INTRODUCTION

Bipolar Disorder (BD) is a serious psychiatric condition in which patient's mood vacillates between periodic extremes of joy or depression **(Goodwin and Jamison, 2007)**. The natural course of BD is characterized by a constant risk of recurrences over a patient's life span, even 30 to 40 years after onset and up to 70 years of age or more, causing impairment of psychosocial functioning, despite the advances in pharmacological and non-pharmacological treatments **(Tohen et al., 2009).**

Bipolar Disorder is a chronic, debilitating illness with a lifetime worldwide prevalence of 4.8% and more disability-adjusted life-years lost than major neurological conditions or cancer as it causes severe suffering for patients and caregivers, and constitute a major health economic challenge for societies **(Gustavsson et al., 2011)**. According to WHO global burden of disease study, BD rank within the top 20 causes of disability among all medical conditions worldwide, and rank 6th among the mental disorders **(Vos et al., 2012).**

The issue of persistent cognitive deficits in euthymia is of profound importance because of its potential as a trait marker for bipolar disorder. The residual impairment in executive functions in euthymic bipolar patients raises the possibility of primary cognitive changes those which are independent of mood state. In

addition to influencing our understanding of the pathophysiology of the disorder, it would also have important prognostic effect for patients **(Clark et al., 2002)**. Euthymic bipolar patients show limitations in a number of cognitive domains especially executive functions, memory, and sustained attention .This seems to be a cause for a continuous impairment in social and occupational functioning in a large number of patients **(Delgado et al., 2012).**

Recently, it has been suggested that neurodevelopmental disturbances, particularly White Matter (WM) alterations, represent an important risk factor for BD1 **(Schneider et al., 2012)**. Evaluating white matter of the brain structure appears to be a promising area of investigation for understanding the potential for altered connectivity between brain regions believed to contribute to bipolar disorder symptomatology. White matter alterations may be responsible for some of the functional activation deficits found in patients with BD. Several hypotheses regarding white matter abnormalities in BD have been suggested **(Mahon et al., 2010; Benedetti et al., 2011).**

With the introduction of Diffusion Tensor Imaging (DTI), structural differences in white matter architecture between psychiatric populations and healthy controls can be systematically observed and measured. In particular, DTI tractography can be used to assess white matter characteristics over the entire extent of

white matter tracts and aggregated fiber bundles. Fractional anisotropy (FA) is a common DTI measure that provides information on the structural integrity and coherence of fibers within white matter regions and tracts **(Goodwin and Jamison, 2007).**

Several studies pointed out that BD patients showed abnormalities within white matter tracts connecting the frontal cortex with the temporal and parietal cortices and the fronto-subcortical circuits **(Lin et al., 2011).** White matter abnormalities seem to persist by the time of remission even after the first manic episodes **(Chan et al., 2010)**, suggesting that disruption of white matter cortical-subcortical networks as well as projection, associative and commissural tracts may be a hallmark of the illness involving prefrontal and frontal regions, associative and commissural fibres **(Heng et al., 2010; Leow et al., 2013)**.

Tractography studies would be the most efficient way to determine which of these bundles are really involved in BD. The uncinate, is the most likely tracts to be involved in BD, as it links the amygdala with the prefrontal cortex and has already been shown to be abnormal in three tractography studies of BD **(Houenou et al., 2007; Lin et al., 2011; McIntosh et al., 2008)**.

Lin et al. (2011) studied frontal white matter cortex connections found lower Fraction Anisotropy in the superior longitudinal fasciculus (SLF). Also Studies in at-risk subjects have suggested that WM abnormalities of the inferior longitudinal fasciculus (ILF) and superior longitudinal fasciculus may be endophenotypes of bipolar disorder (**Chaddock et al., 2009; Frazier et al., 2007).**

Brain regions with significantly decreased FA indices found in the bipolar I patients majorly relate to the cognitive functions. The anterior cingulate cortex is highly involved in the network regulating both cognitive and emotional processing. Particularly, the rostral area locates in the cognitive division of anterior cingulate **(Bush et al., 2000)** and plays an important role in monitoring /signaling conflict or interference, decision making, and response to errors **(Kelly et al., 2009)**.

Thalamus abnormalities were frequently reported in mood disorders, particularly in BD **(Konarski et al., 2008)**. Also the inferior frontal area participates in attention and executive functions in bipolar patients **(Lyoo et al., 2004)** and plays an important role in working memory **(Makris et al., 2005)**.

There is a clear need to improve diagnostic tools and to identify objective biomarkers. Specific functional and structural brain abnormalities underlying cognitive and emotional trait

impairments that are present during both acute episodes and remission have been proposed as promising candidates for biomarkers of bipolar disorder **(Singh and Rose, 2009).**

The investigation of white matter as a biological risk factor for BD and its potential relation to neuropsychological abnormalities is extremely important to improve our etiological knowledge of bipolar disorder, facilitating early and precise diagnosis and development of new therapeutic agents **(Linke et al., 2013).**

Rational of the study

Study of white matter integrity in bipolar I patients and its correlations with clinical data and neuropsychological measures is poorly understood and there is no available national studies to explore this issue. So studying of such correlation may help in understanding the etiology, pathophysiology, course and the outcome of bipolar I disorder as a one of the most debilitating psychiatric disorders.

Hypothesis of the study

The study hypothesized that 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 ascertain whether patients with 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 those patients.

Chapter *I*

BIPOLAR DISORDER

Historical background

Primitive societies thought that mental disorders were caused by magical forces, but in ancient Greece they were already seen as symptoms of underlying biological disturbances **(Goodwin and Jamison, 2007)**. The first classification categories of mental disorders were defined by Hippocrates (460 – 337 BC), and included melancholia, mania and paranoia **(Angst and Marneros, 2001)**. The first noted suggestion that melancholia and mania are associated is dated back to the year 120 when Arateus wrote that mania is a worsening of melancholia **(Angst and Marneros, 2001).**

We owe the categorization of bipolar disorder as an illness to **Falret**, who in 1851 and 1854 on the basis of longitudinal observations developed the entity of "folie circulaire" (circular madness), defined by manic and melancholic episodes separated by symptom-free intervals. In 1854 **Baillarger** used the term folie a` double forme to describe cyclic (manic–melancholic) episodes **(Angst and Sellaro, 2000).**

The first to approach modern bipolar disorder was **Karl Kahlbaum** who in 1883 described cyclothymia. Where circular insanity was a psychotic disorder, with regular and stable features that led to degeneration, cyclothymia was for Kahlbaum a specific mood disorder from which patients could recover **(Angst and Sellaro, 2000).**

In 1899, building on a series of syndromes first outlined by Kahlbaum, and on his principle of disease course, but eschewing brain localization, **Emil Kraepelin** distinguished between two disease entities – dementia praecox and manic depressive insanity **(Kraepelin, 1899).**

Although **Kraepelin (1921)** grouped most major forms of depression under the general rubric of "manic-depressive illness, " it was not until **Leonhard's (1957)** work that patients with both depressive and manic episodes, whom **Leonhard** termed "bipolar", were distinguished from those exhibiting only recurrent depressions. In 1980, the name bipolar disorder was adopted by the Diagnostic and Statistical Manual for Mental Disorders (DSM) to replace the term manic depression **(Johnson and Kizer, 2002)**.

Epidemiology

Bipolar disorder has a population prevalence of 6% **(Judd and Akiskal, 2003)** and lifetime prevalence rates up to 6.5% in the general population **(Vornik and Brown, 2006).**An epidemiological study of BD among adolescent and young adult reported that the lifetime prevalence of BD was 3.0% among (15-18) year-olds, and 3.8% among (19-24) year-olds **(Kozloff et al., 2010).**

Bipolar disorders have no predilection for race, sex, or ethnicity. Although they can occur at any age, bipolar disorders are most common in persons younger than 25 years. The mean age at symptom onset is 18 years in bipolar I disorder. Bipolar disorders are common in primary care settings. Among patients presenting with depression or anxiety, 21 to 26 percent will meet criteria for bipolar disorders using a structured interview **(Price, 2012).**

Bipolar disorder is more common in divorced and single persons, also in patients who didn't graduate from college; this may be due to the early age of onset of illness **(Kaplan and Sadock, 2009).**

Biology and Pathophysiology of Bipolar Disorder

The neurobiological basis of bipolar disorder and the complex interactions of environmental and inherited factors that create vulnerability to abnormal moods remain essentially unknown. However, several lines of research are providing important clues about the type of biological processes underlying moods and their disorders. The established approaches of neurochemistry and pharmacology that gave rise to the present generation of antidepressant and mood-stabilizing drugs have highlighted the importance of neurotransmitters and cell signaling pathways. Advances in neuroimaging techniques have identified several brain regions showing structural or functional changes in subjects with mood disorders, and cognitive deficits found in patients are in keeping with these imaging findings **(Power, 2004)**.

A- Pathohistologic findings associated with bipolar disorder:

Pathohistologic research has uncovered significant cell pathology associated with bipolar disorder. It appears that all three of the glial cell families may be affected, linking the pathogenesis of the condition to abnormalities in astroglia, oligodendroglia, and microglia **(Cotter et al., 2001; Schroeter et al., 2010; Steiner et al., 2008; Uranova et al., 2004)**.

Postmortem studies of bipolar patients have noted a reduction in both glial cell numbers and density**.** Glial alterations have been reported in the subgenual anterior cingulate cortex, dorsolateral Prefrontal cortex, orbitofrontal cortex, and the amygdale of unmedicated bipolar patients **(Öngür et al., 1998)**.

Furthermore, a significant 29% reduction in oligodendroglia numerical density in the dorsolateral PFC white matter was detected in bipolar patients compared with controls. Evidence of diminished myelin staining in the dorsolateral PFC and reductions of immune-positive oligodendrocytes in the hippocampus of bipolar subjects further extend these findings. Indeed, convergent histological and imaging evidence indicates that oligodendroglial deficits may be the key CNS cellular abnormality in BD **(Uranova et al., 2004)**.

With a few notable exceptions, neuronal changes in BD are mostly morphological in character, possibly attributable to apoptosis and thinning of inter neuronal neuropil **(Harrison, 2002)**, and are much less extensive than glial pathology. Nonetheless, one study reported a 16–22% decrease in neuronal density in the dorsolateral PFC of BD patients compared with a control group **(Rajkowska et al., 2001)**. It bears reminding that dorsolateral PFC pyramidal neurons are the main target of thalamic projections and also provide regulatory feedback to the amygdale and anterior cingulate cortex (ACC). These

connections make it likely that neuronal dorsolateral PFC pathology may result in compromised attention, executive function, and top-down emotional regulation, all of which are prominent features of BD **(Maletic and Raison, 2014).**

Additionally, studies have detected a significant reduction in neuronal density in the hippocampus and a prominent decrease in neuronal size in the ACC of bipolar subjects relative to controls. Several studies have examined changes in monoaminergic nuclei that may affect mood regulation. Patients with BD appear to have a higher number of noradrenergic neurons in the locus ceruleus as well as subtle structural deficits of serotonergic neurons in the dorsal raphe **(Maletic and Raison, 2014).**

B- Neuroendocrine and autonomic dysregulation in bipolar disorder:

Alterations in HPA axis function in bipolar disorder have been well studied. Exaggerated release of corticotropin-releasing factor (CRF) contributes to greater adrenocorticotropic hormone (ACTH) secretion and a subsequent elevation of circulating glucocorticoids (i.e., cortisol) **(Taylor et al., 2006)**. These disturbances are most likely attributable to deficits in cortico-limbic regulation in BD, with consequent amygdale over activity, and a compromised hippocampal regulatory role **(Drevets et al., 2008).**

Moreover, glucocorticoid receptors appear to have diminished sensitivity in mood disorders, possibly due to elevation in inflammatory cytokines, thereby disrupting physiological feedback regulation on the HPA axis and immune system **(Pace et al., 2007; Söderlund et al., 2011; Tsigos and Chrousos, 2002).**

Indeed, even euthymic bipolar patients exhibit a flattening of the cortisol curve compared with healthy controls. In patients with multiple episodes, these abnormalities intensify, resulting in higher overall cortisol levels in addition to aberrant reactivity, and even greater flattening of their cortisol curves, compared with patients who have experienced only a few episodes **(Havermans et al., 2011).** Highlighting the relevance of these neuroendocrine abnormalities, a recent study has associated elevated evening cortisol levels in bipolar individuals with a history of suicidal behavior **(Kamali et al., 2012).**

In addition to HPA dysregulation, BD may be associated with excessive sympathetic nervous system (SNS) activity. For example, extra-neuronal norepinephrine was reported to be elevated in a group of bipolar patients relative to healthy controls **(Grossman and Potter, 1999)**. Autonomic dysregulation, more generally reflected by decreased parasympathetic activity and elevated sympathetic activity, may be a trait marker for BD **(Cohen et al., 2003).**

The constellation of Sympathetic Nervous System (SNS) over activity, parasympathetic withdrawal, glucocorticoid receptor insufficiency, and elevated inflammatory signaling may help account, at least in part, for the increased risk of metabolic syndrome, endocrine disorders, and vascular disease seen in bipolar patients **(Taylor and MacQueen, 2006; Vancampfort et al., 2013).** Highlighting the relevance of this pattern of neuroendocrine, autonomic and immune changes is the fact that vascular disease has recently been identified as the leading cause of excess death in BD **(Weiner et al., 2011).**

C- Immune disturbances in bipolar disorder:

Several limbic and para limbic areas implicated in the pathophysiology of bipolar illness, including amygdala, insula, and anterior cingulate cortex (ACC), have an important role in the regulation of autonomic and immune function **(Maletic and Raison, 2009; Irwin and Cole, 2011; López et al., 2005; Amaya et al., 1999)**

Although direct data are not available linking disturbances in these limbic/paralimbic areas to inflammation in BD, is tempting to speculate that their aberrant activity may have a causal role in the ensuing immune dysregulation that has been repeatedly observed in patients with BD. Several studies and two recent meta-analyses have reported elevated levels of peripheral

inflammatory cytokines in bipolar depressed and manic patients compared with healthy controls **(Modabbernia et al., 2013; Munkholm et al., 2013; Munkholm et al., 2012; O'Brien et al., 2006).**

Two meta-analyses indicated higher levels of tumor necrosis factor (TNF) - alpha and IL-4 in bipolar subjects relative to healthy subjects **(Modabbernia et al., 2013; Munkholm et al., 2013)**. IL-4 induces transformation of naïve helper T-cells into Th2 cells and reduces production of Th1 cells and macrophages. As such, IL-4 is a key "switch" regulating the balance between cellular and antibody- based immunity. One might speculate that IL-4 elevation in BD may be of compensatory nature, to buffer against the increase of proinflammatory cytokines seen in the condition **(Maletic and Raison, 2014).**

The data suggest that successful treatment leading to euthymic state may reverse inflammation and normalize peripheral levels of inflammatory mediators **(Maletic and Raison, 2014).**

Imaging studies have reported peripheral inflammation-related changes in the activity of several limbic and paralimbic areas, including subgenual anterior cingulate cortex, amygdala, medial prefrontal cortex, and basal ganglia/ventral