consisted of excluding the two most semantically unrelated words from each list. Finally, semantic assessment excluded lists with a lower mean semantic relationship.

Figure 1 illustrates the translation and adaptation process. We followed instructions from the author of the original scale, who used a similar process in the translation of the scale to other languages.[2]

All study procedures were approved by the research ethics committee of Hospital de Clínicas de Porto Alegre. Written informed consent was obtained from all subjects prior to their inclusion in the study.

Results

During the translation step, there was variation in the translations done by T1 and T2. T3 resolved these differences by selecting the translation that best correlated to the original meaning of the word. Also, T3 chose the word he assumed would be best understood by members of the population under investigation.

For the remaining steps, we included 11 healthy subjects, a number that is similar to the number of people used to create the original scale and to translate it to other languages.[2] Mean age was 27.3 years (standard deviation = 3.634), mean years of education was 13.4 (SD = 2.416), and six (54.54 %) of the subjects were women. Our study population had similar characteristics to that of the original study that validated the English scale.

Five out of 36 translated lists did not have any words considered emotionally negative, therefore these lists were excluded during negative selection. The two most positive words from each list were excluded during the positive selection step. The two least related words from each list were excluded during semantic selection. Eleven lists were excluded during semantic assessment due to the low semantic relationship between the words.

At the end of the five steps, we concluded that 20 lists with 12 words each were valid for use in the Brazilian Portuguese population. Each list has one word considered to be emotionally negative (mean emotional valence between -6 and -3) and 11 words considered to be emotionally neutral (mean emotional valence between -2 and +2). Words from each list were semantically related.

The final version of the Emotional Memory Scale translated and culturally adapted to Brazilian Portuguese is shown in Figure 2. Words considered to have a negative valence are marked with (E). The other 11 words from each list were considered emotionally neutral.

Discussion

Several studies have demonstrated a cognitive deficit in patients with psychiatric disorders.[5] These impairments were already established in diagnoses like bipolar disorder,[6] major depressive disorder[7] and schizophrenia[8] and could be explained by changes in the hippocampus, frontal cortex and amygdala. Studies of cognition in psychiatric disorders are useful to better understand mental illness and to develop new treatments to improve the functionality and well-being of patients.

EM is a cognitive domain which may be altered in patients with bipolar disorder.[4] There is evidence that memory for emotional events may require specific neuroanatomical circuits, which include the amygdala. Also, there is reason to believe that processing of emotions may be disrupted in patients with bipolar disorder: many symptoms associated with mood episodes are controlled by pathways common to emotional processing.[9]

Strange et al.[3] developed a scale to assess EM in healthy subjects and proved that EM was impaired after treating these subjects with propranolol, a beta-blocker that acts in the amygdala. His scale has also been translated to German.[2] However, to our knowledge, this scale has not been tested in patients with bipolar disorder: it would be interesting to do so in order to investigate possible EM changes, compared to EM changes in healthy subjects treated with propranolol. Furthermore, it would be interesting to apply this scale in patients with other psychiatric diagnoses, like major depressive disorder and schizophrenia, in order to assess possible changes in emotional circuits.

Working with two translators and a third blind translator during cross-cultural adaptation of the Emotional Memory Scale helped to reach satisfactory semantic equivalence to the original instrument. This method also ensured that differences between two translations were reconciled to define appropriate translation.

Semantic selection and semantic assessment were important to reach a final list of words which were considered semantically related by healthy controls in our social environment. Negative selection and positive selection were important to verify that the final lists had 11 emotionally neutral words and 1 word considered emotionally negative by our population. Having completed these steps, we believe that the scale is now suitable for research on EM in Brazilian Portuguese speakers.

Study limitations include a small number of participants; however, sample size was similar to studies that validated the scale to other languages. It is also important to note that our methods involved only translation and cross-cultural adaptation. Future studies may corroborate validation of the scale. Furthermore, another limitation of the study would be potential cultural differences between different regions of Brazil: our study population was entirely recruited at the same hospital.

Cross-cultural adaptation is a fundamental step when translating a scale.[10,11] The Emotional Memory Scale designed by Strange et al. had already been translated and adapted to German and has been used in important studies about cognition.[2] The Brazilian version of the Emotional Memory Scale may significantly contribute to this field of study. Future studies should assess the reliability of the instrument.

Conclusion

This study described cross-cultural adaptation of the Emotional Memory Scale to Brazilian Portuguese. Five steps were followed, according to the recommendations from the author of the original scale: translation, negative selection, positive selection, semantic selection and semantic assessment. As a result, 20 lists of words were determined, each containing 11 neutral words and 1 word with an emotionally negative valence. The Emotional Memory Scale is considered adequate for use in the Brazilian population, and we believe it will fill a significant gap in this field of study, contributing to the development of future studies about EM in psychiatry.

Acknowledgments

This study was funded by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

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Received: October 13, 2017; Accepted: December 12, 2017

Disclosure

No conflicts of interest declared concerning the publication of this article.

Figures

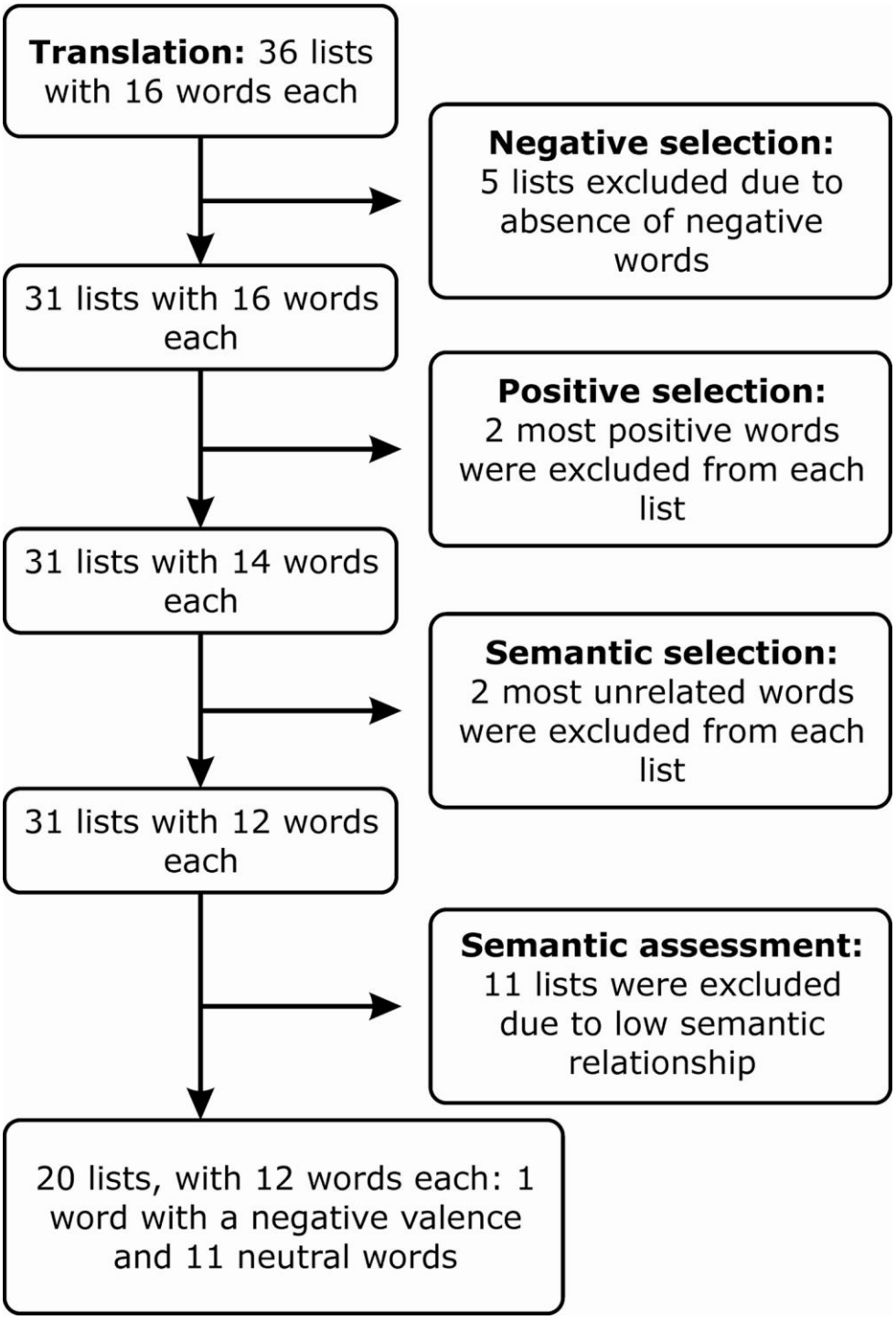

Figure 1 Five steps of the translation and cross-cultural adaptation process of the Emotional Memory Scale

List 1	List 2	List 3	List 4	List 5	List 6	List 7	List 8	List 9	List 10
condutor	comício	articulação	boca	gelo	gengiva	janela	olho	trabalho	carvão
pedestre	pessoa	quadril	nariz	chuva	flúor	mansão	panorama	químico	gás
passageiro	comunidade	calcanhar	oxigênio	lancha	dente	proprietário	vídeo	bancário	caldeira
caminhão	reunião	cotovelo	inalação	nublado	saliva	condomínoi	vista	físico	vapor
camionete	congresso	pulso	pulmão	casaco	pasta	morado	cena	ocupação	tubulação
carro	simpósio	membro	respiração	cidade	canino	apartamento	imagem	advogado	(E) explosão
(E) acidente	congregação	joelho	vento	boia	mandíbula	porta	visão	engenheiro	fogão
ônibus	assembléia	tornozelo	sopro	córrego	(E) afta	garagem	ótica	ator	temperatura
rua	aglomeração	ombro	ventilação	(E) enchente	molar	casa	cinema	vocação	aquecedor
motorista	(E) massacre	braço	(E) sufocamento	luva	oral	chalé	(E) cegueira	(E) assassino	fogareiro
estrada	empresa	(E) amputação	narina	prancha	labial	(E) arromabamento	observador	contador	lenha
avenida	escritório	pé	ar	frio	escova	sobrado	lupa	ofício	forno
List 11	**List 12**	**List 13**	**List 14**	**List 15**	**List 16**	**List 17**	**List 18**	**List 19**	**List 20**
criança	sino	palma	estação	pijama	ferramente	educador	construção	rio	adubo
pai	missa	nervo	baile	dormitório	polir	educação	mirante	lagoa	colina
berço	crença	dedo	festival	lua	parede	professor	telhado	canoa	solo
gravidez	convento	tato	estádio	anoitecer	metal	escola	pico	piscina	cascalho
mamadeira	padre	corpo	show	travesseiro	madeira	faculdade	torre	balsa	jardineiro
cesariana	culto	pele	cobrador	quarto	ferro	(E) reprovação	(E) suicídio	baía	chão
parto	capela	toque	(E) traficante	sono	martelo	colégio	ponte	(E) afogamento	rocha
bebê	pastor	sensação	boate	lençol	(E) crucificação	aula	penhasco	nadador	terreno
nascimento	igreja	textura	rodoviária	cobertor	carpinteiro	universidade	altura	riacho	(E) cadáver
gestação	(E) diabo	superfície	público	escurecer	parafuso	acadêmico	sacada	barco	raiz
(E) aborto	templo	(E) dor	metrô	(E) pesadelo	prego	tutor	alto	água	terra
chupeta	bíblia	vibração	turma	camisola	serrote	prova	prédio	areia	escavação

Figure 2 Emotional Memory Scale translated and culturally adapted to Brazilian Portuguese.
(E) = word with negative emotional valence.

3.2 Paper 2 - Published in the Journal of Affective Disorders - 2020 Jan 1;260:206-213. Epub 2019 Sep 2.

Emotional memory in bipolar disorder: Impact of multiple episodes and childhood trauma.

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Abstract

Background:

Emotional memory is a critical amygdala-dependent cognitive function characterized by enhanced memory for emotional events coupled with retrograde amnesia. Our study aims to assess the influence of bipolar disorder (BD), trauma, and the number of mood episodes on emotional memory.

Methods:

53 subjects (33 euthymic patients with BD and 20 healthy controls) answered a clinical assessment, childhood trauma questionnaire (CTQ), and an emotional memory test composed of lists of nouns, including neutral words, one emotional (E), one preceding (E-1) and one following word (E + 1). We assessed for the influence of type, position, diagnosis, trauma, and number of mood episodes in word recall using generalized estimating equations.

Results:

Controlling for neutral words, BD had a higher recall for E-1 ($p = 0.038$) and a trend for a higher recall of E ($p = 0.055$). There was no difference between patients with and without trauma. Patients with BD who suffered multiple mood episodes had a higher recall of E compared to patients with fewer episodes ($p = 0.016$).

Limitations:

Cross-sectional design and small sample size.

Conclusion:

Our results indicate dysfunction in emotional memory in patients with BD, particularly after multiple mood episodes. While we expected an impaired emotional memory, patients with BD showed an increased recall for emotional stimuli and events preceding them. Childhood trauma does not seem to interfere with emotional memory changes in patients with BD. Emotional memory enhancement seems to be a promising marker of progression in BD.

Keywords: Bipolar disorder; Disease progression; Emotions; Memory; Psychological trauma

Highlights

- Bipolar disorder enhances memory for emotional stimuli and events preceding them.
- Trauma does not lead to emotional memory changes in bipolar disorder.
- Bipolar disorder enhances emotional memory particularly after many mood episodes.

1. Introduction

Emotional memory is an important cognitive function characterized by an enhanced episodic memory for events with an associated emotional valence. Individuals tend to have a higher recall of events which trigger emotions and sensations, and of facts which the individual considers emotionally negative (Bowen et al., 2018). This salient memory is usually coupled with retrograde amnesia, which leads to a decreased recall of neutral events that precede the emotional stimuli (Christianson, 1992). Memory tests with lists of words demonstrated that healthy controls tend to have a higher recall of emotional words and a lower recall of the neutral preceding word (Strange et al., 2003). Temporal lobe regions, particularly the amygdala, play a fundamental role during encoding and retrieval of emotional episodic memories (Dolcos et al., 2017). Changes in structures of the limbic system correlate with a dysfunctional emotional process (Cahill, 1999). This dysfunction seen in patients with neuropsychiatric disorders such as bipolar disorder is triggered by a combination of genetic and environmental factors, including previous exposure to trauma. The study of cognitive-emotional processing in individuals with prior exposure to trauma and with mood disorders is critical to better understanding the neural pathways associated with these conditions.

Bipolar disorder is a progressive condition associated with cognitive impairment. Specific aspects of cognition, such as emotional memory, seem to be impaired in patients with BD, which could be due to mood symptoms sharing common neural pathways with emotional processing (Phillips, 2003). Episodic memory for emotional events involves the activation of the amygdala, which was shown to be hyperactivated in patients with BD (Mercer and Becerra, 2013). It has been theorized that most of the variations between mania and depression are due to the intensity of emotions rather than the occurrence of conflicting emotions (Henry et al., 2003). Patients with BD tend to interpret neutral facts as emotional or traumatic (Kauer-Sant'Anna et al., 2008). Despite BD being one of the most common and debilitating mood disorders, few studies have evaluated emotional memory in these patients, most of which have been limited to facial recognition (Degabriele et al., 2011; Haldane et al., 2008; Malhi et al., 2007). The vast majority of studies that aimed to evaluate emotional processing in BD focused on emotional expression recognition and reaction to emotional stimuli, revealing that patients with BD have difficulty recognizing facial emotions and exhibit an increased response to emotional events (Addington

and Addington, 1998; Campbell and MacQueen, 2006; Degabriele et al., 2011; Getz et al., 2003; Hoertnagl et al., 2011; Rocca et al., 2009). However, emotional perception and emotional memory involve different thought processes (Brierley et al., 2004), while facial recognition seems to not be primarily amygdala-dependent (Hamann and Adolphs, 1999). Therefore, it is crucial to evaluate emotional memory through an amygdala-dependent task in patients with BD.

Patients with BD also present with decline in executive functioning, verbal and visual memory, verbal fluency, and sustained attention, not only during the occurrence of mood episodes, but also during euthymia (Bora et al., 2009; Bourne et al., 2013; Goodwin and Jamison, 2007; L.J. Robinson et al., 2006; Torres et al., 2007). These cognitive deficits result in social and occupational impairment (Martinez-Aran et al., 2004), seem to be progressive, and correlate with the number of mood episodes (F. Kapczinski et al., 2008a; Kauer-Sant'Anna et al., 2009). There are significant differences between patients who underwent few versus many mood episodes, including in neuroanatomy (Lyoo et al., 2006; Strakowski et al., 2002), executive functioning (Rosa et al., 2014), inflammatory and neurotrophic factors (Kauer-Sant'Anna et al., 2009), and systemic oxidative stress (Andreazza et al., 2009). Furthermore, BD patients who suffered from a higher number of episodes tend to have worse clinical features than other patients (Rosa et al., 2012; Schuepbach et al., 2008). Acute mood episodes were associated with systemic inflammation and cognitive deficit in BD (Grande et al., 2012; Kapczinski et al., 2010), and these effects may be cumulative (Magalhães et al., 2011). Moreover, a higher number of mood episodes and a longer length of disease were associated with impairment in coping in patients with BD (F. Kapczinski et al., 2008b).

Subjects with a history of traumatic events during childhood, such as sexual abuse, mistreatment, and neglect, also exhibit emotional processing dysfunction (Grant et al., 2011). There is a higher prevalence of stressor events during childhood in patients with BD (Leverich and Post, 2006). Patients with BD that suffered maltreatment during childhood tend to have worse clinical outcomes (Lu et al., 2008). Childhood trauma also increases vulnerability and exacerbates symptom severity in BD (Hammersley et al., 2003; Etain et al., 2008; Daruy-Filho et al., 2011). Patients with BD and previous history of trauma present with worse response to treatment (Marchand et al., 2005), a higher number of psychiatric hospitalizations (Carballo et al., 2008), worse premorbid functioning level and more frequent forensic history (Conus et al., 2010). These patients have a higher prevalence of family history of affective disorder in first

degree relatives (Carballo et al., 2008). Patients with BD who suffered maltreatment during childhood also have a higher prevalence of suicide than other patients with BD (Halfon et al., 2013; Dilsaver et al., 2007; Garno et al., 2005; Leverich and Post, 2006; Brown et al., 2005). It is unclear, however, how childhood trauma affects emotional memory in patients with BD.

Therefore, this study aims to assess emotional memory in patients with bipolar disorder (BD) and healthy controls (HC). We will also investigate possible emotional memory changes in patients with BD with trauma. Moreover, we will compare emotional memory results between patients with BD with few and many mood episodes. This is the first study to assess the influence of disorder trajectory and traumatic events on emotional memory in patients with BD. Based on previous studies (Kauer-Sant'Anna et al., 2008), we hypothesized that patients with BD, especially those with prior exposure to trauma and a higher number of mood episodes, would have an impaired emotional memory compared to HC with no trauma exposure.

2. Methodology

2.1. Participants

This is a cross-sectional study that included 53 subjects by convenience - 33 patients with BD type I and 20 healthy controls. This sample is similar to previous studies that investigated emotional memory in patients with mood disorders (Bogie et al., 2019): Baños et al. (2001) included 20 patients with major depressive disorder and 20 controls, Delgado and Chaves (2013) included 19 patients with psychotic manic episodes and 12 in nonpsychotic manic episode, KauerSant‘Anna et al. (2008) included 20 euthymic patients with BD and 20 controls.

Patients were included from the Bipolar Disorder Outpatient Clinic (PROTHABI) at the Hospital de Clinicas de Porto Alegre, in Southern Brazil. HC were volunteer blood donors at the Blood Bank Program of Hospital de Clinicas de Porto Alegre. Inclusion criteria for patients were: (1) diagnosis of BD type I according to DSM-5 (SCID), (2) age between 18 and 60 years, (3) meeting euthymia criteria for at least 45 days defined as a score ≤7 on the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) and on the Young Mania Rating Scale (YMRS) (Young et al., 1978). Inclusion criteria for HC were: (1) no psychiatric diagnosis according to DSM-5 (SCID), (2) age between 18 and 60 years of age, (3) score ≤7 on the HAM-D and on the YMRS,

(4) no lifetime history of psychiatric disorder, and (5) no family history of psychiatric disorder. Exclusion criteria for both groups were: (1) severe systemic illnesses, (2) neurological illnesses, (3) inability to answer the emotional memory test, and (4) use of beta-blockers, benzodiazepines or stimulants.

This study was approved by the Ethics Committee of the Hospital de Clinicas de Porto Alegre. After a complete verbal description of the study, all participants provided written informed consent to enter the study.

2.2. Measures

2.2.1. Sociodemographic and clinical features

We obtained the subjects' clinical and sociodemographic data through a structured interview. The 17-item HAM-D and the YMRS were administered by trained raters to assess depressive and manic symptoms, respectively.

2.2.2. Childhood Trauma Questionnaire

This scale investigates the history of abuse or neglect during childhood (Grassi-Oliveira et al., 2014). It has 28 statements related to childhood facts. Subjects estimated the frequency of each item from 1 (never true) to 5 (very often true). The questionnaire was initially developed in English (Bernstein et al., 1994) and was translated and validated to Brazilian Portuguese (Grassi-Oliveira et al., 2006). Childhood Trauma Questionnaire (CTQ) reliability has been demonstrated in patients with BD (Etain et al., 2010) and correlated with neuroimaging findings in this population (Bücker et al., 2014). The CTQ assesses the occurrence of five types of trauma before 18 years old: emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse. Each type of trauma is scored by summing the items corresponding to it. Higher scores indicate a higher level of trauma. According to the manual (Bernstein et al., 1994), specific cut off scores for each type of childhood trauma classify it as none, low, moderate, or severe. Subjects were considered to have a history of trauma if the presence of one or more type of trauma was evaluated as moderate or severe

2.2.3. Emotional Memory Test

We assessed emotional memory with a test that was initially developed by Strange et al. (2003) and was translated to Brazilian Portuguese and culturally adapted by our research group. This test demonstrated the correlation between emotional memory and amygdala function in healthy controls (Strange et al., 2003; Strange and Dolan, 2004). Translation and cross-cultural adaptation were described in detail previously (Fijtman et al., 2018). We followed the instructions described by Strange et al. (2003) when administering the test. In a quiet room, with only an examiner and a computer, participants were shown 20 lists with 12 semantically related nouns. The words "New List" were presented between lists. Words appeared for 3 s on a computer screen. Each list had 11 neutral nouns and one negative emotional (E) noun, which was aversive in content but of the same semantic category as the neutral nouns. One of the neutral words had a perceptual difference (P), displayed in a different font but emotionally neutral and of the same semantic category of other nouns. One word preceding (E1) and one following (E + 1) the emotional noun (E) were included in the neutral noun category. Also, there was one word preceding (P-1) and one following (P + 1) the perceptual word (P). Finally, there were some control nouns on the lists, which were neutral, not one of the first three words of the list, and not directly preceding or following E-1, E, E + 1, P-1, P, or P + 1. Other than the perceptual word, all other words were presented in Times New Roman font. P was exhibited in a different font on each list. To set the context, the first three nouns in each list were always neutral and did not belong to any of the specific word categories. Position of E and P were randomized between position 5 and 11. The relative position of E versus P changed between lists. During the test, subjects were asked to perform an encoding task (Craik and Lockhart, 1972), indicating whether the first letter in the word had an enclosed space. Following the last word of each list, subjects underwent a distractive task, which consisted of subtracting three from a random number that appeared on the screen for 30 s. Immediately after, subjects were asked to perform a free recall of as many words as they could from the list. Similar to the original experiment, recall performance was expressed relative to control nouns randomly selected from lists, and long-term recall was not evaluated.

2.3. Statistical analysis

All statistical analyses were conducted using SPSS 20.0 (SPSS Inc., Chicago, Illinois, USA). Shapiro–Wilk was used for assessing normality. To assess demographic and clinical group differences, a chi-square test was used to compare categorical parametric variables and t-test to compare continuous parametric variables. Mann-Whitney was used to analyze non-parametric variables.

Analyses of the emotional memory test followed what was previously described by Strange et al. (2003). First, we assessed for the validation of each list in the control group to confirm that we were adequately evaluating emotional memory. We checked the emotional vs. perceptual properties of all lists according to what was initially described by Strange et al. (2003) and subsequently translated by Fijtman et al. (2018). We also reviewed the negative valence of each word from our previous paper (Fijtman et al., 2018). The following analyses would be conducted only with validated lists in terms of psychometric proprieties and emotional valence. To assess for episodic memory, we calculated how much each subject recalled words 4 to 12 from each list, disregarding word category. To investigate emotional memory, initially, we calculated the difference between recalling and not recalling each word category within groups. After, we evaluated the difference between recall rate of each of the six categories (E-1, E, E + 1, P-1, P, and P + 1) and control nouns. With these results, we performed generalized estimating equations (GEE) for repeated measures and Bonferroni test for post-hoc analysis. First GEE assessed for the influence of type (E/P), position (−1/0/+1), and diagnosis (BD/ HC) in word recall. Second GEE assessed for the influence of type, position, and trauma in word recall. Third GEE, only in BD group, assessed for the influence of type, position, and the number of mood episodes (few/many) in word recall. GEE were controlled for age, sex, and years of education. All statistical tests were two-tailed with a significance threshold of an $\alpha = 0.05$.

3. Results

3.1. Clinical and sociodemographic characteristics of our sample

Comparisons between BD and HC samples showed no differences regarding age, sex, or years of education (Table 1). We found a trend for higher education in HC ($p = 0.07$). All patients were euthymic and stabilized with their prescribed medications during evaluation. Regarding psychiatric drugs, patients were taking valproic acid (n = 17), risperidone (n = 11), lithium (n = 7), clozapine (n = 3), fluoxetine (n = 2), olanzapine (n = 2), quetiapine (n = 2), chlorpromazine (n = 1), lamotrigine (n = 1), and sertraline (n = 1).

----------(TABLE 1.)----------

3.2. Emotional Memory Test Validation in HC

Five of 20 lists were selected for analysis. These five lists were ones with the most negative valence of the emotional word (E) and most neutral valence of the word that preceded the emotional (E-1) based on our previous study (Fijtman et al., 2018). From the 20 lists initially translated and cross-culturally adapted for the test, lists 2, 11, 13, 18, and 19 were included, with emotional words being "massacre", "miscarriage", "pain", "suicide", and "drowning", respectively. These lists presented psychometric properties similar to that described by the author of the original scale, with HC having a higher recall for E than E-1, but not for P than P-1. These psychometric properties were not observed for the 15 other lists (Fijtman et al., 2018). We conducted the following analysis with results only from five lists. Therefore, we had five words from each category (E-1, E, E + 1, P-1, P, and P + 1) and four control nouns spread amongst the five validated lists. Due to the requirements of the control noun (neutral, not to be one of the first three words of the list, not to directly precede or follow any word from other categories), one of the validated lists did not include a control noun.

3.3. General Word Recall in BD vs. HC

General word recall showed a non-normal distribution only in the BD group. Therefore, Mann–Whitney test was used to assess for differences between groups. HC had a higher recall for all words between positions four to twelve in the five analyzed lists compared to BD [median = 43.33% (IQR = 16.25) vs median = 25% (IQR = 20), $p < 0.001$], as seen in Fig. 1.

----------(FIGURE 1.)----------

3.4. Emotional Memory in BD vs. HC

Generalized estimating equation (GEE) was significant for the interaction type*position*diagnosis ($p = 0.025$). BD had a higher recall of E-1 ($p = 0.038$) and P +1 ($p = 0.001$) when compared to HC. There was also a trend of a higher recall of E in BD compared to HC ($p = 0.055$) (Fig. 2).

----------(FIGURE 2.)----------

3.5. Emotional Memory and Childhood Trauma Questionnaire in BD vs. HC

50% of the patients with BD ($n = 15$) and 31.57% of the HC ($n = 6$) had experienced trauma according to the CTQ. Three patients and one HC did not answer the CTQ. We analyzed the difference between the four groups: BD with trauma (BD + T), BD without trauma (BD-T), HC with trauma (HC + T), and HC without trauma (HC-T). GEE was significant for the interaction type*position*group ($p = 0.005$). There was no difference in terms of word recall between BD + T and BD-T. HC-T had a lower recall than BD-T of E-1 ($p = 0.025$), P ($p = 0.011$), and P +1 ($p < 0.001$). HC-T had a lower recall than HC + T of E + 1 ($p = 0.029$) and P ($p = 0.005$). HC-T had a lower recall than BD + T of P +1 ($p = 0.017$). Sub analysis of HC+T revealed a lower recall than BD-T of P +1 ($p = 0.015$) and did not show other differences when comparing to patient groups. However, findings in healthy controls with previous childhood trauma are preliminary and should be discussed with caution due to small sample size of HC + T ($n = 6$) (Fig. 3).

----------(FIGURE 3.)----------

3.6. Emotional Memory in Early BD vs. Late BD

BD patients had an average of 14.69 previous mood episodes (standard deviation = 16.97). Ten patients did not answer information regarding the number of mood episodes. Our sample was divided based on its median number of episodes to compare groups, as an exploratory analysis in a small sample. A total of 43.47% (n = 10) had 7 or fewer previous mood episodes and were considered as few mood episode patients (FME). A total of 56.52% (n = 13) had 8 or more, considered many mood episode patients (MME). We calculated the density of mood episodes dividing the number of mood episodes by the age of each patient. MME had a higher density of mood episodes than FME [average = 0.483 (SD = 0.354) vs. 0.115 (0.048)] ($p = 0.003$). GEE was significant for the interaction type*position*group ($p = 0.027$). MME patients had a higher recall for E ($p = 0.016$) when compared to FME. Furthermore, FME did not have a higher recall of E when compared to E-1 ($p = 0.651$), contrary to results seen in MME ($p < 0.001$) (Fig. 4).

----------(FIGURE 4.)----------

4. Discussion

In this study, we investigated the influence of BD, trauma, and number of mood episodes in emotional memory changes. Our first finding corroborated an impairment of episodic memory in patients with BD when compared to HC. BD leads to an impairment of multiple cognitive domains, including verbal (L.J. Robinson et al., 2006) and nonverbal (Deckersbach et al., 2004) memory, executive functioning (Dickinson et al., 2017), and functionality (Vasconcelos-Moreno et al., 2016). This impairment is seen not only in mood episodes but also in euthymia (Bourne et al., 2013) and seems to be positively correlated with the number of mood episodes (Robinson and Ferrier, 2006). According to the International Society for Bipolar Disorders, there are significant differences between patients with few and many mood episodes, specifically, higher number of episode patients having a worse overall prognosis and weaker response to standard treatment (Kapczinski et al., 2014).

Interestingly, despite having a lower general episodic memory, patients with BD had a higher recall for emotional stimuli and for words that immediately preceded the emotional words when controlling for neutral stimuli. This finding points toward an enhanced memory associated

with adverse emotional events in these patients, which could be related to a dysfunctional hyperactivation of the amygdala. Euthymic BD patients tend to evaluate neutral events as emotional (KauerSant'Anna et al., 2008). Our study did not investigate the influence of positive emotional stimuli on episodic memory. In a previous study, BD showed higher activation of the hippocampus for emotional versus neutral scenes when compared to HC and patients with other psychiatric disorders including schizophrenia (Whalley et al., 2009). Unmodulated effects in BD may be a consequence of the positive hyper connectivity of the amygdala with the rest of the brain. Despite having a higher recall of E and E-1, patients with BD did not have a higher recall of P or P-1. However, we found a higher recall for P + 1, which could suggest an enhanced memory for perceptually salient stimuli to be associated with BD as well. Compared to controls and patients with unipolar depression, BD showed a hyperactivation of the amygdala, not only when exposed to emotional, but also neutral stimuli (Benson et al., 2014). Furthermore, amygdala, prefrontal, and visual system hyperactivation are demonstrated to play an essential role in the emotional dysfunction present in BD (Wegbreit et al., 2014).

Previous studies assessing emotional memory in patients with BD have presented divergent results. Kauer-Sant'Anna et al. (2008) found a diminished emotional recall in euthymic patients with BD, similar to our findings in patients with few mood episodes. The previous study did not assess for the influence of mood episodes on emotional memory. (Whalley et al., 2009) did not find differences in emotional memory between patients with BD and controls, however this could be due to the inclusion of patients in different mood states. (Delgado and Chaves, 2013) found that patients with BD during manic episodes have a higher recall of positive emotional events than controls. (Lex et al. 2008) found no difference in recall for negative items between euthymic patients with BD and controls through the Stroop Emotional Test; however, their test also did not show any difference in terms of general words recall. Additionally, their analyses did not control for sex, education, and age; and their emotional recall was not normalized to overall recall.

We also investigated whether childhood trauma influences emotional memory in patients and controls. Surprisingly, previous exposure to trauma did not seem to affect emotional memory in BD. HC with prior exposure to trauma had emotional memory results more similar to BD than to HC without trauma; however, our sample only included six healthy controls with previous trauma. Therefore results are preliminary and not conclusive. Patients with a psychiatric

diagnosis associated with trauma, such as post-traumatic stress disorder (PTSD), often exhibit alterations in emotional memory and emotional regulation. These alterations include disrupted memory for trauma-related events, and a negative correlation between hippocampal activation during emotional recall and PTSD symptoms (Hayes et al., 2011). Previous trauma seems to increase memory bias for adverse events in some patients with major depressive disorder (Vrijsen et al., 2015). While in BD, childhood trauma may lead to neuroanatomical and clinical changes (Bücker et al., 2014; Janiri et al., 2017; Xie et al., 2018), there is little evidence on how previous trauma impacts emotional memory in these patients. Based on our study, exposure to trauma during childhood may not be responsible for adverse emotional regulation alteration in BD. Although consequences of trauma and BD appear to be similar in terms of emotional memory changes, these variables may not present with an additive effect.

One of the main findings of this study was the difference between emotional memory in patients with few (FME) versus many (MME) previous mood episodes. While FME patients had a diminished memory for emotional stimuli (having a similar recall of E-1 and E), MME patients had an exaggerated recall for the emotional word, which was associated with retrograde amnesia (lower recall for E-1). Compared to FME patients, MME patients have worse social functioning (TatayManteiga et al., 2018), reduction of gray matter (Duarte et al., 2018), worse reported quality of life (Tatay-Manteiga et al., 2019), shortening of telomere length (Huang et al., 2018), exacerbated hypothalamic-pituitary-adrenal axis dysfunction (Fries et al., 2015), worse functional status (Rosa et al., 2014), smaller hippocampus and worse verbal memory (Cao et al., 2016). To our knowledge, our study was the first to assess emotional memory differences between patients with few and many previous mood episodes, adding important novel information to the field of neuroprogression in BD.

Some limitations of our study should be considered. Our study has a small sample size, and we had some missing data in CTQ and number of mood episodes. Our sample size, however, even after excluding missing data, was similar to the study that initially developed the scale (Strange et al., 2003), which included 12 patients in each group to assess the effect of a beta-blocker in emotional memory and to other studies that investigated emotional memory in patients with mood disorders (Bogie et al., 2019). It is important to clarify that this study included a validation step of the scale in HC. For this validation, we analyzed the psychometric proprieties of each list, and also reviewed the results of our previous translation and cross-cultural adaptation

study (Fijtman et al., 2018). This can lead to a double-dipping bias, but this step was essential to ensure that the lists that were going to be used were accurately identifying an emotional-dependent episodic memory in our population. Also, our test did not randomize items "E-1″, "E + 1″, "P-1″, and "P + 1″, which might have impaired within-group comparisons. Some stimuli will for various reasons show better memory recall than other stimuli. This limitation, however, should not have a significant impact on between-group comparisons, the primary goal of our study. Therefore, for future studies which may also utilize this test, we recommend the analysis of lists 2, 11, 13, 18, and 19 and the randomization of items that surround E and P when assessing for emotional memory. Additionally, we decided to split our sample according to the median number of mood episodes as a strategy to explore a small sample, but it may not reflect precisely early vs. late stage criteria used in previous studies; such as length of illness or first episode versus multiple. It may be more conservative to consider that our results reflect a group of patients with fewer episodes, and perhaps less severe trajectory; compared to a group with greater number of episodes and a more severe course of illness, arbitrarily defined to explore emotional memory outcomes. With these limitations in mind, we included ten patients with seven or fewer episodes and thirteen patients with eight or more episodes. Finally, it is important to consider that this is a cross-sectional study, and recall bias must be taken into account when interpreting the results of previous exposure to trauma. CTQ, however, seems to have good reliability in previous studies. Another limitation to consider was the use of medications. Most of our sample was receiving valproic acid, anti-psychotic, or lithium during inclusion. Due to sample size, we did not test for sub analysis in medication groups. However, medication that could interfere with emotional processing, including beta-blockers, stimulants, and benzodiazepines, were criteria for exclusion.

In summary, our findings show that despite having a lower general recall, patients with BD had a higher recall of adverse emotional events and of events that immediately preceded the emotional events. Additionally, previous trauma exposure did not seem to interfere with the emotional memory of patients. Finally, emotional memory appears to have differing patterns in patients in various stages of bipolar disorder: diminished after few mood episodes and more enhanced with many episodes. Emotional memory seems to be an important cognitive function associated with neuroprogression in BD. Due to the small sample size, our study, particularly the sub analysis of CTQ and number of mood episodes, should be viewed as a pilot study. Further

studies with greater statistical power are needed to clarify our findings. Also, future projects should correlate emotional memory with neuroimaging and molecular findings to continue investigating how brain pathways and biomarkers are associated with progression in BD.

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Conflict of interest:

The authors declare that there are no conflicts of interest regarding the publication of this article.

Author Statement:

We further confirm that we have all approved the order of authors listed in the manuscripts. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, concerning intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property. We further confirm that any aspect of the work covered in this manuscript that has involved human subjects has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

Funding:

This study received financial support from The Brazilian Federal Agency for Support and Assessment of Post-graduate Education (CAPES) and the Brazilian National Council for Scientific and Technological Development (CNPq).

Contributors:

Adam Fijtman, Joana Bücker, and Márcia Kauer-Sant'Anna were responsible for the conception and design of the study.

Joana Bücker, Dayane Santos Martins, Mathias Hasse-Sousa, and Flavia Moreira Lima were responsible for patient inclusion and administration of emotional memory test, childhood trauma questionnaire, and clinical interview.

Adam Fijtman, Ives Passos, and Bryan A Strange were responsible for management and statistical analysis.

Adam Fijtman, Flavio Kapczinski, Bryan A Strange, Lakshmi Yatham, and Márcia Kauer-Sant'Anna were responsible for the interpretation of data and writing of the report.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship who are not listed.

Acknowledgments:

Adam Fijtman thanks Paul A Felder for text review.

Adam Fijtman thanks The Brazilian Federal Agency for Support and Assessment of Post-graduate Education (CAPES).

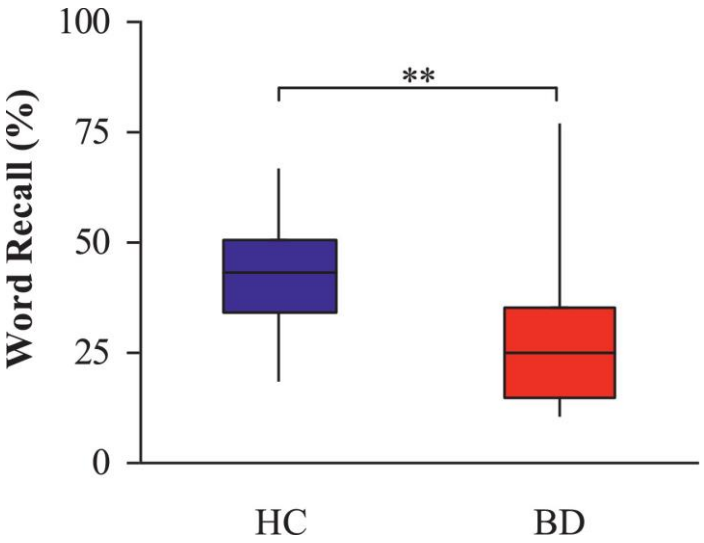

Fig. 1. General Word Recall in Patients with BD and HC[a]

[a]The box represents minimum, first quartile, median (heavy line), third quartile, and maximum.

**P < 0.01. Abbreviations: BD = bipolar disorder, HC = healthy controls.

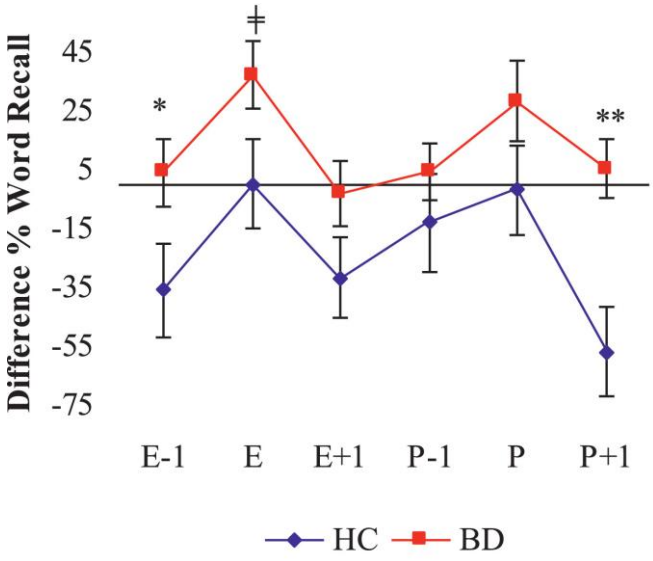

Fig. 2. Emotional Memory in Patients with BD and HC[a]

[a]The lines represent mean and standard deviation. ╪P = 0.055, *P < 0.05, and **P < 0.01; adjusted for age, sex, and years of education.

Difference % word recall = difference between the percentage of recall of each word category and control nouns.

Abbreviations: BD = bipolar disorder, HC = healthy controls, E = emotional word, P = perceptual word, E-1 = word preceding E, P-1 = word preceding P, E + 1 = word succeeding E, P + 1 = word succeeding P.

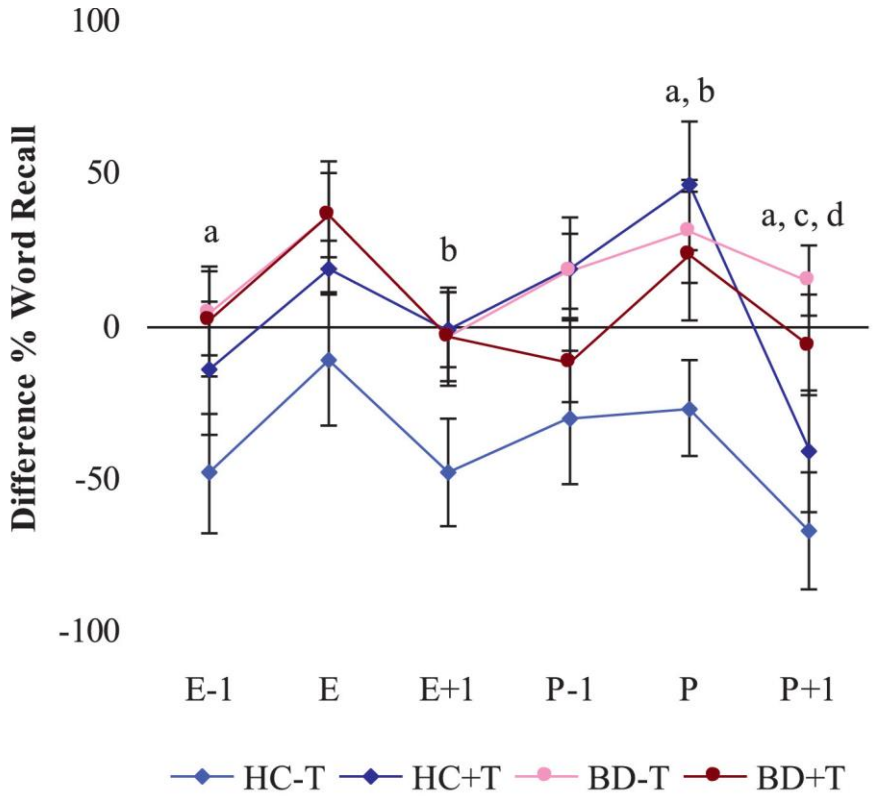

Fig. 3. Emotional Memory and Childhood Trauma Questionnaire in Patients with BD and Hc[a]

[a]The lines represent mean and standard deviation.

a = P < 0.05 BD-T vs. HC-T, b = P < 0.05 HC + T vs. HC-T, c = P < 0.05 BD + T vs. HC-T, d = P < 0.05 BD-T vs. HC + T; adjusted for age, sex, and years of education.

Difference% word recall = difference between the percentage of recall of each word category and control nouns.

Abbreviations: BD-T = patients with bipolar disorder with no previous exposure to trauma, BD+T = patients with bipolar disorder with previous exposure to trauma, HC-T = healthy controls with no previous exposure to trauma, HC + T = healthy controls with previous exposure to trauma, E = emotional word, P = perceptual word, E-1 = word preceding E, P-1 = word preceding P, E + 1 = word succeeding E, P + 1 = word succeeding P.

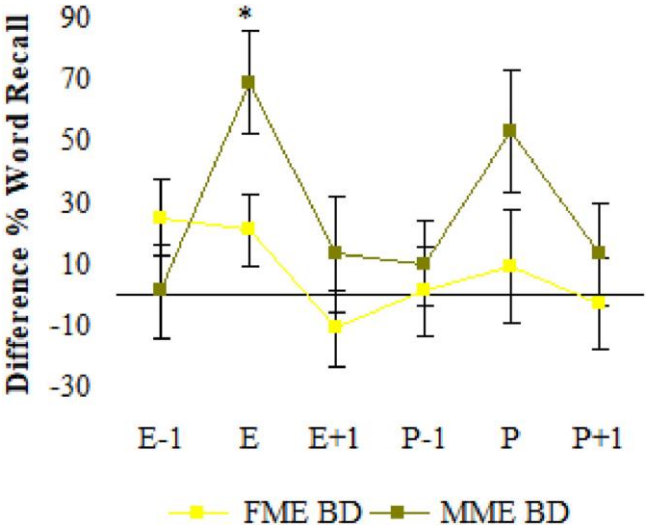

Fig. 4. Emotional Memory in Few and Many Mood Episodes Patients with BD[a]

[a]The lines represent mean and standard deviation.

*P < 0.05; adjusted for age, sex, and years of education.

Difference % word recall = difference between the percentage of recall of each word category and control nouns. Abbreviations: BD = bipolar disorder, E = emotional word, P = perceptual word, E-1 = word preceding E, FME = few mood episodes, MME = many mood episodes, P-1 = word preceding P, E + 1 = word succeeding E, P + 1 = word succeeding P.

Table 1. Clinical and sociodemographic characteristics of the BD and HC subjects.

Demographic variables	**HC (*n* = 20)**	**BD (*n* = 33)**	**Statistical *t* or x^2**	***p*-value**
Age - Mean (SD)	43.00 (15.93)	44.06 (13.01)	2.165	0.15
YOE - Mean (SD)	17.60 (19.60)	11.41 (3.13)	4.526	0.07
Sex -% male	25.00	36.36	0.738	0.39

Abbreviations: SD = standard deviation, HC = healthy controls, BD = patients with bipolar disorder, YOE = years of education.

4. CONCLUSIONS

This thesis adds relevant knowledge regarding emotional-cognitive alterations associated with childhood trauma and bipolar disorder. This work resulted in a test that is now available to evaluate emotional memory in the Brazilian Portuguese speaking population. Results of this test indicate that patients with bipolar disorder have a higher recall for emotional stimuli and for neutral stimuli that directly precede the emotional stimulus. There is no difference in terms of emotional memory in patients with BD who suffered maltreatment during childhood and those patients who did not. However, HC with previous trauma during childhood appear to have EM results more similar to patient groups. Emotional memory seems to be a promising biomarker of progression in bipolar disorder. Patients with fewer mood episodes have a blunted emotional memory, while patients with multiple mood episodes have an enhanced EM.

This thesis fills a significant gap in the field of study, contributing to the development of future studies about EM in the Brazilian Portuguese speaking population. The EM test was adapted from a test initially created by Strange et al. (2003) that was correlated with amygdala function through fMRI (Strange et al., 2004). We contacted the author of the original test who provided the instructions to translate and culturally adapt it accurately. We conducted five steps: translation, negative selection, positive selection, semantic selection, and semantic assessment. As a result, we determined 20 lists of words, each containing 11 neutral words and one word with an emotionally negative valence.

During the application of the test in healthy controls, we included a validation step, to make sure that lists were accurately identifying an emotional-dependent episodic memory in our population. Therefore, we recommend future studies which utilize the same test to use results from lists 2, 11, 13, 18, and 19 only, with emotional words being "massacre", "aborto", "dor", "suicídio", and "afogamento", respectively. Also, we recommend future studies randomize items that precede (E-1 and P-1) and follow (E+1 and P+1) the emotional and the perceptual words. Randomization may improve within-group comparisons by diminishing the effect of confounding variables.

Patients with BD. had a lower general recall for all words when compared to paired HC. This finding is consistent with the previous literature which details impairments in several cognitive domains in euthymic patients with BD, including functionality, executive functioning,

verbal memory and nonverbal memory (Deckersbach et al., 2004; Dickinson et al., 2017; Robinson et al., 2006; Vasconcelos-Moreno et al., 2017).

Despite having a lower general recall ability, patients with BD had an exacerbated emotional memory. When controlling for neutral words, these patients had an enhanced episodic recall for emotional words and for neutral words that immediately preceded the emotional word. This result suggests a dysfunctional hyperactivation of areas of the brain involved with emotional-cognitive control in these patients. BD is associated with higher activation of the hippocampus during exposure to emotional stimuli (Whalley et al., 2009). Euthymic patients with BD exhibit hyperactivity of the amygdala during cognitive tasks when exposed to both emotional and neutral stimuli (Benson et al., 2014). These results can also explain the patients' enhanced memory associated with words preceding and following the perceptual word. It is possible that stimuli seen as out-of-place by patients activates brain pathways that would usually be activated by fear in healthy controls. This theory is corroborated by the fact that euthymic BD patients tend to evaluate neutral events as emotional (Kauer-Sant'Anna et al., 2008).

Emotional memory changes seem to correlate with childhood maltreatment. Psychiatric conditions usually accompanied with exposure to trauma, including PTSD, are associated with alterations in emotional memory and emotional regulation (Hayes et al., 2011). In our sample, HC with exposure to trauma during childhood had EM results more similar to patients with BD than to other HC who did not suffer trauma. Therefore, we believe trauma and bipolar disorder may lead to similar changes in EM. However, these changes may not result in an additive effect. There was no difference between patients with BD who suffered trauma and patients who did not suffer trauma in terms of EM.

Our results also contribute to the understanding of differences between patients with different numbers of previous mood episodes. Patients with multiple mood episodes had a worse overall prognosis, worse cognitive functioning and weaker response to standard treatment (Kapczinski et al., 2014). To our knowledge, this is the first study to assess emotional memory differences in patients in different stages of BD. In our sample, while patients with few mood episodes had a blunted EM, patients with multiple mood episodes had an exaggerated recall for the emotional stimuli, which was associated with retrograde amnesia. Dysfunctional hyperactivation of the amygdala may be a marker of late stages of BD.

This thesis contributes valuable knowledge in the field of behavioral sciences. However, there are some limitations to be considered. These experiments had a small number of participants; however, the sample size was similar to studies that developed and applied the test in other languages and in different populations. In terms of the translation and cross-cultural adaptation to Brazilian Portuguese, it is crucial to consider potential cultural differences between different regions of Brazil: our study population was entirely recruited at the same hospital in the South of Brazil. Additionally, we split our sample according to the median number of mood episodes, as a strategy to explore a small sample, which reflects a group of patients with fewer episodes, and perhaps less severe trajectory and a group with a higher number of episodes and a more severe course of illness. Furthermore, this is a cross-sectional study, and recall bias must be considered.

In summary, this thesis resulted in an emotional memory test translated and cross-culturally adapted to Brazilian Portuguese speakers. Our results indicate that HC with previous exposure to childhood trauma and patients with BD, mostly those with multiple mood episodes, have an enhanced emotional memory, which could be associated with dysfunctional hyperactivation of the amygdala. Furthermore, our findings point towards the importance of studying emotional memory as an essential cognitive function associated with trajectory of BD. Future directions should be to investigate the results of this test in transdiagnostic studies, including patients with PTSD, unipolar depression, schizophrenia, and generalized anxiety disorder. Also, future studies may evaluate emotional memory in BD through fMRI tasks, correlating with markers of severity of the disease, including the number of mood episodes.

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6. SUPPLEMENTARY SECTION

6.1 Informed Consent Form for Controls - Paper 1

Termo de Consentimento Livre e Esclarecido

O objetivo deste estudo é validar uma escala específica sobre memória emocional. Para validarmos esta escala, precisamos aplicá-la em sujeitos sem nenhuma doença psiquiátrica ou demência. Você está sendo convidado a participar deste estudo justamente por não apresentar nenhum tipo doença psiquiátrica ou demência.

A aplicação da escala consiste na leitura de uma lista de palavras e pode durar em torno de 1 hora e 30 minutos. Por se tratar de uma validação, e não termos parâmetros para comparar os resultados, não existe certo ou errado, apenas você deve marcar as alternativas a partir do seu julgamento pessoal. A aplicação não envolve nenhum risco ou desconforto para o participante. Como esta pesquisa consite na validação da escala e não temos parâmetros para a devolução de resultados consistentes, não iremos realizar a devolução do material. O nome do participante será mantido em sigilo pelos pesquisadores, sendo estes dados utilizados apenas para esta pesquisa.

Eu, _____, fui informado dos objetivos especificados acima e da justificativa desta pesquisa, de forma clara e detalhada. Recebi informações específicas sobre cada procedimento no qual eu estarei envolvido, dos desconfortos ou riscos previstos, tanto quanto dos benefícios esperados. Todas as minhas dúvidas foram respondidas com clareza e sei que poderei solicitar novos esclarecimentos a qualquer momento. Além disso, sei que terei liberdade de retirar meu consentimento de participação na pesquisa de acordo com estas informações, sem que isto traga prejuízo ao atendimento que recebo na instituição.

O Termo de Consentimento Livre e Esclarecido será aplicado em duas vias e uma ficará em poder do participante e a outra em poder do pesquisador.

O profissional _____ certificou-me de que as informações por mim fornecidas terão caráter confidencial, sem identificação do paciente.

Em caso de dúvidas, entrar em contato com a pesquisadora responsável Dra. Márcia Kauer-Sant'Anna, da Universidade Federal do Rio Grande do Sul, pelo telefone (51) 3359.8845 no Hospital de Clínicas de Porto Alegre, na Rua Ramiro Barcelos, 2350 - CEP 90035-903 ou com o comitê de ética e pesquisa deste hospital: (51) 3359.8000.

_____ _____

Assinatura do paciente ou responsável legal Assinatura do investigador

Data:

6.2 Translation and Cross-Cultural Adaptation Form

Lista de palavras (primeira etapa)

Marcar se considera a palavra: negaiva (-6 a -3), neutra (-2 a 2) ou positiva (3 a 6)
Lembre-se que nesta tarefa não existe certo ou errado, você apenas precisa marcar a partir do seu julgamento.

	Negativa				Neutra					Positiva			
	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6
grito													
som													
voz													
conversa													
rádio													
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terrorista													
nacionalidade													
visitante													
passaporte													
patriotismo													
viagem													
visto													
origem													
nativo													
conterrâneo													
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superfície													
vibração													
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camisola													
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vida													
planeta													
evolução													
natureza													
humanidade													
paisagem													
crescimento													
país													
mundo													
animal													
universo													
atmosfera													
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polir													
parede													
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arquivo													
madeira													
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martelo													
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brilho													
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professor													
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cascalho													
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jardineiro													
rocha													
terreno													
pedra													
pá													
raiz													
terra													
escavação													
grama													

Lista de palavras (segunda etapa)

Marcar (de 0 a 10), a partir do contexto, se as palavras estão relacionadas entre si
Lembre-se que nesta tarefa não existe certo ou errado, você apenas precisa marcar a partir do seu julgamento.

	0	1	2	3	4	5	6	7	8	9	10
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cultura											
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vibração											
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sonho											
relaxamento											

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público											
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baile											
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estádio											
periferia											
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cobrador											
boate											
rodoviária											
metrô											
turma											
aeroporto											

	0	1	2	3	4	5	6	7	8	9	10
pesadelo											
sono											
pijama											
dormitório											
relógio											
lua											
noite											
anoitecer											
cortina											
travesseiro											
calma											
quarto											
lençol											
cobertor											
escurecer											
camisola											

	0	1	2	3	4	5	6	7	8	9	10
catástrofe											
vida											
planeta											
evolução											
natureza											
humanidade											
paisagem											
crescimento											
país											
mundo											
animal											
universo											
atmosfera											
ambiente											
campo											
planta											

	0	1	2	3	4	5	6	7	8	9	10
crucificação											

prego											
ferramenta											
polir											
parede											
metal											
equipamento											
arquivo											
madeira											
ferro											
martelo											
grampo											
brilho											
carpinteiro											
parafuso											
serrote											

	0	1	2	3	4	5	6	7	8	9	10
reprovação											
universidade											
educador											
educação											
conhecimento											
pedagogia											
professor											
escola											
estudante											
faculdade											
colégio											
aula											
acadêmico											
diploma											
tutor											
prova											

	0	1	2	3	4	5	6	7	8	9	10
suicídio											
altura											
construção											
mirante											
montanha											
telhado											
pico											
terraço											
torre											
prédio											

cachoeira											
ponte											
penhasco											
sacada											
alto											
salto											

	0	1	2	3	4	5	6	7	8	9	10
afogamento											
água											
rio											
lago											
lagoa											
canoa											
piscina											
balsa											
baía											
nadador											
canal											
riacho											
mar											
barco											
areia											
banho											

	0	1	2	3	4	5	6	7	8	9	10
necrotério											
armazenamento											
depósito											
frigorífico											
prateleira											
caixote											
gabinete											
armário											
cofre											
gaveta											
sótão											
caixa											
jarro											
baú											
despensa											
porão											

	0	1	2	3	4	5	6	7	8	9	10
aranha											

cavalo											
gato											
cachorro											
papagaio											
galinha											
periquito											
pato											
canário											
pônei											
chinchila											
ovelha											
coelho											
tartaruga											
pássaro											
boi											

	0	1	2	3	4	5	6	7	8	9	10
cadáver											
chão											
adubo											
colina											
solo											
cascalho											
floresta											
jardineiro											
rocha											
terreno											
pedra											
pá											
raiz											
terra											
escavação											
grama											

6.3 Informed Consent Form for Patients - Paper 2

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO PARA CASOS

Você está sendo convidado(a) a participar do projeto de pesquisa "A memória emocional em pacientes com Transtorno do Humor Bipolar e a relação com marcadores bioquímicos e trauma na infância: um estudo com pacientes em estágio inicial e tardio da doença." O objetivo deste estudo é conhecer características clínicas do Transtorno Bipolar e sua possível relação com determinadas situações enfrentadas ao longo da vida, com alterações existentes na memória emocional e no sangue em uma proteína chamada BDNF. Existe uma possibilidade de associação dessas alterações com o tempo de doença, mas mais estudos devem ser feitos para constatar tal afirmação. Ou seja, esse estudo tem por objetivo, de uma forma geral, entender melhor como funciona a doença bipolar. Os procedimentos que envolvem a sua participação neste estudo são: responder questões através de questionários, realizar uma avaliação da memória emocional através da memorização de palavras e a coleta de uma amostra de sangue (10 mL). Esta coleta de sangue será utilizada apenas para observar alterações nos níveis do BDNF. O tempo previsto para realizar todos os procedimentos é de aproximadamente 2 (duas) horas. Os riscos envolvidos nestes procedimentos são mal-estar passageiro ou mancha roxa no local da coleta de sangue e responder a questionários que envolvem perguntas íntimas tais como abuso sexual. Após um ano você será convidado a participar novamente deste estudo, realizando os mesmo procedimentos, para verificar se houve alguma alteração no seu desempenho. Sua participação no estudo é totalmente voluntária e a não participação ou desistência após ingressar no estudo não implicará em nenhum tipo de prejuízo a você, nem prejuízo ao vínculo com a instituição. Não está previsto nenhum tipo de pagamento pela sua participação no estudo e você não terá nenhum custo com respeito aos procedimentos envolvidos. Os pesquisadores deste estudo se comprometem em manter a confidencialidade dos seus dados de identificação pessoal sendo que os resultados serão divulgados de maneira agrupada, sem identificação dos indivíduos que participaram deste estudo. Todas as dúvidas poderão ser esclarecidas antes e durante o curso da pesquisa, através do contato com a pesquisadora responsável, Profa. Dra. Márcia Kauer Sant'Anna, no Laboratório de Psiquiatria Molecular, Hospital de Clínicas de Porto Alegre, telefone (51) 3359.8845. O Comitê de Ética em Pesquisa poderá ser contatado para esclarecimento de dúvidas, no 2° andar do HCPA, sala 2227, ou através do telefone 33597640, das 8h às 17h, de segunda à sexta. Este documento será elaborado em duas vias, sendo uma delas entregue a você e outra mantida pelo grupo de pesquisadores.

Nome do participante _____ Assinatura _____

Nome do pesquisador_____ Assinatura_____

Local e data:_____

6.4 Informed Consent Form for Controls - Paper 2

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO PARA CONTROLES

Você está sendo convidado(a) a participar do projeto de pesquisa "A memória emocional em pacientes com Transtorno do Humor Bipolar e a relação com marcadores bioquímicos e trauma na infância: um estudo com pacientes em estágio inicial e tardio da doença." O objetivo deste estudo é conhecer características clínicas do Transtorno Bipolar e sua possível relação com determinadas situações enfrentadas ao longo da vida, com alterações existentes na memória emocional e no sangue em uma proteína chamada BDNF. Existe uma possibilidade de associação dessas alterações com o tempo de doença, mas mais estudos devem ser feitos para constatar tal afirmação. Ou seja, esse estudo tem por objetivo, de uma forma geral, entender melhor como funciona a doença bipolar. Para a realização do estudo é necessário comparar o grupo de pacientes que apresentam o Transtorno Bipolar com um grupo de participantes que não apresentam esta doença. Você está sendo convidado a participar deste estudo justamente por não apresentar o diagnóstico de Transtorno Bipolar. Os procedimentos que envolvem a sua participação neste estudo são: responder questões através de questionários, realizar uma avaliação da memória emocional através da memorização de palavras e a coleta de uma amostra de sangue (10 mL). Esta coleta de sangue será utilizada apenas para observar alterações nos níveis do BDNF. O tempo previsto para realizar todos os procedimentos é de aproximadamente 2 (duas) horas. Os riscos envolvidos nestes procedimentos são mal-estar passageiro ou mancha roxa no local da coleta de sangue e responder a questionários que envolvem perguntas íntimas tais como abuso sexual. Após um ano você será convidado a participar novamente deste estudo, realizando os mesmo procedimentos, para verificar se houve alguma alteração no seu desempenho. O estudo contribuirá para o aumento do conhecimento sobre o assunto estudado e os resultados poderão auxiliar na realização de estudos futuros. Sua participação no estudo é totalmente voluntária e a não participação ou desistência após ingressar no estudo não implicará em nenhum tipo de prejuízo a você, nem prejuízo ao vínculo com a instituição. Não está previsto nenhum tipo de pagamento pela sua participação no estudo e você não terá nenhum custo com respeito aos procedimentos envolvidos. Os pesquisadores deste estudo se comprometem em manter a confidencialidade dos seus dados de identificação pessoal e os resultados serão divulgados de maneira agrupada, sem identificação dos indivíduos que participaram deste estudo. Todas as dúvidas poderão ser esclarecidas antes e durante o curso da pesquisa, através do contato com a pesquisadora responsável, Profa. Dra. Márcia Kauer Sant'Anna, no Laboratório de Psiquiatria Molecular, Hospital de Clínicas de Porto Alegre, telefone (51) 3359.8845. O Comitê de Ética em Pesquisa poderá ser contatado para esclarecimento de dúvidas, no 2° andar do HCPA, sala 2227, ou através do telefone 33597640, das 8h às 17h, de segunda à sexta. Este documento será elaborado em duas vias, sendo uma delas entregue a você e outra mantida pelo grupo de pesquisadores.

Nome do participante _____ Assinatura _____

Nome do pesquisador_____ Assinatura_____

Local e data:_____

6.5 Childhood Trauma Questionnaire

Questionário sobre Traumas na Infância (*CTQ*)
Identificação: _____
Idade: _____ Sexo: _____
As afirmações abaixo se referem a algumas experiências de quando você era criança ou adolescente.
Embora estas afirmações sejam de natureza pessoal, por favor, responda o mais sinceramente possível.
Para cada afirmação, **circule a resposta** que melhor descreve o que você acha que ocorreu enquanto crescia.
Se você desejar mudar sua resposta, coloque um **X** na antiga e circule a nova escolha.

Enquanto eu crescia...	**Nunca**	**Poucas Vezes**	**Às Vezes**	**Muitas Vezes**	**Sempre**
1. Eu não tive o suficiente para comer.	•	•	•	•	•
2. Eu soube que havia alguém para me cuidar e proteger.	•	•	•	•	•
3. As pessoas da minha família me chamaram de coisas do tipo “estúpido (a)”, “preguiçoso (a)” ou “feio (a)”.	•	•	•	•	•
4. Meus pais estiveram muito bêbados ou drogados para poder cuidar da família.	•	•	•	•	•
5. Houve alguém na minha família que ajudou a me sentir especial ou importante.	•	•	•	•	•
6. Eu tive que usar roupas sujas.	•	•	•	•	•
7. Eu me senti amado (a).	•	•	•	•	•
8. Eu achei que meus pais preferiam que eu nunca tivesse nascido.	•	•	•	•	•
9. Eu apanhei tanto de alguém da minha família que tive de ir ao hospital ou consultar um médico.	•	•	•	•	•
10. Não houve nada que eu quisesse mudar na minha família.	•	•	•	•	•
11. Alguém da minha família me bateu tanto que me deixou com machucados roxos.	•	•	•	•	•
12. Eu apanhei com cinto, vara, corda ou outras coisas que machucaram.	•	•	•	•	•
13. As pessoas da minha família cuidavam umas das outras.	•	•	•	•	•
14. Pessoas da minha família disseram coisas que me machucaram ou me ofenderam.	•	•	•	•	•
15. Eu acredito que fui maltratado (a) fisicamente.	•	•	•	•	•
16. Eu tive uma ótima infância.	•	•	•	•	•

17. Eu apanhei tanto que um professor, vizinho ou médico chegou a notar.	•	•	•	•	•
18. Eu senti que alguém da minha família me odiava.	•	•	•	•	•
19. As pessoas da minha família se sentiam unidas.	•	•	•	•	•
20. Tentaram me tocar ou me fizeram tocar de uma maneira sexual.	•	•	•	•	•
21. Ameaçaram me machucar ou contar mentiras sobre mim se eu não fizesse algo sexual.	•	•	•	•	•
22. Eu tive a melhor família do mundo.	•	•	•	•	•
23. Tentaram me forçar a fazer algo sexual ou assistir coisas sobre sexo.	•	•	•	•	•
24. Alguém me molestou.	•	•	•	•	•
25. Eu acredito que fui maltratado (a) emocionalmente.	•	•	•	•	•
26. Houve alguém para me levar ao médico quando eu precisei.	•	•	•	•	•
27. Eu acredito que fui abusado (a) sexualmente.	•	•	•	•	•
28. Minha família foi uma fonte de força e apoio.	•	•	•	•	•