

## NEURODEGENERATIVE PROCESSES IN BIPOLAR DISORDER

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## INTRODUCTION

Cognitive impairment has played an important role in the clinical and pathophysiological characterization of bipolar disorder. Patients with bipolar disorder, in the view of Emil Kraepelin in the 19th century, were free of cognitive symptoms, with euthymic intervals between mood episodes (CIPRIANI et al., 2017). Tohen (2000) in one of his studies states that although more than 97% of patients seem to recover clinically within 2 years, only 37% recover functionally during the same period (CIPRIANI et al., 2017). Executive functions, attention, verbal learning and memory appear to be the most affected domains, in addition to impulsivity. However, pre-morbid intelligence seems to be preserved (SOLÉ et al., 2017; KURTZ and GERRATY, 2009; BOURNE et al., 2013; ROBINSON et al., 2006; TORRES et al., 2007; ARTS et al., 2008;). During periods of euthymia, some studies have shown cognitive dysfunction, which may be an important factor for a worse psychosocial outcome (ROBINSON et al., 2006; BOURNE et al., 2013; BORTOLATO et al., 2015; TABARÉS-SEISDEDOS et al., 2008; WINGO et al., 2009a). According to López-Jaramillo (2010) and Hellvin (2012) there is an important association, in many cross-sectional studies, between the number of affective episodes and the neurodegenerative impact, mainly with the recurrence of manic episodes. This hypothesis derives from the evidence that atrophic vermis changes in patients with bipolar disorder appear to be progressive during the course of the disease (SOLÉ et al., 2017; SERATI et al., 2017). Previous behavioral studies have also reported cognitive decline associated with illness duration or number of affective episodes, further supporting the notion of the neuroprogressive nature of bipolar disorder (MARTÍNEZ-ARÁN et al., 2004a; VAN GORP et al., 1998; DONALDSON et al.,

2003). Although many patients show cognitive impairment, these deficits can be attributed to the disease itself, with more pronounced effects in those with more severe or chronic illnesses (CULLEN et al., 2016). The possibility of persistent neuropsychological deficits is of great importance, both for the prognostic pathways of patients and for its potential as a marker of the disease (CIPRIANI et al., 2017).

## BIPOLAR DISORDER

Mood fluctuations are common and even frequent in everyday life, especially when they are concomitant with stressful events. However, when mood swings are striking and persistent and result in notable distress or impairment, there may be an underlying affective disorder.

Bipolar disorder is a disabling and relatively common mental illness with significant morbidity and mortality. According to McDonald (2015) “estimates of the prevalence of bipolar disorder vary. The World Mental Health Survey Initiative reported prevalence estimates of 2.4% (1.5%) in the subtypes of Bipolar I Disorder (TBI), Bipolar II Disorder (TBII), and Subthreshold Bipolar Disorder (TBS). While prevalence rates for each subtype varied across the nine countries studied, TBS was most common at 1.4% (0.8%), followed by TBI at 0.6% (0.4%) and TBII at 0.4% (0.3%).” According to studies by Bauer (2015), the manifestation of bipolar disorder in late adolescence and young adulthood is common, with an overall average age of onset of 25 years. Statistical models suggest the presence of three age-at-onset subgroups within the TBI and can be categorized into a large group of early onset (mean  $\pm$  standard deviation (SD)  $17.24 \pm 3.20$  years) and lower mean onset ( $23.93 \pm 5.12$  years) and late onset groups ( $32.20 \pm 11.96$  years), with the proportion of individuals in each category being 41.7%, 24.7% and 33.6% of the total

sample, respectively (BAUER et al., 2015). Yatham (2018) reinforces that although manic episodes may occur for the first time after the age of 50 as part of TBI, the possibility of organic mania must be considered and investigated in these cases.

Yatham (2018) clearly and succinctly characterizes the subdivisions of bipolar disorder, based on the DSM-5: "TBI is placed on one pole due to the presence of threshold manic episodes, in which features include inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, psychomotor agitation, and risk-taking behavior that leads to significant functional impairment and may include psychotic features and often require hospitalization. At the other end of the spectrum, cyclothymia is characterized by the subthreshold presentation of hypomanic and depressive symptoms that, while chronic, do not meet diagnostic criteria for a major depressive episode or manic/hypomanic episode. TBII falls between the two conditions with hypomanic episodes qualitatively like manic periods but, while distinct and observable, are not of sufficient duration or severity to cause significant functional impairment, hospitalization, or psychosis. Individuals with TBII also experience borderline depressive episodes."

## NEUROANATOMICAL CHANGES

Several theories have emerged over the years regarding brain development and cognitive-behavioral changes. The "early model of neurological development" in recent decades suggested that intrauterine factors (eg, maternal stress and maternal illnesses) could influence normal brain development by altering mood regulation pathways. Therefore, these alterations would continue throughout childhood and adolescence, predisposing to the onset of bipolar disorder and contributing

to the degenerative processes that occur in this severe mental illness (SANCHES et al., 2008; FREY et al., 2008).

The cerebellum, through large interconnections with afferent (cortico-pontine-cerebellar) and efferent (cerebellum-thalamus-cortical) pathways, receives motor and cognitive information (LEINER et al., 1991; GROSSAUER et al., 2015). It plays a central role in neural circuits related to higher cognitive functions, which are often disrupted in patients with bipolar disorder (Rapoport et al., 2000; Middleton et al., 2001). DelBello (1999) and Baldaçara (2011) had already suggested that, in bipolar disorder, cerebellar shrinkage correlates with the number of affective episodes, as well as with the long duration of the disease and age (SANI et al., 2016; BALDAÇARA et al., 2008). Monkul (2008) also associates the fundamental role of the cerebellum in the pathophysiology of the disease, specifically the vermis and its subareas (superior vermis, superior posterior vermis and inferior posterior vermis).

In bipolar disorder, the most widespread neuroimaging findings take into consideration, the greatest cortical thinning - prefrontal and temporal cortex; increased ventricular volume and decreased global brain volume (SERATI et al., 2017; CIPRIANI et al., 2017; RIMOL et al., 2010; HOUENOU et al., 2011; FEARS et al., 2014; BORA et al., 2009). Lloyd (2014) states that failure to integrate information across the cerebral hemispheres may contribute to the pathophysiology of the disorder. There is also a reduction in callous areas and, consequently, a decrease in the interhemispheric tract of the white matter (CIPRIANI et al., 2017).

Age is an important issue for the investigation of the brain-behavior relationship in neuropsychiatric disorders, which is known to have a significant influence on brain morphology and cognition (CASERTA et al., 2009; FRIES et al., 2012; SCHNEIDER et al.,

2012; BUDNI et al., 2013; GAMA et al., 2013). Zimmerman (2006) and Gautam (2011) reinforce the variation between brain volume and thickness related to cognitive functioning in different age groups.

## **NEUROCOGNITIVE DYSFUNCTION**

Little is known about the trajectory of cognitive decline during the course of bipolar disorder (SAMAMÉ et al., 2013). In elderly patients with the disorder, the presence of cognitive deterioration raises the question whether these impairments are age- or disease-dependent. There is an important relationship between environmental factors, mainly early trauma, and genetic susceptibility, generating an alteration in the development of specific brain areas and mood dysregulation (SANI et al., 2016). Neurocognitive dysfunction seems to be multifactorial and some clinical factors must be taken into consideration, such as educational level and pre-morbid intelligence; clinical symptomatology (remission vs acute episode); subclinical depressive symptoms; psychotic symptoms; bipolar disorder subtype; psychiatric or clinical comorbidity; disease duration/chronicity; number of episodes; pharmacological treatment and childhood adversities/traumas (SOLÉ et al., 2017). According to Goldberg and Chengappa (2009) patients with bipolar disorder are at increased risk of several medical disorders and that most are independent of cognitive dysfunction, including cardiovascular and cerebrovascular diseases; neurological disorders such as migraines or epilepsy; and overweight/obesity and metabolic abnormalities such as type 2 diabetes mellitus.

It is important to realize the iatrogenic effects and residual mood symptoms in bipolar disorder, which can lead to cognitive deficits (CIPRIANI et al., 2017). Stip (2000) reinforces that most of the medications

used in the treatment have the potential to aggravate the cognitive dysfunction, and it is necessary to distinguish between the commitment resulting from the disease and that generated by the medications. A study by Hammonds and Shim (2009) investigated the effects of olanzapine, quetiapine and risperidone on cognition in euthymic patients with bipolar disorder: better cognitive performance in unmedicated patients than patients medicated with any of these second-generation antipsychotics.

## **EVALUATION**

As Cipriani (2017) writes: “So far, there is no standard research battery to measure cognition in BD. The International Society for Bipolar Disorders has suggested that *Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB)* is a promising starting point, but that complex verbal learning measures and level II assessment of executive functions must also be included”.

## **THERAPEUTIC MEASURES**

According to Solé (2017) some strategies can be used as a preventive factor in cognitive dysfunction in bipolar disorder, such as the prevention of multiple symptoms with effective pharmacotherapy and the implementation of psychoeducation programs; perform cognitive or functional correction; promote healthy habits; aerobic physical exercise; prescribe adjuvant procognitive treatment; avoid concomitant medications that interfere with cognitive function levels; treating subclinical depressive symptoms; control comorbidities; use of non-invasive brain stimulation techniques (transcranial magnetic stimulation, deep transcranial magnetic stimulation and transcranial direct current stimulation). The presence of these deficits in

the early stages of the disorder also indicates that cognitive dysfunction is a target for early identification and intervention.

After achieving remission of an acute episode, in the case of mania, it will be necessary to use effective pharmacotherapy to prevent relapses, start psychoeducation programs to avoid multiple episodes and promote healthy habits (SANCHEZ-MORENO et al., 2017). A strategy to minimize cognitive impairment is through the treatment of subclinical symptoms that can also affect cognitive and psychosocial functions (BONNIN et al., 2011). Fears (2015) highlights in his findings that probable factors such as education may have the potential to compensate for functional deficits due to brain changes associated with bipolar disorder. In general, providing psychoeducation to all patients and families is recommended for relapse prevention, particularly early in the illness, with selection of other psychosocial therapies based on individual concerns and presentations or deficits (Yatham et al., 2018).

## CONCLUSION

Not only the cognitive deficits, but the bipolar disorder itself has a major impact on the lives of patients, especially if it is not managed in a coherent and responsible manner. Neurocognitive impairment leads to limitations in activities of daily living, daily planning and behavior in general. The relationship between neurodevelopment and its implication in the pathophysiology of bipolar disorder still requires further studies. As several authors and researchers on the subject address, it is necessary to better elucidate the determinants of cognitive impairment that await further research into other possible factors that influence cognition. It is important to clarify that not all bipolar patients suffer from cognitive dysfunction. The factors that can influence cognition and contribute to its diversity must be better understood.

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