

INTRODUCTION

Bipolar disorder (BD) is a debilitating mood condition that affects approximately 1.5% of people worldwide (*Smith et al., 2013*), although some studies report up to 3.9% life time prevalence (*Kessler et al., 2005*) and 4-6% in adults when broad diagnostic criteria are applied (*Johnson and Johnson, 2013*).

There is a growing consensus that persistent cognitive deficits are common in patients with bipolar affective disorder (BD) even when they are euthymic. Apart from certain exceptions (*Sapin et al., 1987*), studies of remitted patients have generally reported deficits in several cognitive domains. However, many of these studies have not controlled for residual affective symptoms, which could have a substantial bearing on their results. When this has been done enduring deficits have been observed in either memory or executive functions, or a combination of these areas. More specifically, there have been reports of impairments in visuospatial memory (*Rubinszstein et al., 2000; Thompson et al., 2005*), verbal learning (*Thompson et al., 2000, 2005*), executive functions (*Ferrier et al., 1999; Thompson et al., 2000, 2005*), and sustained attention (*Clark et al., 2002*) among euthymic patients of BD.

Then again, it is not immediately clear whether cognitive impairment in BD is present right from the onset of the illness, or develops following repeated episodes. Some of the evidence (*VanGorp et al, 1998; Denicoff et al, 1999*) suggests that recurring episodes of BD are associated with greater cognitive disturbance. It has been proposed that successive episodes cause subtle damage to key brain areas leading to the neurological and cognitive impairments observed in BD (*Altshuler, 1993*). However, the evidence linking cognitive deficits with indicators of severity/progression of the illness is not always consistent. Moreover, some studies have also shown that patients with first-episode BD perform significantly worse than normal controls on a wide variety of neuropsychological tests (*Albus et al., 1996*).

There is also increasing evidence that BD is associated with white matter (WM) pathology, as white matter hyperintensities (WMH) appear to be one of the most robust and consistent neuroimaging findings (*Kempton et al., 2008*). Reductions of total intracranial volume and WM volume have been identified in MRI studies (*Vita et al., 2009*). A more sensitive technique for the assessment of WM integrity is diffusion tensor imaging (DTI), which provides quantitative information regarding water mobility through tissue. The most widely employed index, fractional anisotropy (FA), provides an estimate of

the directionality and continuity of fiber tracts. Various methods of analyzing DTI data have been developed based on this technique.

Several DTI studies have investigated the pathophysiology of BD.

Most DTI studies of BD have used a methodology based on manually traced regions of interest (ROI). The results reported depend on the location of the ROI, with most studies reporting a decrease in anisotropy in frontal (*Adler et al, 2004; Adler et al, 2006; Frazier et al, 2007; Haznedar et al, 2005*), cingulum (*Wang et al., 2008*) and occipital (*Macritchie et al., 2010*) the anterior corona radiata (*Pavuluri et al., 2009*), the internal capsule (*Haznedar et al., 2005*) and Some studies have reported anisotropy to be higher in the frontal WM (*Haznedar et al., 2005*) and corpus callosum (*Yurgelun-Todd et al., 2007*). The major limitation of these ROI studies is that they provide information only about selected brain regions, whereas current neurobiological models of BD suggest that a widespread cortical neural network is involved in the pathophysiology of BD (*Phillips et al, 2008a; Phillips et al, 2003*).

Owing to the wide spread nature of WM abnormalities, a few of these DTI studies of patients with

BD employed a tract-based spatial statistics (TBSS) approach that allows a whole brain analysis in an automated and reliable fashion, thus providing a global perspective of WM alterations (*Heng et al., 2010*). The previous TBSS studies in BD confirmed that all major classes of projection, associative and commissural fiber tracts are implicated (*Bauer et al, 2015; Emsell et al., 2013*).

Recently, it has been suggested that neurodevelopmental disturbances, particularly white matter (WM) alterations could have a potential relation to neuropsychological abnormalities which is extremely important to improve our etiological knowledge of BD, facilitating early and precise diagnosis and development of new therapeutic agents. However, studies examining BD patients cannot distinguish whether observed neurobiological and neuropsychological abnormalities represent risk factors or consequences of the disease. Therefore, investigation of healthy individuals at high risk to develop bipolar disorders indispensable (*Linke et al., 2013*).

Rational of the study

Multiple Clinical evidences show that bipolar disorder is characterized by white matter (WM) microstructural abnormalities. However, little is known about their relationship with cognitive functioning studying of such correlation may help in understanding the etiology, pathophysiology, course and the outcome of bipolar disorder as a one of most common psychiatric disorders.

Hypothesis of the study

The study hypothesized that first episode euthymic bipolar I patients would exhibit an impairment in neurocognitive performance that correlate with white matter changes compared to healthy individuals.

AIM OF THE STUDY

This study aimed to

1. To show whether patients with first episode bipolar disorder type I during euthymia show different pattern and deficits in neurocognitive performance compared to well match apparently healthy control.
2. To identify white matter characteristics of those patients compared with control group.
3. To correlate between the white matter characteristics and neurocognitive impairment in these patients.

BIPOLAR DISORDER

Introduction:

Bipolar disorder is a serious psychiatric illness in which a patient's mood vacillates between periodic extremes of joy and depression (*Goodwin and Jamison 2007*) the natural course of BD is characterized by constant risk of recurrences over patient life span causing impairment of psychosocial functioning despite advances in pharmacological treatments (*Tohen et al., 2009*).

The history of mood disorders and specifically Bipolar disorder is dated back to *Hipocrates* who were the first to describe manic depressive illness they classified mania and melancholia for the first time, their view of mania corresponds to what we consider today "excited psychosis" and melancholia corresponds to fearful depression they described mania as worsening to melancholia (*Fountoulakis, 2014*).

In 1851 Falert described for the first time a separate entity of mental illness named 'Folie Circularie' (circular madness) defined by manic and melancholic episodes separated by symptom free intervals (*Angst, 1997*).

In 1921 Kraepelin established manic depressive illness as a separate entity and separated it from schizophrenia, he described depression as state of lowered mood and state of elevated mood.

In 1965 Leonhard proposed that term "Bipolar disorder" should replace "manic depression".

In 1970 the term bipolar disorder started to appear in US research diagnostic criteria BD has continued to be incorporated in following versions of DSM (*Marneros and Angst, 2001*).

In 1992 the term bipolar disorder was first used in International classification of Diseases (ICD-10) (*Marneros and Angst, 2001*).

Epidemiology

It was suggested that mood disorders are among the most frequent psychiatric illnesses both in the community and in psychiatric settings (*Oakley Browne et al. 2006*). Bipolar disorder affects from 1% to 3.8% of the general population (*Subramaniam et al. 2013*). And lifetime prevalence rates up to 6.5% in general population (*Judd and Akiskal 2003*).

BD shows similar rates between males and females. There are some data suggesting that males might be over-represented in those diagnosed with a BD-I and females over represented in those diagnosed with a BD-II disorder (*Parker et al., 2014*).

Although they can occur at any age bipolar disorders are most common in persons younger than 25 years. The

weighted lifetime prevalence of BD was 3.0% among 15–year-olds 2.1% among 15–18-year-olds, and 3.8% among 19–24-year-olds (*Kozloff et al., 2010*).

BD are more common in single and divorced persons also in patients who didn't graduate from college (*Kaplan and Sadock, 2009*). Another meta-analysis revealed that people with an alcohol use disorder (abuse or dependence) were 4.1 times of greater risk of having BD compared to those without an alcohol use disorder. The risks were even higher for illicit drug users where they were 5.0 times of greater risk of having BD compared to non-users (*Grant et al., 2015, 2016*).

Neural model of bipolar disorder

Neural models of bipolar disorder have entailed variants of what has been referred to as a corticolimbic (*Anand et al., 2009*) or anterior limbic (*Adler et al., 2006*) model, which is illustrated in Fig. 1. The corticolimbic model was used to explain altered emotional control after consensus meetings of researchers in bipolar disorder (*Strakowski et al., 2012*) and further elaborated in a review of functional neuroimaging findings in emotion regulation (*Phillips and Swartz, 2014*). The circuits described in the consensus model were proposed to account for internal and external emotional control along with cognition. Thus, a ventrolateral circuit appears to process external emotional

stimuli automatically (*Phillips and Swartz, 2014*) and a ventromedial circuit to process internally-generated emotion (*Phillips et al., 2008*). An additional anterior cingulate circuit was proposed to integrate emotional and cognitive output to modulate behavior. Although many of the structural components of the circuits are interconnected through the amygdala (a subcortical brain structure primarily involved with regulation of fear of potentially threatening stimuli (*Fusar-Poli et al., 2009*) for ease of relating them to clinical phenomena, each of these circuits will be discussed separately in the context of proposed control functions

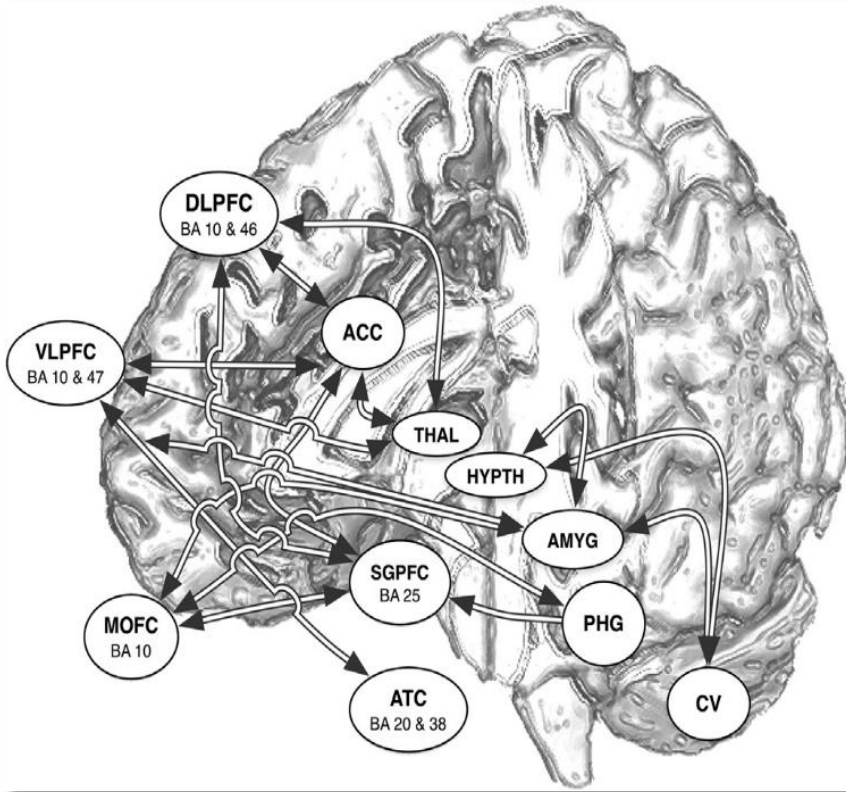


Fig. (1): Key regions of the corticolimbic network and their major network connections relevant to bipolar disorder (**Brooks et al., 2009a**).

ACC = Anterior cingulate, AMYG = Amygdala, ATC = Anterior Temporal Cortex, CV = Cerebellar vermis, DLPFC= Dorsolateral prefrontal, cortex, HYPH = Hypothalamus, MOFC = Medioorbital, Prefrontal Cortex, PHG = Parahippocampal gyrus, SGPFC= subgenual prefrontal cortex, THAL = Thalamus, VLPFC =Ventrolateral prefrontal cortex

A- Ventrolateral circuit

The ventrolateral circuit, illustrated in Fig. 2, includes the ventrolateral prefrontal cortex, generally defined as Brodmann's areas (BA) 10 & 47. Output from the ventrolateral prefrontal cortex is routed to the ventromedial striatum (which includes the ventromedial

caudate, ventral putamen, nucleus accumbens, and olfactory tubercle), then to the globus pallidus, and finally to the thalamus, which regulates emotional expression. The circuit is completed by fibers from the thalamus that project back to the ventrolateral prefrontal cortex (*Almeida et al., 2009*). The anterior temporal cortex, including BA 20 and 38, provides input to the ventrolateral circuit through its reciprocal connections with the ventrolateral prefrontal cortex and the amygdala. Within the ventrolateral circuit, abnormalities of the globus pallidus and ventromedial striatum are thought to precede illness onset, whereas those in the ventrolateral prefrontal cortex may arise afterwards (*Strakowski et al., 2012*).

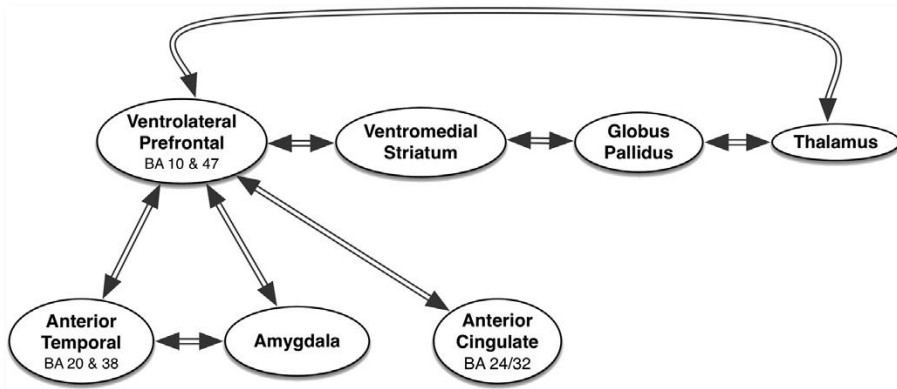


Fig. (2): Regions involved in the ventrolateral prefrontal circuit

B- Ventromedial circuit

The ventromedial circuit, depicted in Fig. 3, includes part of the ventromedial prefrontal cortex defined by BA 11, whose output is directed to the nucleus accumbens and

onward to the thalamus. The thalamus completes a feedback loop through its projections back to the ventromedial prefrontal cortex. The ventromedial prefrontal cortex, nucleus accumbens, and thalamus all maintain reciprocal connections to the amygdala. The insula is involved in the ventromedial circuit through its reciprocal communications with the amygdala and the ventromedial prefrontal cortex (*Strakowski et al., 2012*). Both the globus pallidus and the nucleus accumbens are thought to exhibit abnormalities antecedent to the onset of bipolar disorder (*Strakowski et al., 2012*).

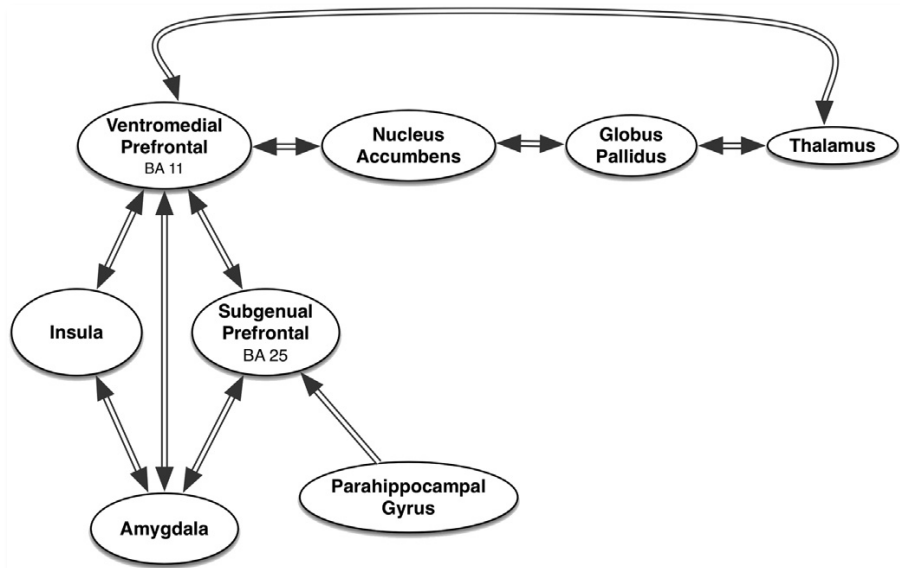


Fig. (3): Regions involved in the ventromedial prefrontal circuit

C- Dorsolateral circuit

As shown in Fig. 4, the dorsolateral circuit includes BA 9 and 10 in the dorsolateral prefrontal cortex, which project to the globus pallidus through the caudate nucleus. This region projects to the ventral anterior and mediodorsal thalamus, which project in turn back to BA 9 and 10 to complete the circuit (*Almeida et al., 2009*).

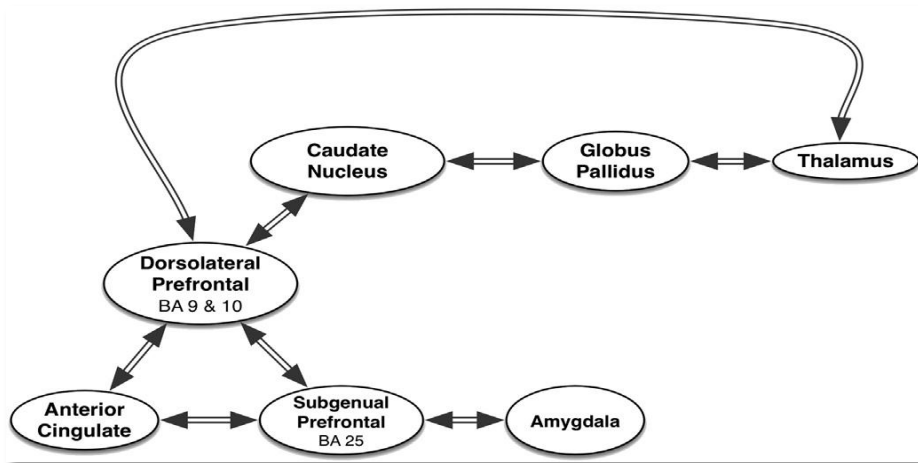


Fig. (4): Regions involved in the dorsolateral prefrontal circuit.

D- Anterior cingulate circuit

The dorsal and ventral subdivisions of the anterior cingulate appear related to cognitive and affective processing, respectively. The subgenual prefrontal cortex (BA 25) has reciprocal connections with the anterior cingulate cortex and the amygdala, and receives input from the ventromedial prefrontal cortex, which presumably accounts for its role in integrating cognitive and emotional

information (*Strakowski et al., 2005*). The anterior cingulate circuit, which is illustrated in Fig. 5, originates in BA 24 in which projects to the ventral striatum (*Mega and Cummings, 1994*). Projections then continue to the ventral pallidum, which in turn projects to the mediodorsal thalamus and then back to the anterior cingulate to complete the circuit.

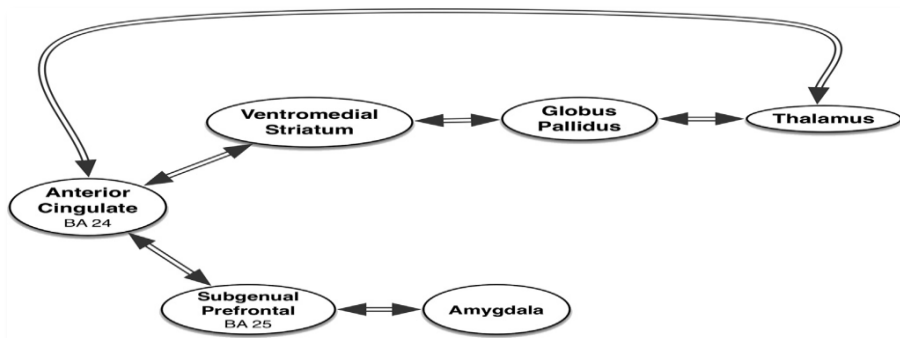


Fig. (5): Regions involved in the anterior cingulate circuit.

Neurobiology of BD

Despite extensive research in the field, the precise etiology of bipolar disorder is not clear. Neither, then, do we have a fulsome understanding of the neurobiology of bipolar depression. Some insights have been gained from knowledge of the mechanisms associated with major depressive disorder (MDD); however, it is largely believed that bipolar depression is unique because of its differential response to conventional antidepressant treatment as well as its divergent prognosis and course of illness (*Zarate, 2016*).