UNIVERSIDADE FEDERAL DE MINAS GERAIS
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PROCESSOS COGNITIVOS CONTROLADOS E AUTOMATIZADOS NO TRANSTORNO AFETIVO BIPOLAR: AMPLIANDO A COMPREENSÃO DA RELAÇÃO ENTRE COGNIÇÃO E MANIFESTAÇÕES CLÍNICAS

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RESUMO

INTRODUÇÃO**:** O Transtorno Bipolar é uma condição altamente incapacitante. Apesar de existirem tratamentos baseados em evidências, as taxas de recaída e disfuncionalidade permanecem altas. Problemas no processamento cognitivo e emocional ocorrem mesmo em períodos de eutimia, o que fazem com que tais problemas possam compor aspectos centrais subjacentes à vulnerabilidade ao transtorno. O principal objetivo deste estudo foi o de descrever possíveis interações entre o processamento cognitivo e emocional no transtorno bipolar e discutir suas implicações sobre tratamentos. MÉTODO: O estudo maior foi subdividido em três estudos menores. O primeiro foi uma revisão de literatura, com o objetivo de esclarecer o estado da arte em cognição e emoção no transtorno bipolar e suas interações. O segundo estudo objetivou teste algumas interações entre contextos emocionalmente relevantes e aspectos cognitivos em uma amostra de pacientes e familiares. O estudo três considerou a dinâmica hierárquica do processamento cognitivo-emocional e discutiu como níveis automáticos de processamento podem se associar a sintomatologia e desfechos clínico no Transtorno Bipolar. RESULTADOS: Foi observado que, em contextos emocionais, aspectos cognitivos específicos estão relacionados a respostas disfuncionais, como as funções executivas – mais especificamente, o controle inibitório. O controle inibitório de familiares bipolares está associado a mais experiências traumáticas relatadas por pacientes. Pacientes que experienciaram elevados níveis de abuso emocional e que apresentam baixos níveis de controle inibitório são mais vulneráveis a ter reincidentes tentativas de suicídio. Em pacientes bipolares, elevada reatividade foi associada a aspectos clínicos mesmo em estágios básicos de processamento emocional, acessado pelo tempo de fixação ocular, medido em milissegundos. DISCUSSÃO: É possível que contextos de elevada carga emocional demandem elevados níveis de controle inibitório para que sejam manejados de forma funcional. No entanto, em pacientes bipolares, controle inibitório está particularmente comprometido nestes contextos, levando a desfechos disfuncionais, como os índices elevados de tentativas de suicídio. Além disso, tratamentos desenvolvidos para melhorar desfechos clínicos precisam considerar que a reatividade emocional observada pode ocorrer mesmo em níveis automáticos de processamento cognitivo e emocional. Apesar de cognição e processamento emocional estarem tradicionalmente descritos como tópicos separados, a interação entre eles representam um aspecto importante a ser considerado na tentativa de promover expectativas factíveis de tratamentos.

Palavras-Chave: Transtorno Bipolar, Cognição, Emoção, Viés atencional.

ABSTRACT

INTRODUCTION: Bipolar is a highly disabling disorder. Although there are evidenced-based treatment approaches available, relapse rates and dysfunctionality remain high. Cognition and emotional processing problems occur even in euthymic states of the disorder; therefore they are in the mainstream to elucidate underlying mechanisms for bipolar vulnerability. The major aim of this study was to describe possible interactions between cognition and emotional processing and discuss their implications upon treatments. METHODS: This major study was divided into three smaller ones. The first was a review that aimed to unfold the up-to-date research in cognition and emotionality, as well as their possible interactions. Study two aimed to test some of cognition-emotion interaction in a Brazilian bipolar sample and their relatives. Study three considered the hierarchical complex dynamic of cognitive-emotional processing and discussed how automatic levels of emotional responses can be associated to bipolar symptomatology and clinical outcomes. RESULTS: It was observed that, in emotional contexts, specific cognitive aspects are related to dysfunctional responses, such as executive functioning - more specifically, inhibitory control. Bipolar relatives' Inhibitory control may foster traumatic childhood experiences in patients. Patients who have experienced high levels of emotional abuse and who present low levels of inhibitory control are more vulnerable to attempt suicide recurrently. Increased emotional reactivity is observed even in basic levels of emotional cognitive processing, such as eye fixation time (measured in milliseconds). DISCUSSION: It is possible that high emotional contexts require greater inhibitory control capacity to deal with them in a functional way. However, in bipolar patients, inhibitory control is specially compromised in these contexts, leading to dysfunctional outcomes such as higher incidence of history of suicide attempts. Furthermore, treatment approaches designed to improve clinical outcomes need to consider that the emotional reactivity observed in this population occur in automatic levels of emotional-cognitive processing. Although cognition and emotional processing are traditionally described as separate topics, their overlap is an important aspect to be taken into account to promote realistic treatment outcomes expectations.

Key-words: Bipolar Disorder, Cognition, Emotion, Attentional bias.

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1. INTRODUCTION

Bipolar Disorder is one of the 20 leading causes of disability (World Health Organization, 2011). It is a chronic mental condition which prevalence is approximately 0.8% in Brazilian population (Ferrari et al., 2016). There are two main subtypes. Type one is characterized by at least one manic episode, which is a period of elevated, expansive or irritable mood that lasts at least one week or leads to hospitalization. Conjointly, the manic period presents abnormality in at least three of the following aspects: Grandiosity, reduced need of sleep, pressure to talk, flight of ideas, distractibility, psychomotor activation and excessive involvement in risky activities. Type two is defined by the presence of at least one hypomanic and one depressive episode. Criteria for hypomanic episodes are similar to mania, however, symptoms duration are of at least 4 consecutive days (American Psychiatric Association, 2013).

The disability burden can be assessed by different ways. One of them is to compute the number of years lived with disability according to longitudinal follow-up. According to the Global Burden Disease Study, when Bipolar Disorder is compared to other disease and injuries, it accounts for 1.3% of the total of years lived with disability (Ferrari et al., 2016). This proportion is similar to conditions such as Alzheimer's disease (Ferrari et al., 2016).

In an attempt to promote functionality, there are some evidence-based treatment approaches. Among them, there are the pharmacological and also non-pharmacological ones (Samalin, de Chazeron, Vieta, Bellivier, & Llorca, 2016). However, even patients who achieve symptoms reduction present dysfunctional outcomes. From patients who are not in acute phases of the disorder, 42% present poor overall functioning, impacting on autonomy, occupational functioning, financial issues and interpersonal relationships (Samalin et al., 2016). It is possible that subsyndromic symptoms may paly a role in contributing to the high relapse rates observed in bipolar, being considered one important treatment target (Samalin et al., 2016)

Cognitive and emotional functioning are known to be impaired even in remitted states (Arts, Jabben, Krabbendam, & Van Os, 2008; Caseras et al., 2015; Mary L. Phillips, Drevets, Rauch, & Lane, 2003; Cecilia Samamé, Martino, & Strejilevich, 2014) and also in bipolar relatives (Glahn, Bearden, Niendam, & Escamilla, 2004). These deficits are closely related to functionality (Mackala, Torres, Kozicky, Michalak, &

Yatham, 2014; Muhtadie, Johnson, Carver, Gotlib, & Ketter, 2014), turning out to be potential vulnerability markers for the dysfunctionality seen in remitted mood states.

Cognition is the intermediate process through which subject interacts with the environment. It is the mechanism by which input information is perceived, recognized and integrated in order to produce responses to modify and interact with the context. Neurocognitive assessment regards the characterization of cerebral functioning, considering cognitive models targeting constructs such as attention, memory, and executive function (Lezak, 1995). Emotional responses are immediate changes in internal environment - such as muscle tension, hart rate – that occurs when the organism interact with internal (thoughts, memories) or external stimuli (Damasio & Carvalho, 2013). Therefore, it is an immediate contextual emotional evaluation that prepares the body to act in order to regulate itself and reestablish homeostasis (Damasio & Carvalho, 2013). This definition make it comprehensible that the higher the perceived threat to homeostasis, higher the importance to reestablish it, and therefore, higher the emotional responses. Homeostasis can also be unbalanced as a consequence of perceived reward. In these cases, the urge to respond to it also increases, as it is observed in the context of substance use (Noël, Brevers, & Bechara, 2013). This dynamics makes short-term benefits of great value in contexts of high emotional arousal.

Perceiving, integrating and responding to environment - cognitive process - occurs in contexts with low emotional load, such as abstract problem solving, but it is also required to process information in high emotional contexts (Zelazo & Müller, 2002). In these contexts, the interaction between cognitive abilities and emotional aspects may be determinant in modulating the levels of functionality raised by patients' behavioral reactions. Therefore, it is possible that cognitive deficits, such as in inhibitory control (a core component of executive function) foster dysfunctional behaviors such as aggressiveness and abuse, leading to dysfunctionality. On the other hand, it plausible that an impaired emotional processing may lead to increased emotional reactivity, what also may contribute to dysfunctional behaviors and low quality of life.

Beyond considering cognition and emotion influences upon clinical outcomes and functionality, it is important to consider that there are different levels of cognitive and emotional processes. The neurocognitive processing occurs in a modular hierarchical pattern, in which perceptual and executive connectivity happens in different complexity levels (Fuster, 2008; Mesulam, 2000). For instance, some of them require cortical functioning, but some do not. For example, it is known that fear processing

present an important evolutionary subcortical pathway, but also important role of cortical processing (Pessoa & Adolphs, 2010). Therefore, part of the cognitive and emotional processing may be assessed through consciousness, although some may not.

Then, to clarify cognitive-emotion interaction upon clinical outcomes, it is important to consider that different levels of complexity are intricate in both constructs and this hierarchy may influence the intensity, presence and the management of clinical dysfunctional outcomes observed in bipolar. Therefore, this study will be divided in three specific objectives. The first will be to review cognitive and emotional literature on bipolar disorder. Secondly, considering the review outcomes, specific cognitive and emotional aspects shown to be clinically relevant will have their associations investigated. Third, automatic non-conscious emotional reactions to emotional salient stimuli will be observed to in bipolar patients and their clinical implications will be discussed. Lastly, cognitive and emotional hierarchical process implications upon treatments and functionality improvement will be discussed.

2. OBJECTIVES

General Objective:

The objective of this study is to clarify and discuss cognitive and emotion associations to clinical aspects in bipolar disorder - considering the hierarchical complexity underlying this interaction.

Specific objectives:

1) Studies that target cognition and also those which target emotionality will be reviewed. Hypothesis of their interaction will be drawn – Study one of this thesis.
2) Secondly, one possible interaction between these two aspects (cognition and emotionality) will be tested. It will be investigated whether dimensions of impulsivity (inhibitory control and non-planning) can be associated to harmful emotional experiences (early trauma). Furthermore, it will be examined how these cognitive and emotional aspects are related to clinical outcomes in a bipolar sample (suicide attempt history) – Study two of this thesis.
3) Third, automatic emotional responses to emotionally relevant stimuli will be assessed in bipolar patients. The associations between automatic emotional responses and clinical symptoms will be described.

3. STUDY ONE: COGNITIVE DEFICITS IN BIPOLAR DISORDERS: IMPLICATIONS FOR EMOTION

3.1 ABSTRACT

Prominent cognitive deficits have been documented in bipolar disorder, and multiple studies suggest that these deficits can be observed among non-affected first-degree relatives of those with bipolar disorder. Although there is variability in the degree of cognitive deficits, these deficits are robustly relevant for functional outcomes. A separate literature documents clear difficulties in emotionality, emotion regulation, and emotion-relevant impulsivity within bipolar disorder, and demonstrates that these emotion-relevant variables are also central to outcome. Although cognitive and emotion domains are typically studied independently, basic research and emergent findings in bipolar disorder suggest that there are important ties between cognitive deficits and the emotion disturbances observed in bipolar disorder. Understanding these relationships has relevance for fostering more integrative research, for clarifying relevant aspects related to functionality and vulnerability within bipolar disorder, and for the development of novel treatment interventions. Bipolar disorder (BD) is a severe psychiatric illness that has been ranked as one of the 20 leading medical causes of disability (WHO, 2011). BD has been shown to be the psychiatric disorder with the highest rates of completed suicide across two major cohort studies (Ilgen et al., 2010; Nordentoft, Mortensen, & Pedersen, 2011). In a cross-national representative sample, one in four persons diagnosed with bipolar I disorder reported a suicide attempt (Merikangas et al., 2011). Rates of relapse remain high despite available treatments (Gitlin, Swendsen, Heller, & Hammen, 1995), and in the year after hospitalization for manic episode, two-thirds of patients do not return to work (Strakowski et al., 1998). Poverty, homelessness, and incarceration are all too common (Copeland et al., 2009). Despite the often poor outcomes, there is also evidence for outstanding accomplishments and creativity among those with milder forms of the disorder and their family members (Coryell et al., 1989; Jamison, 1993; Murray & Johnson, 2010). Some individuals appear to achieve more than the general population, suggesting the importance of understanding the variables that predict differential outcome within bipolar disorder. Within this paper, we focus on two key predictors of outcomes within bipolar disorder: cognition and emotionality. We review evidence that problems in cognition and emotionality are prominent among those diagnosed with the disorder, are not artifacts of symptom state, and relate substantively to poorer outcomes. Although

traditionally studied separately, new work points toward the idea that cognition and emotionality are intricately linked within bipolar disorder. Drawing from research within bipolar disorder as well as outside of bipolar disorder, we build a model of how cognition and emotionality might be tied within bipolar disorder. We then provide suggestions for future research. Before considering findings, it is worth noting that there are several forms of the disorder, defined by varying degrees and duration of manic symptoms (APA, 2013; WHO, 1993). Manic episodes are defined by abnormally elevated or irritable mood, accompanied by increased activity and at least three symptoms (four if mood is only irritable) such as decreased need for sleep, increased self-confidence, racing thoughts or flight of ideas, rapid speech, distractibility, goal-directed activity, and engagement in pleasurable activities without regard to potential negative consequences. To meet criteria for mania, these symptoms must persist for at least one week or require hospitalization, and must lead to difficulties with functioning. If functional impairment is not more than mild and duration is between 4 and 6 days, the episode is considered a hypomanic episode. Bipolar I disorder (BD I) is diagnosed on the basis of at least one lifetime manic episode within the DSM-5 and by at least two episodes within the ICD, whereas bipolar II disorder is diagnosed on the basis of at least one hypomanic episode (and no manic episodes) as well as major depressive episodes. Cyclothymic disorder is defined by chronic but milder fluctuations between manic and depressive symptoms. Most research focuses on BD I. In addition to diagnosed samples, research has focused on those at high risk for bipolar disorder, including first-degree relatives of those with BD. This work draws on the evidence for extremely high heritability of BD I, with estimates from community-based twin studies of 0.85 (Kieseppä, Partonen, Haukka, Kaprio, & Lönnqvist, 2014). Other research has considered high risk for BD by virtue of lifetime subsyndromal symptoms, as measured by scales such as the Hypomanic Personality Scale (Eckblad & Chapman, 1986) or the General Behavior Inventory (Depue, Krauss, Spoont, & Arbisi, 1989). The study of high-risk individuals provides a way to decipher whether deficits are present before the onset of the disorder, of importance given models suggesting that episodes of the disorder may change brain function (Chang, Steiner, & Ketter, 2000; Strakowski, 2012) as well as individuals' perceptions of their emotion regulation. Beyond defining BD, it is worth defining some of the many different neuropsychological tasks that have been widely studied in BD. Perhaps no area has received more attention than executive function. Executive function is related to three core functions: 1) inhibition, the ability to

suppress irrelevant information in working memory in order to accomplish an established goal; 2) working memory, the ability to hold and manipulate information in mind; and 3) cognitive flexibility, the ability to shift strategies in response to feedback (Diamond, 2013; Miyake et al., 2000). Attention (defined as the process of selecting information reception from internal or external cues) is implicated in all three of these aspects of executive function. Much of the literature we will discuss focuses on response inhibition, or the ability to suppress a prepotent response, which is considered a subtype of inhibition. Some tests measure multiple facets of executive function; for example the Trails B test likely requires working memory and cognitive flexibility (Sánchez-Cubillo et al., 2009). Aside from executive function, multiple other facets of cognition have been widely studied in bipolar disorder. Verbal and non-verbal memory are related to the ability to register, store and retrieve verbal or visual information (Lezak, 1995). Verbal fluency is measured as the number of verbal responses a person can generate to a given target, such as a specific semantic category (e.g., animals, furniture) or phonetic category (e.g., words that begin with letter F) (Diamond, 2013). Although cognitive tasks have been designed to evaluate these specific functions, it is important to note that most measures are highly inter-correlated and may assess multiple overlapping functions to some extent (for example, the Trails B test is often described as an "executive function" task, although this task likely involves both working memory and cognitive flexibility. Not surprisingly, then, some authors label the function of certain tests differently, and this is particularly evident in meta-analyses of cognition. As we describe findings in this paper, we will use the terms proposed by the authors but will also identify key tests used to define a cognitive construct. With this background in mind, we turn to a discussion of cognitive deficits, then of emotion-related traits. Our hope is that those concise summaries provide evidence for the importance of both domains, but also specificity regarding the facets of emotion and cognition that are most impaired in BD. This specificity then guides our consideration of models that integrate cognition and emotion.

3.2 COGNITION AND EMOTION IN BIPOLAR DISORDER

Cognitive Deficits in Bipolar Disorder

A large body of work identifies prominent cognitive deficits, as measured using neuropsychological tests, in BD (Bourne et al., 2013; Kurtz & Gerraty, 2009; Robinson et al., 2006). Although depressive and manic symptoms relate to lower performance on

cognitive tests (Kurtz & Gerraty, 2009) and lower self-reported cognitive functioning (Peters et al., 2014), a more important question for mapping vulnerability is whether these deficits persist after remission. Findings of one meta-analysis suggest that the severity of impairment for those with remitted BD as compared to healthy control groups varies across domain and task, with higher effect sizes for verbal and nonverbal memory, attention, and the Trails B test, relevant to both attention and working memory (Kurtz & Gerraty, 2009). For verbal memory, the most frequently used task was the Rey and California Verbal Learning Test (deficits in the range of d = .81 across 18 studies). Parallel effect sizes were observed for a nonverbal memory task, the Delayed Recall Task of the Rey Complex Figure Test, (d = .80 across 3 studies). Executive function, as assessed using the Trails B measure, yielded an effect size of d = .73 across 18 studies. Comparable effect sizes were also observed for attention on the Trails A task (d= .65 across 17 studies) and Continuous Performance Task (d = .69 across 13 studies). Other domains appear to be less affected, with smaller between-group effect sizes, including Verbal Fluency (d = 0.51 across 15 studies, measured by FAS phonetic fluency and animal naming) and visuospatial abilities (d = 0.55 across five studies, assessed by Block Design). Findings of a different meta-analyses converge in suggesting that remitted BD was related to a similar profile of larger deficits in verbal memory (d > 0.8, assessed by California Verbal Learning Test in 10 studies), executive function (d > 0.8, assessed by Trail B in 10 studies) and and smaller deficits in visuoperception (d <.5, assessed by the copy version of the Rey Complex Figure Test in 4 studies) (Arts et al., 2008). A more recent meta-analysis confirmed this pattern, with deficits also evident on verbal learning, trail-making, and verbal working memory tasks (Bourne et al., 2013). This literature provides substantial evidence that cognitive deficits persist after remission.

Congruent with findings of the correlational research showing cognitive deficits during remission, longitudinal research documents that symptom fluctuations do not seem to explain most cognitivedeficits. In one longitudinal study of individuals who were re-tested as episode status varied, attention and processing speed deficits appeared stable as manic and depressive symptoms fluctuated, although verbal fluency deficits appeared more prominent when depressive symptoms were present (Chaves et al., 2011). Another longitudinal study found that cognitive deficits in BD were stable across five years, with the exception of worsening in verbal memory (Santos et al., 2014); in parallel, a review of meta-analyses concluded that cognitive deficits were generally

stable (Szmulewicz, Samamé, Martino, & Strejilevich, 2015). Taken together, evidence from the large number of cross-sectional studies and available longitudinal research indicates on average, those with BD experience cognitive deficits after remission.

Although fewer researchers have compared bipolar subtypes, meta-analytic findings indicate that persons with BD II also show cognitive deficits of the same form but slightly less severe than those observed in BD I (Bora, Yücel, Pantelis, & Berk, 2011). More specifically, those with BD II show less severe deficits than those with BD I, with moderate effect sizes for the contrast of BD I versus II for verbal memory (d > .5, seven studies), and smaller effect sizes for visual memory (d= .38, six studies), processing speed (d =.28, six studies) and general cognition (d = .26, eight studies). Findings did not indicate that BD I and II differed significantly in attention, planning, working memory, shifting and inhibition. The relatively greater impairment in verbal memory among those with BD I could reflect severity of the illness vulnerability, or the effects of antipsychotic medications, which are more commonly prescribed for BD I than II, as iatrogenic effects of antipsychotic medications have been observed on verbal memory and processing speed (Balanzá-Martínez et al., 2010).

These findings of cognitive deficits do not appear to be strictly an after-effect of years of illness, in that youth with BD show cognitive deficits that appear parallel to those observed among adults. As with adults, treatment, and concomitant symptom improvements can improve cognitive performance among those with pediatric BD (Lera-Miguel, Andrés-Perpiñá, Fatjó-Vilas, Fañanás, & Lázaro, 2015). Nonetheless, in a meta-analysis of pediatric BD, effect sizes indicated greater deficits among the BD compared to controls. The effect sizes varied, with larger effect sizes for verbal learning and memory (Z = 4.65, nine studies), followed by processing speed (Z= 3.61, seven studies), working memory (Z = 4.19, seven studies), executive function (Z = 4.07, nine studies) and attention (Z = 3.81, eight studies). Smaller, but significant, group differences of those with BD compared to controls were observed in verbal fluency, visual memory, visuospatial skills, and general cognitive ability, with particularly small effects for motor skills (Z = 1.76), assessed in only one study (Nieto & Castellanos, 2011).

These results indicate that adults and children with BD demonstrate cognitive deficits, and that these deficits can be observed even during remission. The most prominent deficits involve executive function, attention, verbal memory and non-verbal memory, indicating that the profile of deficits is quite broad.

Although BD is clearly related to cognitive deficits, these deficits do not appear to be universal. It has been estimated that about 30% of patients with remitted BD will show cognitive performance levels within the normative range (Gualtieri & Morgan, 2008; Martino et al., 2014). This suggests the importance of considering how individual differences in cognition will relate to other domains, such as emotion and functioning.

Cognitive Deficits before Onset

Given the robust evidence that many adults and children with BD show cognitive deficits, a key question is whether cognitive deficits can be observed before onset. Much of this work has focused on IQ (Gale et al., 2013; Tiihonen et al., 2005). Here, though, we focus on executive function, as prospective research indicates that executive function more robustly predicts BD onset than does IQ (Meyer et al., 2004). In one study, offspring of mothers with BD, unipolar depression or no history of BD (n = 74) completed general intelligence tests between ages 8 and 15, executive function tests between ages 11 and 19, and diagnostic interviews (SCIDs) in early adulthood. Nine offspring were diagnosed with BD as young adults. Those 9 participants showed an average IQ score, but had lower performance on executive function tests (ds = 0.58-1.34) than did those who were not diagnosed with BD. These effects persisted when two offspring who had developed bipolar II disorder during adolescence were removed from analyses.

In a study of younger children at high risk for psychosis as indicated by symptom ratings on the Comprehensive Assessment of At-Risk Mental Status, the 16 children who developed BD during the eight-year follow-up period showed substantially lower performance on Trails A and B indices compared to those who did not develop BD (Ratheesh et al., 2013). In sum, two small studies suggest that lower executive function and visuospatial ability can predict the onset of BD.

Cognitive Deficits in Relatives of Those with Bipolar Disorder

Two meta-analyses have been conducted with first-degree family members of those with BD as compared to healthy controls (Arts et al., 2008; Bora, Yucel, & Pantelis, 2009). Although the effect sizes observed in unaffected relatives suggest less profound disturbance than the deficits observed in those diagnosed with the disorder, cognitive deficits can be consistently observed in unaffected relatives as compared to controls. These studies provide a different window into the nature of deficits that might be most

tied to genetic vulnerability. In one meta-analysis of 17 studies, the family members of those with BD showed the largest deficits in response inhibition (measured by the Stroop Task), (d = .51 in 6 studies), followed by other executive function measures (d =.36-.38), with smaller effects for verbal learning and memory measures ($d \leq .33$) (Bora, Yucel, & Pantelis, 2009). A meta-analysis with slightly different selection criteria replicated findings for response inhibition (Stroop d = .49, four studies) and other executive function deficits (Trails B, d = .37,seven studies), and also identified significant bipolar deficits in verbal memory (CVLT immediate and delayed recall d = .42 and .56, respectively assessed in four studies) (Arts et al., 2008). Effects for IQ, FAS, digit span backward, Wisconsin Card Sort Task perseverative errors (assessing shifting, Miyake et al., 2000) and Trails did not reach statistical significance. Despite the clear evidence that deficits are common among unaffected relatives, there is evidence of cognitive heterogeneity in relatives of those with BD. For example, one twin study found that healthy twins with a bipolar sibling showed enhanced verbal fluency and verbal learning, relative to controls (Higier et al., 2014). This opens the door to considering how cognitive measures relate to emotionality and function among unaffected family members.

Findings of multiple studies indicate that these cognitive deficits can be observed early in life, among child or adolescent offspring of those with BD, although these deficits are not as severe as those observed among probands of those with schizophrenia (for review, see Olvet, Burdick, & Cornblatt, 2013). In one study, deficits in executive function, as measured by the Wisconsin Card Sort Task were more severe among adolescent offspring of mothers with BD (n = 43) than among the offspring of mothers with major depressive disorder (n = 72) (Klimes-Dougan, Ronsaville, Wiggs, & Martinez, 2006), and these effects remained significant when controlling for IQ and current symptoms. In a second study, researchers focused on 45 offspring at risk for schizophrenia or BD, defined as at least one first-degree family member with the disorder and at least four relatives with the disorder (first degree or more distant). The 23 offspring from bipolar families demonstrated impairment in executive function measures of problem solving (d = .98), initiation (d = .72), planning (d = .58), verbal memory (d = .94 for immediate and 1.03 for delayed recall) and visual memory (d= .73 for immediate and d = .88 for delayed recall) as compared to controls (Maziade et al., 2009). Deficits in response inhibition have also been identified in offspring of those with BD I (Frangou, Haldane, Roddy, & Kumari, 2005).

In sum, multiple studies indicate that a broad range of cognitive measures are impaired among unaffected family members of those with BD, even at an early age, including executive function, verbal learning, and visual learning. Of note though, a clearer profile emerges in these at-risk studies of response inhibition as a particularly robust indicator of risk.

Cognition as a Predictor of Functional Impairment

Given the cognitive deficits observed in those diagnosed with and at risk for BD, a key question is whether these deficits can help explain functional impairment. In a qualitative review of 52 studies, cognitive deficits were consistently associated with lower functioning within BD, in both cross-sectional and longitudinal studies (Baune, Li, & Beblo, 2013). Findings of a quantitative meta-analysis also indicated that cognitive deficits were tied to worse functional impairment, and effects did not appear to be moderated by clinical state, age, or study design (Depp et al., 2012). Multiple cognitive domains were tied to functional impairment, with aggregate *r*s ranging from .21 to .29, but working memory was the domain most specifically related to functional outcome.

The effects of cognition on functional impairment are also observed in longitudinal studies that control for baseline symptom severity. For example, when cognitive deficits were measured just after a first manic episode among young adults, more severe cognitive deficits significantly predicted lower quality of life six months later when controlling for baseline symptom severity (Mackala et al., 2014). Although cognitive deficits tend to be stable over time (Samamé, Martino, & Strejilevich, 2014; Santos et al., 2014), a subgroup of patients show declines in cognitive function over time, and faster decline predicted lower functioning (measured via the FAST) at six-year follow-up (Mora, Portella, Forcada, Vieta, & Mur, 2013).

The strength of relationships between cognition and functional outcome likely depend on the measures of functioning employed. (Baune and collegues (2013) noted that effects were smaller when researchers relied on the Global Assessment of Functioning (GAF), which is not surprising given the low inter-rater reliability of the GAF. In a meta-analysis of 22 studies of cognition and psychosocial function (N = 1344), stronger effects were observed for performance-based (r = .32) and functional milestone (e.g., achievements such as autonomy, marriage, employment, r = .33) measures of functioning as compared to clinician- or self-rated measures (r = 0.23 and r

= 0.20 respectively). In this meta-analysis, an overall average correlation of .27 was observed between cognitive measures and everyday functioning (95% CI = 0.22- .32, $p < 0.001$; (Depp et al., 2012).

Cognitive impairment can predict declines in functioning above and beyond the role of symptom status. Parallel with the profile of cognitive findings in BD, evidence implicates a broad range of cognitive variables tied to functional impairment but supports the key role of executive function indices such as working memory indices.

Summary of Cognitive Deficits

A large literature indicates that executive function and other facets of cognition are impaired in adults and youth with BD, even during remission. Such deficits can be observed in unaffected family members, with particularly robust evidence for deficits in response inhibition. Although not universally present, cognitive deficits can predict the onset of BD among those at-risk. Cognitive indices, including executive function measures, appear closely tied to functional impairment in cross-sectional and longitudinal studies, particularly when strong measures of function are used. Taken together, these findings suggest that cognition could serve as a vulnerability marker for BD.

Emotion in Bipolar Disorder

Euphoria and anger are defining features of mania, and accordingly, researchers have placed considerable emphasis on understanding emotionality in BD. Findings indicate that even after remission, those with BD display heightened or more frequent negative affectivity on self-report measures (Heerlein, Richter, Gonzalez, & Santander, 1998; Keitner et al., 1996), experience sampling (Knowles et al., 2007), and laboratory-based measures using standardized stimuli (Gruber, Harvey, & Johnson, 2009; Pavlova, Uher, Dennington, Wright, & Donaldson, 2011; Rich et al., 2010). This does not appear to be limited to negative valence, in that those with BD also display heightened or more frequent positive affectivity, again across self-report measures (Gruber et al., 2009), experience sampling (Knowles et al., 2007), and laboratory-based measures (Gruber, Dutra, Eidelman, Johnson, & Harvey, 2011; Gruber et al., 2009; Gruber, Harvey, & Purcell, 2011). Given the heterogeneous nature of emotion problems that have been observed, one study considered a broad range of emotion-related difficulties, and findings indicated that BD was more strongly tied to elevations of negative emotion as

compared to positive affectivity problems (Johnson, Tharp, Peckham, & McMaster, 2016).

Beyond reactivity, researchers have found that those with BD tend to feel less confident in their ability to use adaptive emotion regulation strategies (Gruber, Harvey, & Gross, 2012). Disentangling the emotion regulation literature is not straightforward. Perhaps in response to the frequent emotion states, those with BD often report using many different emotion regulation strategies more frequently than those with no mood disorder do (Gruber, Kogan, Mennin, & Murray, 2013). In addition to the more frequent use of adaptive strategies, they tend to endorse using more maladaptive forms of emotion regulation, such as rumination, more than those without mood disorders do (Gruber, Dutra, et al., 2011; Gruber, Eidelman, & Harvey, 2008; Johnson, McKenzie, & McMurrich, 2008; Rowland et al., 2013; Thomas, Knowles, Tai, & Bentall, 2007). Beyond the large literature on responses to negative emotions, those with severe forms of the disorder endorse frequent use of strategies to dampen positive emotions (Edge et al., 2013; Gruber, Harvey, et al., 2011).

Beyond these typical domains of emotion and emotion regulation, findings have indicated that in the face of a given emotion state, those with BD report more difficulty controlling their speech and behavior. This phenomenon has been referred to as emotion-related impulsivity, and those with BD endorse significantly more concern about this form of impulsivity than other forms of impulsivity, even after remission (Muhtadie et al., 2014). This tendency toward emotion-triggered impulsivity does not appear to be just the aftermath of the episodes, as it has also been observed among samples at risk by virtue of subsyndromal manic symptoms (Giovanelli, Hoerger, Johnson, & Gruber, 2013; Johnson, Carver, Mulé, & Joormann, 2013). Intriguingly, effects of emotion-related impulsivity do not appear to be just an effect of a higher level of emotionality or arousal, but rather, a more specific problem with constraint in the face of an emotion state (Johnson, Tharp, Peckham, Sanchez, & Carver, 2016).

There is also some mixed evidence that difficulty accurately identifying facial displays of emotion can be observed in adults and children with BD. Because these difficulties are not observed in most studies of remitted samples of adults with BD (Samamé, Martino, & Strejilevich, 2012), we focus on other facets of emotion here.

Given the well-established emotionality among those with BD, a key question is whether emotion problems can be observed before onset. Several studies suggest that problems with emotionality are apparent in the offspring of those with BD, including

prolonged duration of emotion responses (Chang, Blasey, Ketter, & Steiner, 2003), greater lability of negative emotions and to a smaller extent, positive emotions (Birmaher et al., 2013). Indeed, by preschool, offspring of those with BD tend to show increased reactivity to negative emotions in others and difficulty regulating their own negative emotions (Zahn-Waxler, McKnew, Cummings, Davenport, & Radke-Yarrow, 1984; Zahn-Waxler, Cummings, McKnew, & Radke-Yarrow, 1984). The TEMPS-A cyclothymic scale, comprised of items capturing the tendency to experience overly pronounced shifts in emotion states, has been shown to predict the onset of BD among youth (Kochman et al., 2005).

Given evidence that multiple emotion problems are observed in those diagnosed with and at risk for BD, researchers have considered how individual differences in emotion regulation relate to outcomes within BD. Within BD, more maladaptive approaches to regulating negative emotion relate to more severe depressive symptoms cross-sectionally (Gilbert et al., 2013; Green et al., 2011; Johnson et al., 2008; Rowland et al., 2013; Thomas et al., 2007) and longitudinally (Johnson, Tharp, Peckham, & McMaster, 2016; Van Rheenen & Rossell, 2014).

Beyond depression, emotion regulation also appears of import for functional outcomes. In one study, greater tendencies to engage in suppression were related to significantly lower function in BD, even after controlling for indices of negative and positive emotionality (Johnson et al., 2016). When those with BD I over-use dampening of positive mood states, lower functioning and quality of life are observed (Edge et al., 2013). Hence the ability to effectively regulate both positive and negative emotions appears important for outcomes in BD.

Higher emotion-related impulsivity has been found to relate to greater suicidality and aggression among those with remitted BD I. Given this, perhaps it is not surprising that emotion-related impulsivity is tied to substantially lower quality of life and functional outcomes for those with BD I (Johnson & Carver, 2016; Johnons, Carver, & Tharp, 2017; Muhtadie et al., 2014; Victor, Johnson, & Gotlib, 2011).

In sum, findings indicate that BD is related to increased negative emotion reactivity, and perhaps slightly less robustly degree, positive emotional reactivity. Those with BD may use emotion regulation strategies more often than others do, but they feel less confident about the effectiveness of these strategies. BD is also tied to emotion-related impulsivity. Many of these facets of emotionality can be observed before onset among those at risk for the disorder. Emotion variables also are important for outcomes.

Those who use more rumination and suppression are prone to depression, and those who use more reappraisal may develop less depression over time. Negative emotionality, maladaptive strategies for regulating negative emotions, and dampening of positive emotion all relate to lower function. Emotion-related impulsivity relates to worse functional outcome, more aggression, and more suicidality in BD.

Links between Cognition and Emotion

Above, we have outlined evidence that both cognitive deficits and emotion disturbances are closely tied to BD, of central importance for functional outcomes in BD, observable before onset, and predictive of the onset of BD. Surprisingly, research in these two important domains has evolved in a largely separate manner within BD. That is, relatively little behavioral research has considered the interface of cognitive deficits and emotionality in BD. Accordingly, we focus on the rich literature outside of BD on the interface of cognition and emotion regulation.

Cognition and Emotion Outside Bipolar Disorder

Nearly all theories of emotion and emotion regulation involve cognitive processes. According to several theories of emotion, cognition provides a framework for appraising internal and external stimuli (Oatley & Johnson-Laird, 2014). Many experimental approaches provide insight into the ways in which variations in the valence and arousal of specific affective states influences cognition. Certainly, considerable research suggests that high levels of emotion may interfere with executive function, in part because of the resources consumed by prioritizing attention to highly salient, emotion-relevant stimuli (Pessoa, 2009). This prioritization of cognitive attentional resources is frequently observed when stimuli have high "motivational intensity" or induce high arousal (Gable & Harmon-Jones, 2010; Harmon-Jones & Gable, 2009). In contrast, low-arousal positive emotions have been theoretically and empirically linked with greater cognitive flexibility and broader attention, yet more difficulty inhibiting attention to distractions (Ashby, Isen, & Turken, 1999; Dreisbach & Goschke, 2004; Fredrickson, 2003).

In addition to effects of emotion on cognitive processes, experimental and correlational research in healthy populations and in other clinical disorders has provided understanding of the opposite direction-- ways in which cognitive processing ability can

influence emotion regulation (for review, see Hofmann, Schmeichel, & Baddeley, 2012; Schmeichel & Tang, 2015). Better skill in regulating emotions, as reflected in the tendency to use reappraisal more and to gain more benefit from reappraisal, has been tied to higher performance on measures of executive function (von Hippel & Gonsalkorale, 2005), and more specifically working memory (Hendricks & Buchanan, 2015; McRae, Jacobs, Ray, John, & Gross, 2012; Schmeichel, Volokhov, & Demaree, 2008), cognitive flexibility (Malooly, Genet, & Siemer, 2013), and cognitive inhibition (see Joormann & Vanderlind, 2014), with particularly strong effects when cognitive inhibition is tested under conditions of stress (Quinn & Joormann, 2015). Other findings show that higher verbal fluency scores are related to greater emotion regulation success, as reflected in physiological measures and changes in facial affect (Gyurak et al., 2009; Gyurak, Goodkind, Kramer, Miller, & Levenson, 2012).

Other research focuses on cognitive abilities related to maladaptive regulatory strategies. The cognitive underpinnings of rumination have been correlated with each of the major domains of executive function: cognitive flexibility, inhibition, and working memory. Perhaps not surprisingly then, cognitive inflexibility, which involves the inability to switch strategies after negative feedback and related tendencies to perseverate, has been correlated with ruminative tendencies (Davis & Nolen-Hoeksema, 2000). To assess other domains of executive function in relation to rumination, multiple studies have used tasks that contrast negatively valenced and neutral stimuli. Multiple studies suggest that rumination is related to poorer executive function—including inhibition, working memory updating, and switching—when valenced stimuli are used as distractors or when the stimuli to be processed are negatively valenced (Beckwé, Deroost, Koster, De Lissnyder, & De Raedt, 2014; Bernblum & Mor, 2010).

Finally, a large body of work has focused on executive function measures and emotion-related impulsivity. Across a set of studies, a recent meta-analysis indicated that emotion-related impulsivity was specifically tied to response inhibition, particularly when samples with more extreme deficits in this form of impulsivity were tested (Johnson et al., 2016).

Studies demonstrating a role of executive function in emotion regulation and emotion-related impulsivity dovetail with findings from functional MRI and electroencephalography (EEG) research. Although a full discussion of the rich literature on the neurophysiological basis of the emotion-cognition interactions is beyond the score of this review, recent approaches in this field increasingly highlight evidence

showing substantial overlap in brain regions involved in both emotion and cognitive processes (e.g., Pessoa, 2009). Within this literature, much work has focused on the important role of prefrontal cortex (PFC) for emotion processing and emotion regulation (Banich et al., 2009; Beckwé et al., 2014; Bernblum & Mor, 2010; Davis & Nolen-hoeksema, 2000; Goodkind et al., 2015; Kahl et al., 2012; Ochsner et al., 2004). The PFC is centrally implicated in executive function domains including cognitive control, cognitive flexibility and working memory (Diamond, 2013).

Some of this work has focused on brain regions that are activated when individuals are asked to inhibit attention to emotionally relevant content. These studies broadly show that activation of the right ventrolateral PFC is heavily involved in inhibition, both in the presence of affective and non-affective stimuli (Chiu, Holmes, & Pizzagalli, 2008; Dillon & Pizzagalli, 2007), while the rostral anterior cingulate cortex (rACC) may specifically support inhibition of emotional distractions (Chiu et al., 2008; Etkin, Büchel, & Gross, 2015). To test working memory in the face of emotion distractors, researchers assessed the ability to store goal-directed information after the presentation of an emotional interference (Banich et al., 2009). The results show heightened activation in PFC regions suggesting their engagement in down-regulating activity in emotion-related region, such as amygdala.

Understanding neural underpinnings of effective emotion regulation rests on considering specific forms of emotion regulation (for review, see Ochsner & Gross, 2005). A large body of work has focused on the neural underpinnings of reappraisal, most commonly using experimental designs in which participants are asked to view emotionally-relevant stimuli and asked to engage in emotion regulation or as a control condition, to view the stimulus. In a meta-analysis of 48 studies, reappraisal was consistently associated the frontoparietal network, including lateral prefrontal cortex (LPFC), dorsal anterior cingulate cortex (dACC), and the intraparietal sulcus (IPS), and deactivation of the amygdala (Buhle et al., 2014; Messina, Bianco, Sambin, & Viviani, 2015). Emotion distancing, a form of reappraisal in which people try to distance themselves from negative emotions elicited by thinking of the stimulus as far away, long ago, or less relevant to them, has been found across seven studies to activate the frontoparietal network (Belden, Pagliaccio, Murphy, Luby, & Barch, 2015; Lewis, Todd, & Honsberger, 2007). Of interest, this same frontoparietal network, has been tied to response inhibition (Aron, 2011; Braver, Paxton, Locke, & Barch, 2009; Jamadar, Fielding, & Egan, 2013). Finally, although less is known, emotion-related impulsivity

has been linked to diminished activation of some of these same regions, including dACC as well as bilateral inferior frontal gyrus/insula during response inhibition (Wilbertz et al., 2014). Taken together, the findings highlight the range of neural regions that must be effectively coordinated to produce effective regulation of emotion.

Recent meta-analysis findings suggest that rumination is also tied to regions of the PFC, although in a different manner. That is, rumination appears related to increased functional connectivity of the subgenual prefrontal cortex with the default-mode network, and to elevated activation of the medial PFC in particular (Disner, Beevers, Haigh, & Beck, 2011; Hamilton, Farmer, Fogelman, Gotlib, 2015).

Much of the research on neural and cognitive mechanisms in emotion, though, is correlational. Certainly, deficits in executive function, such as the ability to inhibit interference from emotion stimuli on a working memory task, can prospectively predict rumination (Zetsche & Joormann, 2011). Moreover, addressing deficits in executive function via computerized training (involving working memory training, or the combination of working memory training with attentional control training) can lead to reductions in rumination in those diagnosed with clinical depression (Siegle et al., 2014; Siegle, Ghinassi, & Thase, 2007; Vanderhasselt et al., 2015), in people with remitted depression (Hoorelbeke, Koster, Demeyer, Loeys, & Vanderhasselt, 2016), and in student samples (Hoorelbeke, Koster, Vanderhasselt, Callewaert, & Demeyer, 2015). In addition, 20 sessions of training on a working memory task involving affective stimuli enhanced the efficiency of the frontoparietal network, and in turn, enhanced ability to down-regulate response to an emotion picture (Schweizer, Grahn, Hampshire, Mobbs, & Dalgleish, 2013). These findings indicate that deficits in executive functions and related neural activity appear to exert an important influence on emotion regulation effectiveness. With these models as backdrop, we turn to the smaller literature on cognition and emotion in BD.

Links between Cognition and Emotion in Bipolar Disorder

Considerable neurobiological evidence supports the premise that prefrontal control of affective states is impaired in BD (e.g., Green, Cahill, & Malhi, 2007; Strakowski, 2012). Reviewers consistently conclude that BD is tied to elevated neural activation in regions involved in responding to salient stimuli, such as the amygdala and ventral striatum compared to other, as well as deficient activation of regions involved in emotion regulation, such as prefrontal cortical areas (Chen, Suckling, Lennox, Ooi, &

Bullmore, 2011; Green et al., 2007; Strakowski, Delbello, & Adler, 2012). Reviewers have also identified a consistent pattern of diminished connectivity of regions involved in top-down control with those involved in reactivity for those with BD (M L Phillips, Ladouceur, & Drevets, 2008). Not only are key emotion-relevant neural regions impaired in BD, but specific work confirms that activity in these regions is relevant to effective emotion regulation for those with BD. For example, frontoparietal activation has been shown to correlate negatively with amygdala activation levels during reappraisal in BD I (Kanske, Schönfelder, Forneck, & Wessa, 2015). The imaging findings fit with a profile of heightened emotionality and diminished emotion regulation in BD.

Although the biology of BD has been proposed to give rise to pervasive difficulties regulating emotion, including rumination (Ghaznavi & Deckersbach, 2012), surprisingly little behavioral research in BD has considered how specific cognitive deficits relate to emotion and emotion regulation strategies. One approach has been to consider whether the deficits in executive function observed among those with BD are heightened in the context of emotion stimuli as compared to non-emotion stimuli. A second approach has been to more directly consider the facets of cognition that relate to effective emotion regulation within BD. We consider both approaches here.

We begin by considering research on affective stimuli during executive function tasks. The BD studies on this front have focused on response inhibition tasks such as the go-no go or anti-saccade tasks (Van Rheenen & Rossell, 2013). Those with BD, even during remission, have been found to have difficulty on the affective go-no go task compared to control participants, while showing less impairment on non-affective trials (Bauer et al., 2015; Gopin, Burdick, Derosse, Goldberg, & Malhotra, 2011). Similar effects have been observed with a version of the antisaccade task. That is, persons with BD and those with ADHD showed comparable deficits in a standard version of the antisaccade task; for those with BD, though, emotion faces interspersed between trials of the antisaccade task led to significant decay, such that those with BD performed significantly more poorly than those with ADHD when the emotion faces were presented between trials (Soncin, Brien, Coe, Marin, & Munoz, 2016).

Beyond the use of distractors with negative valence, one team used a variant of the antisaccade task in which participants were asked to rapidly look away from positive stimuli on some trials, in contrast to neutral stimuli on other trials. Those with BD

showed particular deficits compared to controls when asked to rapidly look away from emotion stimuli (Mueller et al., 2010).

Drawing on the behavioral evidence for difficulties with executive function when emotion stimuli are present, one neuroimaging study examined neural responses to an executive function task involving emotion stimuli among those with BD. More specifically, participants were asked to complete a working memory task (the N-back task) with and without emotional distractors (Mullin et al., 2012). Patients diagnosed with BD showed reduced activity in several areas implicated in executive function and regulation, such as the dorsolateral PFC, dACC and inferior parietal cortex, compared to healthy controls. When emotion distracters were present, however, the bipolar patients showed increased activity in these regions as well as in emotion processing regions such as the amygdala and striatum; the authors argued that this increased activity reflected compensatory responses due to difficulties in regulating in the face of emotion stimuli. Atypical connectivity was also observed between the dACC and the amygdala when emotion distractors were present. The findings support the idea that executive function may be particularly difficult for those with BD when emotion-relevant stimuli are present.

Researchers have extended this approach to consider whether deficits in response inhibition for emotion stimuli can be observed among unaffected family members of those with BD. In the first study, 20 unaffected siblings of those with BD showed a nonsignificant trend toward poor performance on the affective go-no go task compared to controls (Brand et al., 2012). In the second study, seven unaffected offspring did not display significant deficits on the affective go-no go task (Bauer et al., 2015). The null findings are difficult to interpret, though, given the small sample size and meta-analytic evidence that emotion stimuli are not related to performance on the go/no-go task for those with emotion disorders (Wright, Lipszyc, Dupuis, Thayapararajah, & Schachar, 2014). It will be important to consider response inhibition and emotion in at-risk populations using other tasks and larger samples.

Early findings on whether cognitive indices can predict emotion regulation among those with BD have been more mixed. In one study, a composite measure of executive function based on Trails, Stroop, and Matrics scores did not predict self-rated Difficulties with Emotion Regulation scores among 51 persons with BD (Van Rheenen & Rossell, 2014). Although that study relied on "cold cognition" measures that did not integrate emotion-relevant stimuli, a measure of cognitive flexibility (task-switching) in

the context of affective faces was found to predict self-rated ability to use Reappraisal, as measured by the Emotion Regulation Questionnaire among persons with remitted BD (Gul & Khan, 2014). Although preliminary, these findings suggest that it will be important to consider the influence of affective stimuli and contexts in using neuropsychological indices to predict emotion regulation within BD.

Summary of Cognition and Emotion

A large body of basic behavioral and neural research suggests that effective emotion regulation rests on strong executive function, and particularly inhibition. Beyond the evidence that cognitive ability supports effective emotion regulation, the presence of heightened emotion appears to lead to decays in executive function ability. One might expect that persons with clinically relevant deficits in cognition, then, could be prone to heightened emotion states, which in turn, would contribute to decays in cognitive performance. BD, then, is a natural place to consider the interface between cognition and emotion.

Nonetheless, emotionality has often been considered separately from the cognitive deficits in BD. The few integrative findings within BD suggest a more nuanced profile of cognitive deficits than has been observed in the general neuropsychological literature. That is, those with BD show more pronounced difficulties on cognitive tasks which integrate emotion stimuli than tasks without such stimuli. Moreover, performance on tasks with emotion stimuli may be more powerfully predictive of emotion regulation capacity than tasks without such stimuli. This research highlights that in the study of cognition, researchers would do well to include measures that incorporate emotion stimuli, as those may be a more powerful window into vulnerability.

3.3 FUTURE DIRECTIONS

The few available findings support the idea that cognitive deficits are centrally involved in the emotion difficulties observed in BD. This has some overlap with transdiagnostic models of the importance of cognitive deficits (Goodkind et al., 2015), and particularly executive function deficits, with emotion-related symptoms across syndromes (Snyder, Miyake, & Hankin, 2015). If the idea that cognition can explain the emotion problems is supported, this model provides a different way to view the source

and treatment of emotion difficulties within BD. Before considering those implications, we turn to several questions that have not been addressed in the bipolar literature.

To begin, it is often assumed that either cognition or emotion are central starting points for the eventual cascade into bipolar symptoms. Nonetheless, multiple variables may be involved in shaping both cognition and emotion. Of particular relevance, among those with BD, early trauma and adversity are tied to deficits in both cognition (Savitz, Van Der Merwe, Stein, Solms, & Ramesar, 2008) and emotion lability (Aas et al., 2014). Overall, it will be important to consider contextual factors that might contribute to the overlap between cognition and emotion before concluding that cognition is truly a central driver for other outcomes. Given that emotion and cognitive difficulties have been observed in unaffected family members, genetically-informed designs are likely to be of particular importance in understanding these links.

Beyond a better understanding of the context linking emotion and cognition, relatively little is known about whether cognition can explain the full range of emotion problems observed in BD. To date, researchers have been particularly focused on emotion regulation, and yet emotion experience and reactivity may be more closely tethered to disorder. Given how tightly correlated reactivity and regulation are, these facets of emotionality should be conjointly investigated in relation to cognition. Laboratory studies which examine responses to standardized emotion-relevant challenges can be particularly powerful ways to consider the time course of initial reactivity and recovery. Understanding this question could help disentangle whether it is appropriate to consider cognition as a driver of all facets of the emotionality profile in BD, or more strictly of relevance to emotion regulation, or even regulation only of negative stimuli.

Perhaps of most importance, there are key questions about which facets of cognition are most centrally involved in emotionality within BD. Although early research has focused on specific facets of cognitive inhibition or executive function, it remains possible that a much more general cognitive factor guides performance on specific cognitive tasks, as well as a range of emotional and functional outcomes. The facets of executive function are highly correlated, and that there may be general factors that explain much of the variance in specific facets of executive function and that explain emotion-relevant symptoms (Snyder et al., 2015). If true, then hunting for the singular cognitive process that explains these problems could be a flawed approach.

In addition to considering that there may be a general cognitive vulnerability to multiple facets of executive function deficits, the bipolar literature may be prematurely focused only on executive function. That is, multiple studies indicate that a range of cognitive functions beyond executive function are requisite to effective emotion regulation. For example, memory is required to consider alternative perspectives (a key aspect of reappraisal) (Schneider, Gur, Gur, & Shtasel, 1995). Similarly, processing speed is relevant for rapidly processing dynamic emotion stimuli, such as facial expressions as they occur in the real world (De Sonneville et al., 2002). Verbal fluency has been found to mediate the ability to down-regulate responses to expected, but not unexpected, laboratory stimuli (Gyurak, Goodkind, Kramer, Miller, & Levenson, 2012; Schmeichel & Tang, 2014). Drawing on such findings, Van Rheenen & Rossell (2013) argued that language processing, processing speed, memory, and attention might all be relevant for understanding emotion in BD. Disentangling the true nature of the cognitive deficits underpinning emotionality in BD will require work using a battery of cognitive indices, as well as more sophisticated modeling that considers latent variables constructed to consider the role of measurement error.

Beyond the need for greater specificity of the models linking cognition and emotion, there is a need for understanding how cognitive deficits and emotionality conjointly relate to functional outcomes, given that emotion and cognitive deficits are both clearly linked to functional outcomes in BD, when examined separately. At the current time, studies have not examined whether the effects of cognitive deficits fully explain the functional outcomes observed among those with emotion dysregulation. That is, it remains unclear whether emotion qualities will explain functional outcomes above and beyond the role of the cognitive deficits. Understanding the overlapping and unique contributions of cognition and emotion to functionality will be important in choosing the most important targets for intervention. Overall, given the complexity of ways in which cognition and emotion may interface, experimental designs would be particularly helpful to understand these relationships.

Notwithstanding the gaps in testing a fuller model of cognition and emotion in BD, findings of the current review have several implications. Most importantly, the idea that cognition might drive emotionality in this disorder suggests that treatment might focus on relieving cognitive deficits. This is a marked shift from current approaches to treatment, which employ many emotion regulation techniques drawn from cognitive behavioral therapy or Dialectical Behavior Therapy (Linehan, 1993). Although such

work remains a vital part of the research agenda in BD, if cognitive deficits precede and drive the emotionality observed in BD, it may be more important to focus on relieving cognitive concerns and hope that this leads to emotion improvements.

Certain pharmacological treatments may help reduce cognitive deficits in BD. For example, cognition has been found to improve with treatment lamotrigine (Pavuluri, Passarotti, Mohammed, Carbray, & Sweeney, 2010) or mifepristone (A. H. Young et al., 2004) in BD. It would be helpful to map the time course of changes in cognition and whether this precedes improvements in emotion with receipt of these medications.

To the extent that emotion difficulties improve when cognition problems are treated, this would also provide a clearer test of directionality of links between these two domains. In this way, some of the recent cognitive remediation work is particularly relevant and may provide cleaner information about the direction of effects. To date, a 24-session cognitive remediation program targeting a broad array of 21 cognitive tasks was shown to lead to significant improvements in global executive function and depression, but did not significantly shift working memory in BD. In one open trial of a treatment for BD that included mood monitoring, as well as cognitive coaching on how to improve planning, attention, and memory, participants self-reported improved cognitive and occupational function (Deckersbach et al., 2010). While these studies indicate that cognitive training could potentially address core cognitive concerns in BD, no research is available on whether this improves emotion regulation.

Again, the literature outside of BD provides helpful insights. That is, cognitive remediation has been shown to be helpful in addressing emotionality when applied with persons who were not diagnosed with BD. In part, these programs may have been successful because they targeted cognitive domains that seem particularly relevant for emotion outcomes. For example, several investigators have developed programs to improve working memory when viewing negative stimuli or completing a stressful task. These working memory training programs have been found to be efficacious in reducing rumination and depressive symptoms (Cohen, Mor, & Henik, 2015; Hoorelbeke et al., 2015; Porter et al., 2017). Taken together, the success of the more specific cognitive remediation programs outside of BD highlight how important it will be to understand which facets of emotionality are driven by cognition, and which facets of cognition make the most appropriate targets in BD. Studies applying cognitive remediation in BD would do well to consider whether improving "cold" cognitive processes alone are sufficient to improve emotion outcomes, as some evidence indicates is the case, or

whether cognitive engagement with emotional stimuli amplifies improvement. This line of research may contribute to the development of optimized treatments, based on specific profiles of neurocognitive abilities or emotion dysregulation.

In sum, researchers have gained considerable traction in understanding both cognition and emotion in BD. Given the considerable support for both domains as key facets of vulnerability to the disorder, it is time for a more integrative perspective. We hope this review provides some backdrop that will foster this quest.

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4. STUDY TWO: INTEGRATIVE UNDERSTANDING OF FAMILIAL IMPULSIVITY: EARLY ADVERSITY AND SUICIDE RISK

4.1. ABSTRACT

Introduction: Impulsivity is a core characteristic of bipolar disorder and it was observed as elevated in individuals with the disorder and in their relatives. Both impulsivity and history of maltreatment are risk factors for suicide attempts, however, these two key variables may not be independent, given the fact that parental impulsivity and associated social context could increase the risk of child maltreatment. In this study it was examined the association between the impulsivity of relatives and child maltreatment taking into consideration the conjoint and unique effects of these two variables on the risk of suicide attempts among the patients.

Materials and Methods: Participants of the study consisted of 117 patients diagnosed with bipolar disorder and 25 first-degree relatives. Linear regression model was conducted to describe associations between facets of impulsivity of relatives and levels of child maltreatment reported by patients. The independent associations of suicide attempt history with the dimensions of impulsivity of the patient and maltreatment were tested by multinomial logistic regression.

Results: Impulsivity of relatives and, more specifically, inhibitory control can predict the maltreatment of the patient. Inhibitory control and emotional abuse were related, conjointly, to a greater likelihood of having a history of more than one suicide attempt.

Discussion: Considering that the impulsivity of relatives predicts child maltreatment, it is possible that a genetically shared impulsivity is an underlying feature associated with the history of multiple suicide attempts. These findings highlight the importance of considering child maltreatment, impulsivity and suicide attempt history in integrative models.

4.2. INTRODUCTION

Bipolar Disorder (BD) consists of a heterogenic group of mood pathologies, which varies in terms of amount and severity of depressive and/or manic episodes, presence of psychotic symptoms, comorbid diagnostics, number of hospitalizations and suicide risk.

There are at least two main BD subtypes. *Bipolar I* disorder is characterized by the presence of at least one manic episode. Mania, in turn, is characterized by a period of at least one week of elevated, expansive or irritable mood, increased energy, and more talkativeness and engagement in risky activities (American Psychological Association (APA), 2013). *Bipolar II* is described as the presence of at least one previous major depressive episode for at least two weeks and one hypomanic episode that lasts a minimum of four days (APA, 2013).

Approximately one quarter of patients with *Bipolar I* report suicide attempts (Merikangas et al., 2011) and suicide accounts for 10% and 6.7% of deaths in *Bipolar I* and *II*, respectively (Hengartner, Gamma, von Zerssen, & Angst, 2013). Hence, BD presents the highest absolute risk of suicide among different psychiatric conditions (Nordentoft, Mortensen, & Pedersen, 2011). The focus of this paper is to understand the conjoint effects of two key factors for suicidality within BD: child maltreatment and impulsivity. With the aim to shed light into how impulsivity, maltreatment and suicidality interact, the goal of this study is to develop and test a more integrative model of these variables.

Impulsivity is considered to be a core feature of BD (Swann, Pazzaglia, Nicholls, Dougherty, & Moeller, 2003). To begin with, the diagnostic criteria for mania involves impulsivity. Even after manic episodes clear out, however, a growing body of research suggests that high levels of impulsivity persist (Swann et al., 2003). It is also noteworthy that impulsive behaviors can be transmitted through generations since it is observed to be elevated even in family members who do not meet diagnostic criteria for BD (Fortgang et al., Hultman, van Erp, & Cannon, 2016). According to the Self-Regulation Intergenerational Transmission Model, the diminished self-regulation that contributes to impulsive behavior is multifactorial, involving prenatal, social mechanisms of transmission, such as marital and parent-child interaction, as well as neurobiological mechanisms (Bridgett, Burt, Edwards & Deater-Deckard, 2015). Impulsivity is associated with low quality of life (Victor, Johnson, & Gotlib, 2011) and dysfunctional behaviors such as aggressiveness within BD (Johnson & Carver, 2016).

Particularly, impulsivity seems to be related to suicidality within BD (Johnson, Carver, & Tharp, 2016). Impulsive behavior triggered by emotion is related to history of suicidal ideation, self-harm, and suicide attempt in BD (Johnson et al., 2016) and also among those without BD (Auerbach, Stewart, & Johnson, 2016; Black & Mildred, 2013; Kasen, Cohen, & Chen, 2011). These findings converge with the results of a longitudinal study, which indicates that impulsivity may predict suicide attempts over a 15-year period in the general population (Kasen et al., 2011).

A separate literature indicates that early adversity and maltreatment are major concerns within BD. Rates of child abuse and neglect are quite high in those with the disorder, with exposure estimates as high as 51% (Daruy-Filho, Brietzke, Lafer, & Grassi-Oliveira, 2011). Early adversity and maltreatment have been associated with early bipolar onset and also to contribute to a poor prognosis within BD, including more symptom severity, more relapse and lower levels of functioning (Daruy-Filho et al., 2011). Child maltreatment is also a predictor of the risk of suicide within BD (Norman et al., 2012). Indeed, a wide range of forms of child maltreatment, including sexual abuse, emotional abuse, physical abuse and emotional neglect, have been individually associated with the risk of attempted suicide within BD (Norman et al., 2012).

Although both impulsivity and childhood adversity seem to be important in understanding bipolar suicidality, these two variables have been studied separately in the literature on BD. However, it is possible that impulsivity among family members may increase the risks of exposure to childhood adversity in offspring.

Considering this background, it was hypothesized that patients whose relatives have high levels of impulsivity may be in a social context that could increase the risk of abuse. First, the degree of overlap of early adversity and impulsivity among individuals with BD was assessed, then the conjoint and unique effects of early adversity and patient impulsivity as correlates of suicide attempt were considered. That is, it was examined: 1) whether the impulsivity of relatives can predict the levels of child maltreatment; 2) the extent to which the impulsivity of the patients and maltreatment dimensions are associated with suicide attempts.

4.3. MATERIALS AND METHOD

Sample:

The sample consisted of a group of 117 bipolar patients and 25 first-degree relatives. The inclusion criteria taken were being aged between 18 and 60 years. Exclusion criteria were based on neurological conditions. The bipolar group consisted ofindividuals who had been previously diagnosed with BD by a psychiatrist and were being treated in a bipolar outpatient clinic which is part of Brazilian Public Health System. The bipolar diagnosis was confirmed through the administration of the MINI Plus 5.0 diagnostic interview (Sheehnan et al., 1997). Each patient was asked to indicate a first-degree adult relative to compose the sample of relatives. However, only part of them attended to the scheduled appointment. Only a few of them met the inclusion criteria, resulting in a small sample of 25 relatives. Inclusion and exclusion criteria were the same applied to patients with the addition that they could not present psychiatric diagnosis, assessed by the administration of MINI Plus 5.0 diagnostic interview (Sheehnan et al., 1997). First degree relative was considered as being parents' siblings or children of patients. No more than one relative per patient was assessed. Fifteen of the 25 relatives assessed were parents of patients,on the majority being their mothers. The Ethics Committee of the Federal University of Minas Gerais approved this study (N^o 064/09) and all of the participants filled a written informed consent procedures before taking part in the study procedures.

Measures:

Interviews and instruments were administered to patients in order to assess impulsivity, child maltreatment, suicide attempt history and mood states. Family members completed parallel measures of their personal levels of impulsivity and mood states.

Barrat Impulsiveness scale – BIS – 11 (Patton, Stanford & Barrat, 1995).

The BIS – 11 is a 30-item self-rated scale designed to assess impulsive thought and behavior. The Brazilian version of the scale was used, which has already been validated (Malloy-Diniz et al., 2010, 2015). Previous analysis identified two factors from the extracted of the Brazilian version of the scale: Inhibition control (α= 0.79), defined as the ability to inhibit a proponent behavior and attentional control, and Non-planning (α= 0.62), defined as the decision making that requires cost-benefit evaluation between short and long term consequences within an emotional context (Malloy-Diniz et al., 2015).

Childhood Trauma Questionnaire - CTQ (Bernstein et al., 2003).

The CTQ is a 28-item self-report questionnaire of frequency of traumas experienced

before the age of 12, in 5-point likert scale, ranging from *never* to *always*. The Brazilian version of this scale was taken into consideration, which presents five subscales: emotional (α= 0.88), physical (α= 0.92), and sexual abuse (α= 0.97), as well as emotional (α= 0.94) and physical neglect (α= 0.66), (Grassi-Oliveira et al., 2014; Grassi-Oliveira, Stein, & Pezzi, 2006).

Suicide attempt history Suicide attempt history was assessed through a self-report question that classified patients as those who never attempted suicide, the ones that attempted once or those who attempted more than once. The question was "Have you ever attempted suicide?" The patient was asked to mark one of three options: Never attempted suicide, attempted once, attempted more than once. In the end, suicide attempt was defined as an act with clear intention to kill oneself.

Beck Depression Inventory – BDI (Beck, 1961).

The BDI is one of the most commonly used self-rated depression scales. The 21-item cover depressive symptoms such as energy level, hopelessness, suicide ideation and self-punishment. Each item is rated on a scale of 0 to 3 and higher scores reflect greater depression severity. The Brazilian version shows internal consistency of 0.81 (Gorenstein & Andrade, 1996)

Young Mania Rating Scale – YMRS (Young, Biggs, Ziegler, & Meyer, 1978).

The YMRS scale is a semi-structured interview and rating system used to quantify severity of mania symptoms observed during clinical interview and in the past 48 hours. It consists of 11 questions that asses mood, activity level, psychomotor agitation, sexual interest, appearance, irritability, insight, sleep, aggressiveness and content of thoughts. Each item is scored on a scale of 0 to 4, with the exception of items assessing irritability, speech, content of thoughts and disruptive behavior. These have double the scoring weight and are scored from 0 to 8. Maximum score possible is 56 points. A trained clinician who had at least two years of experience in a bipolar outpatient clinic completed the interview and ratings. The Brazilian version of YMRS was used, which presented intra-class correlation coefficient of 0.80 and internal consistency of 0.67 (Vilela, Crippa, Del-Ben, & Loureiro, 2005).

Statistical analysis:

All of the statistical analysis were performed in SPSS software, version 21.0. The following methods were selected to describe the associations of 1) impulsivity of relatives and levels of child maltreatment of patient; and 2) impulsivity and maltreatment dimensions of patient with history of suicide attempts and its reocurrence. Since the sample size was unbalanced for relatives and patients, the analysis were divided in those two steps. First , principal components factor was conducted, using the oblimin rotation on the child maltreatment items of all 117 patients, in order to determine the number of statistically independent dimensions of trauma and reduce subsequent dependent variables in subsequent linear regression model. This was considered a preliminar requirement for step one, since the sample size was not enough to allow consideration of all dimensions of maltreatment as a depedent varible in further regression.

To examine the effect of impulsivity of relatives scores on child maltreatment of patients, a linear regression model was conducted with both BIS factors as independent variables. This step considered 25 patients and their respective relatives.

As a second step, a multinomial logistic regression model was computed to assess whether maltreatment and impulsivity predicted suicide attempt history among the 117 individuals with BD. The targeted categories were *No history of suicide attempt; One previous suicide attempt;* and *More than one previous suicide attempt.*

Depression and mania ratings were considered as potential confounds and were controlled as needed in both steps.

4.4. RESULTS

The demographic characteristics of the sample, as well as levels of impulsivity and child maltreatment, are described in Table 1. Approximately 67% of the patients met diagnostic criteria for *Bipolar I* and 32.3% for *Bipolar II* disorder.

Table 1.

Sample characteristics

	Patients (N=117)		Relatives (N=25)	
	N	%	N	%

Level of education				
Secondary education or below	69	58.9	15	60.0
Partial undergraduate	14	12.0	4	16
Undergraduate	29	24.8	5	20.0
Graduate degree	5	4.3	1	4
Gender – Women	78	66.7	17	68.0
Suicide attempt history				
No history of suicide attempt	81	69.2	-	-
One previous suicide attempt	20	17.1	-	-
More than one previous suicide attempt	16	12.7	-	-
	Mean	SD	Mean	SD
Age	43.60	12.16	41.89	15.75
Beck Depression Inventory	14.34	11.29	11.32	10.67
Young Mania Rating Scale	1.90	3.18	3.09	3.86
BIS – Inhibition control	40.55	9.14	35.52	6.96
BIS – Non-planning	23.87	6.01	25.28	4.54
Physical Neglect (3 items)	4.60	1.96	-	-
Emotional Neglect (7 items)	13.87	6.12	-	-
Physical Abuse (5 items)	7.99	3.92	-	-
Emotional Abuse (5 items)	10.32	4.99	-	-
Sexual Abuse (5 items)	6.85	3.80	-	-

Principal components analysis of the childhood abuse scale

The results showed no multicollinearity and the sample size was in accordance to Kaiser-Meyer-Olkin measure of sample adequacy (KMO = .71), and KMO for individual variables were equal or higher than .67. Sphericity as tested by Bartlett's test indicated that the correlations between variables were adequate for Principal Components Analysis (X^2 = 177.41, df= 10, p < .001). One factor surpassed Kaiser's criterion of Eigenvalue higher than 1 and explained 52.58% of the variance. Considering that the statistical requirements to consider maltreatment as an unique factor were met, maltreatment was taken as one factor on analysis regarding associations between

impulsivity of relatives and maltreatment. These results show that the frequency of specific types of maltreatment are not dissociated from others. That is, those patients who tend to experience elevated levels of one type of maltreatment may also have higher probability to experience other forms of it.

Table 2
Factor loading of Childhood Trauma Questionnaire subscales

Subscale	Factor 1: Maltreatment
Emotional Neglect	.877
Physical Neglect	.736
Emotional Abuse	.802
Psysical Abuse	.699
Sexual Abuse	.431

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization.

Impulsivity of relatives levels correlate with levels of childhood maltreatment of patients

Before conducting the analysis of the impulsivity effects, potential confounds of manic (YMRS) and depressive (BDI) symptoms were considered by testing correlations with maltreatment of patient scores. Neither the YMRS, r (DF) = -.07 (24), p = .74 nor the BDI, r (DF) = .31 (24), p = .13 were correlated with maltreatment. More specifically (as shown in Table 3), results of the linear regression show that first-degree BIS Inhibitory Control scores of relatives correlate significantly with patient report of General maltreatment, although Non-planning scores did not contribute to additional variance.

Impulsivity of relatives explains a considerable proportion of the variance, $r^2 = .30$, $N = 25$, $p < .05$. Therefore, relatives impulsivity of relatives accounts for 30 percent of variance in self reported levels of maltreatment, showing that inhibitory control in relatives seem to impact on frequency of perceived maltreatment of patients.

Table 3. Linear regression of Family Impulsivity Scores as Predictors of Maltreatment of Patients Scores ($N = 25$).

	B	*SE* B	b
Constant	-.10	1.12	
BIS – Inhibitory Control	.05	.02	.43*
BIS – Non-Planning	-.06	.03	-.36

$r^2 = .30$, $N = 25$, *$p < .05$

Maltreatment of patients and impulsivity predict the number of previous suicide attempt

As shown in Table 4, multinomial logistic regression was performed with BIS and Maltreatment scores as predictors of suicide attempt (never, once, more than once) as an outcome variable. Diminished inhibitory control was robustly correlated with number of suicide attempts, distinguishing specifically those who attempted suicide once or more from those who never attempted.

Child Maltreatment scores were considered separately to provide richer information regarding factors associated with presence and/or recurrence of suicide attempt. Only the Emotional abuse factor was significantly related to suicidality and it was only significant in differentiating repeated attempters from those with only one attempt.

Table 4. Multinomial logistic regression for history of suicide attempt

			95% CI for Odds Ratio	
	B (SE)	*Lower*	Odds Ratio	*Upper*
No history of SA vs. more than one SA				
Intercept	7.56 (2.81)			
BIS – Inhibition control	-.11 (.04)*	,83	.89	.97
BIS – Non-planning	.01 (.06)	.90	1.01	1.13

Physical Neglect	.21 (.23)	.79	1.23	1.93
Emotional Neglect	-.14 (.08)	.74	.87	1.02
Sexual Abuse	-.07 (.08)	.80	.93	1.09
Physical Abuse	-.14 (.09)	.73	.87	1.04
Emotional Abuse	.14 (.09)	.96	1.15	1.38
One previous SA vs. more than one SA				
Intercept	6.71 (3.34)			
BIS – Inhibition control	-.15 (.05)*	.78	.86	.95
BIS – Non-planning	-.09 (.08)	.79	.92	1.07
Physical Neglect	.23 (.25)	.77	1.26	2.08
Emotional Neglect	-.08 (.09)	.77	.92	1.11
Sexual Abuse	.02 (.08)	.87	1.02	1.20
Physical Abuse	-.11 (.11)	.73	.89	1.10
Emotional Abuse	.27 (.11)*	1.06	1.31	1.62

Note: R^2 = .29 (Cox & Snell), .36 (Nagelkerke). Model x^2 = 39.99, $p < .001$. *df = 14,* *$p <$. 05.

Table 5: Spearman's rho correlations between BIS-11 and CTQ patient's subscale scores

	1	*2*	3	*4*	*5*	*6*
(1) BIS – Inhibition control	-	-	-	-	-	-
(2) BIS – Non-planning	-.35**	-	-	-	-	-
(3) Physical Neglect	.10	-.14	-	-	-	-
(4) Emotional Neglect	.15	-.21*	.64**	-	-	-
(5) Sexual Abuse	.18	-.02	.18	.20*	-	-
(6) Physical Abuse	.13	-0.00	.36**	.45**	.23*	-

(7) Emotional Abuse	..36**	-.09	.30**	.58**	.40**	.51**

4.5. DISCUSSION

Many studies indicate that impulsivity and early adversity experiences are both correlated with suicidality within BD. Despite evidence that familial impulsivity may feature a context prone to greater risk of abuse, researchers have tended to consider these two variables separately. The goal of this study was to develop a more integrative understanding of familial impulsivity and early adversity, and also to consider whether patient's impulsivity and abuse contributed independently to the risk of suicide attempts for individuals with BD. Since those that repeatetly attempted suicide may represent a subset of more severe patients, beyond discrimination of the presence of suicide attempt history, it was also an aim to describe aspects that could account for reincidence of suicide attempt.

Our findings confirmed that problems of patients with inhibitory control were tied to suicidality. Furthermore, findings extended previous work outside the BD diagnosis by showing that poor inhibitory control in relatives was related to the frequency of child maltreatment experienced by patients. Although these findings do not test direct influences of impulsivity of relatives and risk of suicide attempt in patients, it highlights that emotional abuse is related to a greater risk of recurrent suicide attempts even after accounting for deficits in inhibitory control in patients. These novel findings provide initial data to foster investigations on further unified and transgenerational perspective on impulsivity, adversity and suicidality.

This study, such as previous ones, suggests that the effects of impulsivity on suicidality within BD do not seem to generalize across measures of impulsivity, which indicates that it must be considered a multifaceted construct (Johnson et al., 2016; Malloy-Diniz et al., 2009; Malloy-Diniz et al., 2011; Watkins & Meyer, 2013). Previous works have found that impulsivity in the context of emotion is particularly predictive of suicidality, moreover this form of impulsivity would be helpful to be considered in future models of links between early adversity, impulsivity and bipolar suicidality.

The findings of this study dovetail with other researches that increasingly documents the complex interplay between maltreatment and impulsivity. Child maltreatment may not be independent of impulsivity of relatives. However, the results do not show the

underlying causes that link them. Within BD, relatively few relatives meet full diagnostic criteria for the disorder, but many experience high levels of impulsivity when compared to healthy controls (Hıdıroğlu et al., 2013). One possibility is that lack of inhibitory control in relatives is a marker of familial contexts which are prone to maltreatment behaviors. Higher familial impulsivity may lead to a more chaotic family environment that allows these other adversities to unfold. History of maltreatment, in turn, influence cognitive and emotional development, which intensify the risks of impulsivity and poor constraint over harmful behaviors (Braquehais et al., 2010; Daray et al., 2016). Inhibitory control shared by patients and relatives as an impulsivity dimension fosters dysfunctional behaviors such as maltreatment and suicide behavior. The reasons for relatives and patients to present dysfunctional may be diverse, possibly involving learnt behavior, developmental interferences of one behavior over another as well as shared genetic aspects that this study could not assess. That is, above and beyond the genetic influences, maltreatment has been shown to predict impulsivity over time (Braquehais et al., 2010; Daray et al., 2016).

Current findings indicated that inhibitory control and emotional abuse set the stage for recurrent suicide attempts rather than single attempts. The number of suicide attempts is a particularly robust predictor of suicide completion (Watkins & Meyer, 2013). Those that attempted suicide repeatedly also tend to present more severe dysfunctionality, as evidenced by their higher numbers of hospitalizations. Therefore, the clarification of inhibitory control as an specific aspect related to this subset of patients may be a promissing target for treatments that aim to reduce recurrent suicide behavior and its dysfunctional consequences. If replicated, the current findings highlight the importance of considering specific types of early abuse as serious markers of more pronounced suicide risk.

Despite the potential clinical importance of these findings, the study is limited by the reliance on self-report measures of impulsivity and maltreatment, and also by the small number of relatives assessed. It is also important to consider that siblings and children were included in sample of relatives. Therefore, since it is less plausible that their impulsivity leads to maltreatment, it is not possible to conclude that the impulsivity observed in relatives leads to maltreatment. Instead, it may be more plausible to consider that impulsivity observed in relatives can be considered a family vulnerability marker to impulsive behaviors such as maltreatment. The small sample size precluded the ability to examine more refined dimensions of suicide attempts, such as lethality and age of

onset. Furthermore, medication or comorbidities were not controlled. Despite the limitations, this study supports the relevance to develop approcahes encompassing the transgenerational perspective on impulsivity and maltreatment in relation to suicide attempts in BD.

Current findings, if replicated, would have important clinical implications. First, emotional abuse and inhibitory control were independently associated with number of suicide attempt so they both represent important potential treatment targets. Second, interventions to address impulsivity may need to consider that this personality trait evolved in a family context.. One possible approach for those who are seeking family therapy might be to integrate a consideration of family levels of impulsivity into that work. Impulsive behaviors of patients and family members could be addressed by teaching self-regulatory strategies, but also by considering communication effects and strategies in contexts in which multiple members of a family may have these concerns. By doing so, it may reduce the risk of high levels of conflict and potentially provide some protection from emotional abuse. As a whole, it is expected that these preliminary findings provide insight into some important links between variables that have been studied separately in understanding suicidality within bipolar disorder. Future studies should investigate causal relationships using larger samples and longitudinal designs.

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5. STUDY THREE: ATTENTIONAL BIAS TO EMOTIONAL CONTEXTS AND ITS ASSOCIATION WITH CLINICAL SYMPTOMS IN BIPOLAR DISORDER

5.1 ABSTRACT

Introduction: Cognitive and emotional processing are important aspects related to bipolar disability. Attentional bias, as measured by eye movements, is considered to be one potential candidate to evidence automatic altered processing that enhances bipolar mood reactivity. Beyond emotional reactivity observed when dealing with basic emotions, it is also relevant to investigate the reward-salience reactivity, since this aspect seem to be related to manic episodes. Considering these aspects, this study aimed to investigate attentional bias towards emotional expression as well as to food-related cues in bipolar disorder, in comparison to controls.

Materials and Methods: In step one, twenty-four bipolar patients and 23 control volunteers participated in an eye tracking attentional bias task designed to assess fixation time on emotional faces expression. In step two, thirty-eight bipolar patients, twelve overweight/obese and 39 control subjects comprised the sample in which attentional bias towards food images were assessed. Attentional bias was compared between groups. The associations between attentional bias and clinical aspects (mood and Body Mass Index) were described.

Results: It was observed the tendency to less attendance to happy expressions for bipolar sample and higher attentional bias towards food-related cues. Manic symptoms were positively correlated to attentional bias towards surprise expressions and negatively associated to sad and fear attentional bias. The decreased attendance to sad and fear expressions explained 36% of the manic symptoms variance.

Discussion: These results highlights the importance to consider different hierarchical levels of emotional processing and evidence the association between automatic attentional bias and clinical outcomes, such as mood symptoms.

5.2 INTRODUCTION

Bipolar disorder is highly debilitating. Cognitive and emotional mechanisms are potential candidates to help clarifying mood vulnerability. Bias in attention and memory are hypothesized to contribute to the maintenance of anxiety and depression (Beck, Rush, Shaw, & Emery, 1979). In these conditions, attentional bias towards affective stimuli has been studied and it has been observed that negative stimuli are particularly salient to these patients and that attentional bias can predict the course of illness (Beevers, Lee, Wells, Ellis, & Telch, 2011).

However, in bipolar context, fewer studies have been conducted to address attentional bias towards affective stimuli (A. C. García-Blanco, Perea, & Livianos, 2013; A. C. García-Blanco, Perea, & Salmerón, 2013; A. García-Blanco et al., 2015; Jabben et al., 2012). Except for A. García-Blanco et al. (2015), all of them used reaction time measures to address attentional bias. In these studies attentional bias was considered to occur when reaction time was faster for affective information when compared to neutral stimuli. None of these studies have demonstrated differences between euthymic patients and controls, only for symptomatic patients. However, when attentional bias was measured by eye-tracking, differences between euthymic patients and control were found (A. García-Blanco et al., 2015).

There are evidences that eye movement have been associated to basic attentional processing (Baudisch, DeCarlo, Duchowski, & Geisler, 2003). Therefore, recent studies have been assessing attentional dynamics according to eye tracking results. Reaction time is an output behavior that requires immediate stimuli processing, as well as sustaining the task instruction and a motor response as an outcome; therefore, when compared to eye tracking assessment, it may be related to more complex and cognitive function overlap. Taken this methodological issue into account, it is possible that the attentional bias differences observed in euthymic patients may represent a latent mood vulnerability aspect that is observable only through the use of sensible measures such as eye tracking. However, in mood states this altered emotional processing becomes prominent enough to be observed though reaction time tasks.

Although these are just possible explanations for the up-to-date findings, there are only a few studies addressing attentional bias in bipolar. More research comparing patients and controls need to be performed, as well as the investigation of the clinical

relevance of the bipolar attentional processing profile. Given the relevance of these topics, step one of this study attempted to address these questions.

Beyond clarifying the presence as well as the clinical relevance of attentional bias in bipolar, it is also important to describe if this would be specific to affective emotional expressions, or if it could also be related to reward salient stimuli, as this tendency seem to be related to manic symptoms. For example, a food-related stimulus, such as images of food, is known to activate reward cognitive processing. Therefore, to describe attentional bias specificity, step two of this study was designed to compare bipolar, obese/overweight patient's attentional bias towards food-related cues.

5.3 MATERIALS AND METHOD

Participants

A sample of 24 bipolar patients participated in the assessment of emotional faces expression (step one), and 38 were included in the assessment of attentional bias towards food related cues. Bipolar patients were recruited from an outpatient bipolar clinic that is part of Brazilian Public Health System. Inclusion criteria were being from 18 to 60 years old and having had the diagnosis confirmed. The diagnosis was assessed through the administration of the MINI Plus 5.0 diagnostic interview by the researchers who had at least five years of experience in using the interview mentioned. Type one and two were included in the sample, although clinical conditions such as stroke, parkinson as well as having had the history of etectroconvulsotherapy were the exclusion criteria. Control group was comprised of 23 subjects for step one and 39 participants in step two. They were included if they were between 18 and 60 years old and if they have not had any mental disorders screened by the MINI Plus 5.0 diagnostic (Amorim, 2000). Exclusion criteria were presenting regular neurological attendance. Overweight/obese clinical sample was compounded of 12 adults volunteers that participated only on step two of this study, which was the assessment of attentional bias towards food-related cues. Inclusion criteria involved presenting BMI higher than 25, as measured by the researcher during the research appointment. Although mild depression and anxiety were permitted in this group, other mental disorders were considered as exclusion criteria. Those participants who had any abnormal vision in any of the groups were asked to bring glasses to undergo the eye-tracking task. Each of the volunteers was informed about the research procedures and signed the informed consent form. This study was approved by Local Ethics Committee (COEP n^{o} 064/09).

Assessment

Symptoms assessment

Depressive and manic symptoms were measured by the use of Hamilton Depression Rating Scale (Carneiro, Fernandes, & Moreno, 2015) and The Young Mania Rating Scale (Vilela, Crippa, Del-Ben, & Loureiro, 2005), respectively. Both of them are based on clinical observation of symptomatology and present satisfactory psychometric properties. Hamilton Depression Rating Scale is comprised of 17 items that evaluates symptoms intensity in a scale from 0 to 4. The data used in this study is the sum of the scores for each patient, which may vary from 0 to 50. Higher the score, more severe the depressive symptoms. The Young

Mania Rating Scale (R. C. Young, Biggs, Ziegler, & Meyer, 1978) addresses manic symptoms used to diagnose manic states: increased energy, psychomotor activation, sexual drive, urge to speak, flight of ideas and reduced need for sleep and level of insight. The scores range from 0 to 4. Higher the score, more severe the manic symptoms.

BMI

Body Mass Index was calculated by the body mass self-reported by the volunteer divided by the square of the body height. For classification of overweight/obese the weight and height were measured and recorded by the researcher during the appointment.

Eye tracking

Attentional bias was assessed by the fixation time (in milliseconds) that were collected by the I-View X Eye Tracking system, version 2.8 (Instruments, 2002). This is a non-invasive technology based in infrared emission, that collects data from the frequency of 250 Hz. Eye tracking was positioned at a 80cm of distance from the volunteer. Raw data were analyzed by the BeGaze, complementary software that enable data analysis according to the area of interest of the images presented by the computer. In this case, the area of interest addressed was the food and emotional facial expressions.

The images were presented as part of the Dot probe task. This is a common used task to investigate attentional bias (MacLeod, Mathews, & Tata, 1986). Although the main Dot Probe Task outcome measure used in the task is the reaction time, as in this study it was possible to assess the eye tracking fixation time, we considered this as the main task outcome measure. The procedure involved the computerized presentation of a fixation point, followed by a randomically-selected pair of images. Subsequently a dot appeared either in right or the left side of the screen and the volunteer was asked to press the congruent-side joystick button. The reaction time provided by the task was not considered in this study. The task was developed through E-PRIME, which is software used to program experimental tasks in psychology (Schneider, Eschman, & Zuccolotto, 2002).

In step one of this study neutral faces were paired with an emotionally relevant expression. Thirty-six pairs of emotionally relevant facial expressions were used. Each pair was presented four times to enable alternating the side the targeted area of interest (food or emotionally relevant expression) appeared, as well as the side the dot was displayed. The images used in step one were provided by an internationally used emotion expressions pool

named NimStim (Tottenham et al., 2009). These images were selected because it represents facial expressions of different ethnicities, and there is evidence of accuracy in the identification of the emotions linked to each expression, showing construct validity. This is a large dataset of images that covers the basic six emotions: Anger, Disgust, Fear, Sadness, Surprise and Happiness. Six images of each emotion were chosen, being three male and three female. Each of these faces was paired with the neutral expression of the same actor or actress. The selection criteria were those images that had the best indexes of accuracy in identifying the type of emotion, since this would indicate the possibility of inferences about the emotion specificity of the attentional bias evaluated. This resulted in the 36 pairs of facial expression images.

In step two; food cues were matched with neutral stimulus – musical instruments – to assess attentional bias towards food. There were 20 pairs of food related cues. The images used, as well as the pairing were in accordance to (Werthmann et al., 2013). High caloric food image (chips, chocolate, sandwich, for example) were paired with non-food pictures (musical instruments).

The type of images as well as the exposure time used in the task varies considerably. Some authors, for example, use emotionally charged words. However, in this study, face images were used because they were associated with higher reactivity – emotional arousal (W. J. Phillips, Hine, & Thorsteinsson, 2010). Time of exposure was 500ms, since the evidence for changes in attention during emotional processing in mood disorders are related to processing stages that occur during this time range (De Raedt & Koster, 2010).

Raw data was converted in an index calculated as following: fixation time upon the targeted area of interest (either food or emotionally relevant facial expression) minus the fixation time upon the neutral paired image for each trial. The delta calculated for each trial was summed according to the area of interest it was associated. Therefore, each participant present the summed delta that represents his/her attentional bias for each of the six emotions, as well as for food.

Statistics

Step one

Bipolar patients and controls were compared in terms of fixation time (measured in milliseconds) for each type of emotional facial expression. Effect sizes (*who*), for the differences observed between groups were calculated.

Within bipolar sample, a linear regression model was performed considering mood symptoms as the dependent variable and fixation time for the variables that had shown a significant correlation with mood as the independent variables. Backward stepwise method was performed to avoid redundant predictors. All statistical analysis were performed in Statistical Package for Social Science- SPSS (Spss, 2012) and the statistical significance considered was of $p < 0.05$.

Step two

Bipolar and overweight/obese patients, as well as controls were compared in terms of fixation time index (measured in milliseconds) for food images. Effect sizes for the differences observed between controls, bipolar and overweight/ obese patients were calculated according to the same method used in step one.

5.4 RESULTS

Descriptive data regarding attentional bias and clinical assessment as well as effect sizes for group differences are depicted in table 5.4.1 for both steps procedures.

Table 5.4.1 Descriptive and group comparisons regarding step one: Emotional Faces Task

	Control (n=23) Median (Q1 - Q3)	Bipolar (n=24) Median (Q1 - Q3)	Mann-Whitney U/ X^2	Effect size
Age	27.5 (20.75 – 39.0)	38.0 (32 – 53)	72.0*	0.38
Sex - Female (%)	76.5	84.2	1.44	-
Level of education (%)				
Secondary School	0	21.1		
Incomplete Undergraduation	61.5	31.6	0.28	-
Undergraduated	38.5	42.1		
HAM	-	11.0 (3 – 13)	26.0	-
YMRS	-	2 (0 – 5)	55.0	-
Angry	-4 (-412.4 – 592.1)	119 (-411.8 – 252.0)	250.5	0.08
Fear	-360 (-984.2 – 226.1)	-97.9 (-719.9 – 443.9)	231.5	0.14
Disgust	223 (-288.2 – 1270.7)	-281 (-827.9 – 1046.8)	220.5	-0.17
Sad	-20 (-859.7 – 451.9)	-258.4 (-267.9 – 852.8)	210.5	-0.20
Happy	108 (-573.9 – 780.2)	-248 (-978.1 – 267.1)	196.5	-0.25
Surprise	0 (-1011.9 – 748.0)	68.1 (-381.8 – 664.2)	239.5	0.11

* $p < 0.05$

Controls and patients were not paired in terms of age and showed significant differences regarding this aspect. Seventy-three of the patients were diagnosed with bipolar type I, whereas 26.3% presented bipolar II subtype. For both groups, the majority of the volunteers were female. Regarding educational level, it possible to observe that patients presented lower levels of education when compared to controls.

Mann-Whitney testing showed that there are no significant differences in attentional bias between patients and controls regarding emotional faces task. However, comparisons regarding effect sizes showed that bipolar patients present shorter fixation time towards happy

5.4.2 Linear regression for emotional attentional bias and clinically relevant variables

	B	SE *B*	β
Step 1			
(Constant)	3.39	.801	
Fear	-.001	.001	-.412
Sad	-.002	.001	-.334
Surprise	.001	.001	.181
Step 2			
(Constant)	3.512	.772	
Fear	-.001	.000	-0.44*
Sad	-.002	.001	-0.43*

Note: $R^{2 =}$ .38 for Step 1, $R^{2 =}$ .36; p <0.05 for Step 2 (p <0.001).

Both fear and sad attentional bias showed to be significant negative predictors of manic symptoms and comprise the model that best explains manic symptoms. The proportion of manic symptoms explained by sad and fear attentional bias is 36%.

Table 5.4.3 Descriptive regarding step two: Food Cues Task

	Control (n=39) Median (Q1 - Q3)	Bipolar (n=38) Median (Q1 - Q3)	Overweight/ obese (n=12) Median (Q1 e Q3)
Age	24 (21 – 36)	41.5 (34 – 53)	36 (27 – 45)
Sex – Female (%)	71.4	77.8	90.9
Level of education (%)			
Secondary School	0	25	18.2
Incomplete Undergraduation	69.2	36.1	54.5
Undergraduated	30.8	38.9	27.3
Food	- 1515.9 (-2549.4; -483.4)	-287.9 (-1533.1 – 1353.7)	-273.9 (-3483.5 – 3831.4)

Regarding food-related cues, Kurskall-Wallis test did not show significant differences in attentional bias. However there were significant differences in controls X bipolar comparison (U= 537; p = 0.04), but bipolar X overweight/obese did not reach statistical significance (U= 226; p = 0.96). Effect sizes are higher for bipolar X controls (r = .24) than for bipolar X overweight/obese (r=0.06) comparison, what shows that the food bias observed in bipolar towards food was similar to what is observed in overweight/obese patients.

5.5 DISCUSSION

In terms of attentional bias, no significant differences were found between bipolar and controls, except for food attentional bias. The non-significance observed in this study in coherent with previous study that showed no group differences between patients and controls regarding emotional task (Peckham & Gotlib, 2017).

Although still weak, the higher effect sizes observed (approximately r = .25), were related to food attentional bias and less attendance to happy stimuli for bipolar. Patients presented less fixation time in happy facial expressions when compared to controls. During the presence of manic symptoms, some of the patients present the tendency to amplify and

some tend to dampen them, in an attempt to avoid positive emotions (Edge et al., 2013a; Gruber, Eidelman, Johnson, Smith, & Harvey, 2011). Positive affect dampening has been related to less attention paid in happy expressions (Peckham & Gotlib, 2017). Although positive affect dampening was not measured in this study, it is possible that the less fixation time observed in happy expressions may be related to this type of strategy. A second explanation is that manic and depressive symptoms are moderately correlated in patients (r = .54), suggesting that symptomatology is mixed; therefore less attendance to happy stimuli may be associated to the influence of depressive symptoms on their attentional processing.

A second aim was to investigate if the conjoint emotional attentional bias observed in bipolar would be related to their mood symptoms. It was found that the shorter the fixation on sad and fear facial expressions, the higher the manic symptoms were presented on the moment of the assessment. Fear and sad attentional bias could predict the manic symptoms variation in around 36%, which a substantial proportion of the variance. This analysis does not allow inference about whether manic symptoms enhances their fixation on these type of stimulus or if their attentional bias profile fosters symptoms triggering. Although in bipolar depression it was observed bias towards threatening information (Carvalho et al., 2015), lower level of fear processing was observed to be related to manic symptoms in this study. These findings suggest that fear processing may be modulated by bipolar mood swings. These may represent complimentary information in describing the basic attentional bias processing in bipolar according to patients states.

Concerning food-related cues, it was hypothesized that bipolar patients would present higher drive towards salient stimuli and it was confirmed by the significant difference observed in food fixation time. Food-related cues were more salient to bipolar patients, having more fixation time on these stimuli, when compared to controls. Bipolar patients presented a similar pattern of attentional orientation towards food as those observed in overweight/ obese volunteers. This is consistent with other findings that suggest that bipolar patients present increased reward salience, observed in basic attentional levels (Mason, Trujillo-Barreto, Bentall, & El-Deredy, 2016). Although in this previous study reward salience was observed through a task that involved loss and gain, in this study it was assessed through food-related cues. Since there are only two studies and the stimuli used are different, the attentional in reward-salient contexts need to be considered with cautious.

Although these are interesting findings, there are several limitations that need to be highlighted. It was not observed the specific factors that influence the attentional bias towards specific emotional stimuli, as it can be associated to several genetic or environmental aspects. The sample size was limited, especially for overweight/ obese group, what indicates that these results may be considered with cautious.

However, these results have the potential to clarify emotional and cognitive underlying aspects that may be related to bipolar mood-related disabilities. These findings also highlights the importance to consider emotional vulnerability as hierarchically organized, since symptomatology was observed to be related to basic physiological reactions, such as eye fixations measured in milliseconds. Therefore, aspects that are not accessible to consciousness may be associated to disturbances in bipolar emotional processing.

6. GENERAL DISCUSSION

At least at a certain degree, cognitive and emotional aspects may be recruited simultaneously. Considering this, in an attempt to clarify persistent vulnerability and dysfunctional behaviors in bipolar disorder, it is relevant to understand the possible interactions between cognition and emotion. To accomplish this goal, cognitive and emotional research and their potential interactions were reviewed in Study One. The results suggested that problems in cognition and emotionality are exacerbated in bipolar disorder even in subsyndromic phases of the disorder. These constructs are closely linked and their deficient interaction contributes to poorer clinical outcomes. Particularly, executive functions (more precisely, inhibitory control) were shown to be one of the key cognitive aspects to be compromised in emotional contexts.

Since the review showed that executive function (more precisely inhibitory control) accounts for levels of dysfunctionality in cognition-emotion interaction, study two was conducted to exemplify this dynamics in a specific Brazilian bipolar sample and their relatives. The study showed that a dysfunctional emotional context, characterized by the higher presence of childhood abuse was more prone to occur when patient's relatives had lower levels of inhibitory control. Although this study did not directly test this association, it is possible that familial-shared cognitive and emotional processing aspects represent a latent vulnerability factor that contributes to higher familial and individual dysfunctionality.

In addition, inhibitory control deficits and emotional abuse are independently associated with the risk of a history of recurrent suicide attempts. This result suggests inhibitory control as a central aspect related to the dysfunctionality seen in patients and their relatives. It occurs not only because of its straight association to suicide attempt, but also because it fosters a condition (early trauma) that is especially hard to manage for individuals that are emotionally reactive such as bipolar patients.

An interesting treatment target would be to help patients to improve inhibitory control as well as to develop resources to deal with their history of abuse. This approach could reduce the emotional arousal to trauma history triggers, therefore reducing the chances of suicide attempts. Although there is evidence for psychosocial interventions in bipolar, it would be interesting to include special topics targeting inhibitory control for patients and also relatives.

However, these interventions mostly rely on insight-based approach and it is not known to which extent the emotional reactions triggered by those emotional abuse experiences (and many others) are automatic and possible to be controlled in a top down based-intervention. To

clarify the complexity of prepotent reactivity involved in emotional context, study three assessed eye movements fixation time upon emotionally salient images in comparison to neutral ones. Results suggest that automatic and implicit emotional processing is associated to mood. More precisely, less attention paid to fear and sad stimuli as well as higher attentional to surprise information are associated to higher levels of manic symptoms. Furthermore, bipolar patients are more vulnerable to reward-salient stimuli, as observed by the food attentional bias task results.

Implicit processes such as lower inhibitory control basal levels, and higher reactivity to emotional cues may determine the strength of prepotent emotional and behavioral responses to occur. This may activate even more an automatic decision making system, since the homeostasis associated to the context is highly perceived as being threatened (Damasio & Carvalho, 2013). The dynamic between automatic and reflexive decision making is addressed in dual process theories (Evans & Stanovich, 2013). According to the dual-process theory there are two main types of decision-making. Type one is automatic and intuitive. This type of decision-making is economic and does not require deliberative intervention upon a prevalent default-mode developed by previous experiences. Type one is based in rapid autonomous system and the automatic responses triggered by this type of processing be will yielded whenever no deliberative intervention occur upon its functioning. Type two processing enables intervention in default-mode automatic course of action (type one), making it possible to perform new behaviors in face of previously known triggers. However, the main feature of type two processing is the high demand on working memory. Therefore, to perform a new behavior it is required to keep different information and instructions in mind to decrease the chances of a default-mode type of reaction. Considering the definition of the two types of processing, if bipolar patients need to improve their automatic ways of responding to emotional relevant situations, it would be recommended that they use their deliberative type of processing in attempt to build a new pool of experiences that would constitute their new automatic approach in future or, at least, would weaken a previously existent automatism. However, intriguingly, bipolar patients present deficits in execute functions, the type of cognitive ability that is highly required for deliberative processing. Taken together, these evidences highlight the difficulty in relying exclusively in deliberative process to enhance quality of life in this clinical context.

Beyond the deficits observed in functions required for the intervention on the automatic mode of response, there is an additional aspect underlying type one and two interaction. The

strength and tendency to act in default-mode will vary according to context (Noël et al., 2013). The urge to reestablish the balance depends on the level of threat or reward perceived by the subject. Therefore, in situations in which the patient is threatened, the capacity to present a new approach to the situation will decrease. So, if patients are often in situations that triggers high emotional arousal, it is possible that they are frequently in situations in which the urge to perform rapid responses is prevalent. This dynamic may decrease even more the possibility of modifying emotional and behavioral prepotent responses.

These results, as well as the aspects highlighted by the dual-process theory, show that the perception of self-control is one of the central aspects to be addressed during a intervention. The variables that influence treatment outcomes go beyond what is popularly called willpower. In an attempt to improve treatments, patients and professionals need to understand and accept the existence of the dynamics between these three forces – automatic and deliberative system, as well the urge role. If treatment can target the three of them, it is possible that the positive outcomes and patients' quality of life will be increased.

7. PERSPECTIVES

Since at least part of the emotional responses are automatic, and not consciously controlled, It may be recommended the combination of deliberative-based treatment with those that access more implicit levels of cognitive and emotional processing. For this reason, in other psychiatric contexts such as for anxiety, treatments that targets automatic levels of functioning have been developed, such as Attentional Bias Modification – AMB (Linetzky, Pergamin-Hight, Pine, & Bar-Haim, 2015).

The knowledge that automatic and implicit levels of emotional processing is related to symptomatology and possibly quality of life not only shed light to the importance of including automatic attentional processing as a treatment target, but also highlights important aspects to be taken into account when conducting insight-based approaches. First, it is important to consider that the assumption that symptomatology can be controlled or modified may be not correct. Therefore, the acceptance of the existence of emotional processing bias, instead of trying to modify them seem to be a promising strategy. Targeting on acceptance of automatic emotional processing seem to be a promising strategy, what can be observed by the increasing evidences and interest on acceptance-based psychotherapies, such as Acceptance and Commitment Therapy and Mindfulness-based Cognitive Therapy (A-tjak et al., 2015; Hill & Updegraff, 2012; Ros, Ricarte, Ros, Latorre, & Beltrán, 2015; Tang, Hölzel, & Posner, 2015)

This study aims to unfold possible cognitive and emotional interactive aspects that contribute to these recurrent relapses and persistent dysfunctionality. This is an attempt to foster the development of treatment targets that enhances functional outcomes out of patients and clinicians treatment efforts.

Although this research highlights the importance to consider cognitive and emotional automatic levels as associated to bipolar symptomatology and functionality, there are several limitations to be considered. First, the analysis performed is mainly based on correlations, and the meditational inferences on emotional processing upon symptomatology could not be described. Furthermore, based on the analysis performed it is not possible to assume if automatic processing fosters symptomatology or the other way around.

Future research should investigate the conjointly effects of treatment that explicitly target automatic and deliberate treatments in an acceptance-deseing protocol. This should be also testes in relatives, as they seem to present a similar cognitive and emotional pattern according to the review presented.

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