**ABSTRACT**

The present paper provides a critical review of the evidence of ongoing clinical issues in bipolar disorder. However, the literature supports a strong association of smoking and alcohol dependence in bipolar disorder patients. Growing evidence suggests that higher suicidal ideation and higher risk for attempted suicides in individuals is associated with BPD. A family-based association study shows that first-degree relatives and monozygotic twins are probably more chances to affect with bipolar disorder. Specifically, brain structural abnormalities in limbic-cortical-striatal-pallidal-thalamic tract have been reported in patients with BPD. Creativity and realism are correlated with hypomania and depression. However, people with bipolar disorder are more creative when effectively treated than when they are not treated. Consistent with the depressive realism effect, depressed individuals are more realistic than the non-depressed. Here, we discussed the findings from clinical, epidemiological, neuroimaging and post-mortem studies, as well as the implication of the available data, identify current challenges impeding progress and define areas for future investigation.

Key words: Bipolar disorder, Creativity, Genetics, Neurotransmitter, Realism and Sucidality.

**1. INTRODUCTION**

**1.1 General background:** Bipolar disorder is a mood disorder, characterized by long term episodic, cyclical patterns involving extreme fluctuations of mood that cause significant disruptions in one’s social, interpersonal and occupational life [1]. Psychotic symptoms are common features of BPD. In fact, more than half of all BPD patients experience psychotic mood episodes during their lifetime [2-3]. BPD affects approximately 1.5% of the population [4,5] and remains a leading worldwide cause of disability, morbidity and mortality from suicide [6-7]. The disorder usually occurs in both men and women between 18 and 24 years of age, but it can affect all age groups. However, early onset of BPD is possible and is a major health problem [8]. Pregnancy and especially the post-partum period are stressful periods for women, and increase the risk of relapse for women with bipolar disorder [9,10]. Patients suffering from BPD have reported difficulties with their jobs, and around 20% of them have permanent disability. In addition, they report fewer social interactions with their friends and family, lower interest or pleasure in their leisure activities, less autonomy to maintain duties and worse cognitive functioning [11]. People with BPD have also been found to experience more frustration after goals are thwarted compared to other people [12]. About 20%-66% of patients with BPD rely on spiritual belief and practice their faith without negative impact on their affective illness [13,14]. Eating disorders particularly binge eating or weight gain, other than those associated with medicinal effects; are common in BPD [15]. Studies in bipolar individuals who reported low parental care and high overprotection on a self-report questionnaire had more hospitalizations for both depression and mania than those who did not [16]. Cooke, using a family environment questionnaire, found that within the bipolar group, lower ratings of family expressiveness were associated with a history of comorbid dysthymia and lower ratings of family cohesiveness were associated with a history of past suicide attempts [17]. BPD represents a significant risk factor for both suicide attempts and suicide itself [18,19].
recent study suggests that preschool children with family histories of depression or bipolar disorder correlate with increased risk of developing manic symptoms, and they recommend long-term follow-up of preschool samples [20]. Children with untreated BPD often experience an academic failure, behavioral trouble, including suspension and possibly expulsion, and severe social problems [21]. Studies have demonstrated that the annual costs of the BPD range between 1.8 and 45 billion US dollars, mainly reflecting indirect costs attributable to work loss [22,23].

2. SMOKING / ALCOHOL DEPENDENCE AND SUICIDALITY

Tobacco smoking, a global epidemic, is one of the greatest challenges of our time. Currently about 1.1 billion people are cigarette smokers worldwide, and their consumption is 5.5 trillion cigarettes annually. Approximately 5 million people are killed a year by tobacco in the world, and the number of annual deaths will increase to 10 million by the year 2030 [24,25]. Smoking and substance abuse are common in BPD patients [26]. The association between bipolar disorder and elevated smoking rates is obviously true from the opposing perspective, too. For example, according to data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), an individual with nicotine (NIC) dependence has an approximately four times higher chance of suffering from bipolar-I disorder [27]. Cigarette smoke containing reactive oxygen species (with its known damaging effects on cellular membranes, DNA, carbohydrates, etc.) may also contribute to structural brain abnormalities in smokers [28-30].

The majority of the above studies found a dose-dependent association between cigarette smoking and suicidal behavior. Blood and urine levels of NIC were higher among smokers who committed suicide compared with smokers who died of non-suicide-related causes according to an autopsy study. This result suggests that cigarette smokers who have committed suicide smoked more heavily than other cigarette smokers [31-33]. A great number of studies also suggest that smoking habits may significantly influence the clinical characteristics of bipolar disorder found that smoker patients with a current episode of mania showed poorer treatment response compared to their non-smoker counterparts [34]. Researchers found in their cross-sectional study that bipolar patients who smoke have more (and more serious) previous episodes of both mania and depression compared to non-smokers with bipolar disorder. In addition, they reported that smoking was positively associated with rapid cycling, suicidal behavior, psychiatric comorbidity, and the use of alcohol, caffeine, and illicit drugs [35]. Bipolar patients that are moderate or heavy smokers are more likely than nonsmokers to consume alcohol and abuse psychoactive substances [36]. Males with bipolar disorder have higher rates of substance abuse than females (59.7% Vs 37.8% for alcohol; 54.5% Vs 33.8% for other drugs) [37].

In the national comorbidity survey of a community-based, US household sample of 8,098 people aged 15 to 54 years, 6.5% of alcoholic men and 10.6% of alcoholic women had a lifetime history of mania [38]. The more recent and largest US epidemiological survey on alcohol-related disorders has confirmed that mania/hypomania have one of the highest associations with alcoholism compared to other primary psychiatric disorders [39]. Although, alcoholism is more prevalent among males than among females with BPD, the odds ratio for alcoholism compared to the general population is much higher for females than for males with BPD [40]. Alcoholic bipolar patients are more severe [41], have a longer inpatient stay [42] and a poorer prognosis overall [43] than non-alcoholic bipolar patients. Researchers have consistently found that individuals with bipolar disorder are at increased risk for alcohol and substance related disorders [44-46]. Disruption in sleep architecture resulting from chronic alcohol use [47,48] may also detrimentally affect mood regulation [49]. Some studies and anecdotal reports have described an “inversion” of the melatonin rhythm during chronic alcohol use in some alcohol dependent patients, [50,51] referring to a reversed secretion pattern in which daytime melatonin levels are higher than night time levels. Recent findings suggest that sleep problems like insomnia may developmentally precede and predict early onset of alcohol, cigarette and marijuana use in adolescents and young adults [52-54]. Bipolar patients who drink excessive amounts of alcohol have higher burdens of manic and depressive symptoms, marked impulsivity and violence [55]. Aggressive and impulsive traits, alcoholism and substance abuse are also associated with serotonergic abnormalities and all carry an elevated risk of suicide [56,57]. Impulsivity is associated with a number of negative outcomes in patients with BPD. The most consistent finding in BPD is a positive

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association between impulsivity and suicide [58-60]. Suicide attempters score higher on questionnaire measures of impulsivity [61] as well as certain behavioral measures, specifically premature responses [62,63]. Regarding history of suicide attempt(s), bipolar patients were much more likely to have it than were unipolar patients (37.3% vs. 19.2%). This was similar to that of previous studies indicating high suicidality in bipolar patients [64,65]. In a study from the University of Barcelona in Spain, bipolar patients with psychiatric comorbidity had more mixed features, depressive episodes, and suicide attempts; poorer outcome and treatment compliance; and greater frequency of depressive onset than their counterparts without psychiatric comorbidity [66]. Higher rates of suicide attempts have been reported in bipolar patients whose drug abuse began after the onset of affective illness [67]. Alcohol dependence is an important risk factor for suicidal behavior, and lifetime mortality due to suicide in alcohol dependence has been reported to be as high as 18% [68]. Studies show that 60% of patients with bipolar type I disorder and 50% of patients with bipolar type II disorder abuse drugs or alcohol [69]. Among bipolar patients committing suicide, 10 of 18 male victims, but none of 13 female victims, had alcohol dependence [70]. The literature reporting higher suicidal ideation and higher risk for attempted suicides in individuals with alcoholism compared to persons without a history of alcoholism [71-73].

A prospective cohort study conducted in Japanese men indicated a significant positive association between the daily amount of alcohol consumption and suicide risk [74]. The co-occurrence of alcohol abuse/dependence with BPD increases the risk for suicide attempt, which may reflect in part the greater severity of symptoms and impaired functioning [75]. The US National Depressive and Manic-Depressive Association 2000 Survey of individuals with BPD showed that 37% reported alcohol and substance abuse during the time that they were not or improperly treated for their BPD, while alcohol and substance abuse dropped to 14% when treatment was initiated [76]. The role of genetic factors in psychiatric disorders has received much attention recently. Some evidence is available to support the possibility of familial transmission of both bipolar disorder and alcoholism [77,78]. Monozygotic twins have a significantly higher concordance rate for completed and attempted suicide than dizygotic twins [79]. Serious suicide attempts and suicide have been previously linked to mixed/cycling bipolar phenomenology in a long-term prospective design [80]. Out of the three different clinical phenotypes of major mood disorders (unipolar depression, bipolar I and bipolar II disorder), bipolar II patients carry the highest risk of both completed and attempted suicide [81,82].

3. PROPOSED THEORY OF BIPOLAR DISORDER:

3.1 Genetic factors:
Genetic factors contribute to the etiology of this disorder as evidenced by twin, adoption and family studies [83]. A recent complex segregation analysis of bipolar families supports the existence of a single major locus [84,85]. About 50 Percent of patients with bipolar illness have a family history of the disorder, and in some families, known as multiplex families; there are many members with the disease across several generations. Studies of twins suggest that the concordance for bipolar illness is between 40 percent and 80 percent in monozygotic twins and is lower (10 to 20 percent) in dizygotic twins, a difference that suggest a genetic component to the disorder [86]. Patients with bipolar disorder more often have affected mothers than fathers, and more often have affected maternal relatives than paternal relatives [87]. This non-Mendelian gender-related pattern of inheritance is now referred to as ‘parent-of-origin effect’. Mc Mahon first proposed that this might be caused by mitochondrial inheritance. In their 31 pedigrees selected for linkage studies, 7 (22%) seemed to be exclusively maternal. Family studies have provided (a) a familial nature of the condition (increased risk in first-degree relatives, such as parents, siblings and offspring), (b) a complex mode of inheritance and (c) a range of disease phenotypes associated with defective gene(s). In some cases, the sex of the transmitting parent may influence the transmission of BPD [88,89]. The presence of a positive family history of affective illness may indicate that a neurologic insult results in mania by triggering an existing bipolar predisposition [90]. It is now thought that gene-gene and gene-environmental or stressful life events (divorce, job loss, poor health, loss of a family member, child abuse, drugs, hormones, diet) interaction may contribute to the disorder [91,92,93]. The clock mechanisms and clock genes in many animal species and human beings are similar [94,95]. The disruption of the circadian timing system, possibly on a genetic basis, is thought to contribute to the etiology and course of mood disorders and it is implied in suicidal
behavior too [96,97]. A mutation in clock genes may accelerate or delay circadian cycles by representing a transcriptional factor, and abnormalities in those are possibly related to mood disorders [98]. Some of the regulated genes are related to circadian rhythms and to wakefulness, with one of them (Dbp or D-site binding protein) proposed as a candidate gene in BPD [99]. BPD may involve more than one gene and a complex mode of transmission. Linkage studies have identified markers, particularly on chromosomes 18 and 22. These results have been replicated in more than one study [100]. Genetic linkage studies have identified chromosomal regions, including Possible susceptibility genes for bipolar disorder are in chromosome regions 4p, 12q, 18p, 16p, 21q, 18q, 22q, Xq, 1q, 6q, 10p, 10q, and 13q [101-103]. A family-based association study showed that polymorphisms in BDNF genes are related to bipolar disorders [104]. Interestingly, the levels of the glial marker protein S100B are specifically altered in the lateral prefrontal and parietal cortices in BPD [105]. Studies demonstrated that S100B is a susceptibility gene for BPD with psychosis [106]. The glycogen synthase kinase 3 (GSK3-β) gene is involved in energy metabolism, neuronal cell development and body pattern formation [107]. It is expressed in the brain and several other tissues from a pharmacological perspective; GSK3β is a prime candidate gene for bipolar disorder (BPD, MIM 125480) because lithium inhibits GSK3β in vitro [108,109] and because GSK3β inhibitors reverse the neuroanatomical and behavioral abnormalities induced by a Disrupted in Schizophrenia 1 (DISC1) expression silencing in mice [110]. DISC1 loss of function-a translocation that may lead to bipolar disorder-is primarily modulated by GSK3β-β-catenin signaling [111]. Bipolar patients with the T/T allele of GSK3β show an earlier age of onset of bipolar disorder and enjoy less improvement from lithium therapy than patients with the T/C or C/C alleles [112,113]. The genetic association of the AKT gene in bipolar disorder as well as in schizophrenia has been reported [114,115,116]. Akt is a downstream signaling effector of dopamine receptors [117], which are critical mediators of a neurotransmitter system related to bipolar disorder [118]. Recent studies also observed that Wnt cascade would appear to be particularly well suited as a relevant molecular pathway that regulates brain functions and its dysregulation might be involved in the pathophysiology of BPD [119]. An increased mitochondrial DNA deletion in the neural tissue or mitochondrial DNA mutations/polymorphisms is associated with BPD patients [120,121,122]. There is emerging body evidence suggesting that mitochondrial dysfunction may be associated with the pathophysiology of BPD [123]. Studies conducted in postmortem brain tissue demonstrated that mitochondrial genes are down-regulated in the hippocampus [124] and dorsolateral prefrontal cortex of BPD patients [125,126]. A recent study showed that telomere shortening, which is thought to occur as a consequence of increased oxidative stress, is increased among patients with BPD [127]. The protein kinase C pathway has also been the subject of recent investigation as it is known to play a vital role in regulating pre-and post-synaptic neurotransmission [128]. Elevated intracellular sodium and calcium altered the expression of TRPM2L-transient receptor potential (TRP) melastatin and TRPM2S. These observations demonstrate that ion dysregulation may induce neuron apoptosis and these changes may be involved in the pathophysiology and pathogenesis of bipolar disorder [129]. Postmortem studies of brains of patients with BPD have shown changes in cyclic adenosinemonophosphate (cAMP) binding and in protein kinase A (PKA) activity in temporal cortex [130,131]. Studies are consistent with a post-mortem study showing altered D1 mRNA expression in the hippocampus of individuals with BPD [132]. Additionally Polymorphism of methylenetetrahydrofolate reductase variants MTHFR 1298A>C and MTR 2756A>G were shown to be associated with BPD [133,134].

3.2 Neuropathophysiology
The period of life when most of the psychiatric disorders have their onset (adolescence and early adulthood) coincides with major brain maturational events, such as reductions in the cortical gray matter content and increase in the white matter content, which may reflect neuronal and/or synaptic elimination and axonal growth/myelination, respectively [135,136]. Brain structural abnormalities associated with BPD have been less extensively investigated, but may include lateral ventricular enlargement, an excess of white matter hyperintensities and volume reduction in some prefrontal regions [137]. Histopathological postmortem findings consistently showed reductions in glial cell density or glial cell numbers in prefrontal brain regions, such as the (subgenual) anterior cingulated cortex, the orbito frontal cortex and...
dorsolateral prefrontal cortex in association with reduced prefrontal gray matter in patients with mood disorders [138,739,40]. Glial reduction in the subgenual prefrontal cortex has also been found in post-mortem tissue of persons with familial MDD or bipolar disorder compared to those with schizophrenia or healthy controls [141]. Several recent neuroimaging studies in adult BPD reported inconsistent findings of dysfunctional dorsal and ventral prefrontal-cortical and subcortical-striatal neural systems implicated in mood-regulation.

Specifically, patterns of increased amygdala and striatal, and decreased dorsal prefrontal-cortical (DPFC) activity to emotionally-salient stimuli, and during cognitive control tasks have been shown [142,143]. However, recent findings observed that smaller amygdala volume was found among adolescent bipolar patients [144,145] and also volumetric neuroimaging studies shown that increased amygdala volume is more in adult patients with BPD [146,147]. Data on amygdala volumes in patients with bipolar disorder have been conflicting, but recent studies using high-resolution magnetic imaging resonance (MRI) have convincingly shown that amygdala volume is smaller in unmedicated patients with bipolar disorder and larger in patients with bipolar disorder of mood-stabilizer treatment [148]. Researchers have found that dysregulation of the various nodes in the limbic system may produce affective symptoms, including depression and mania. Limbic system structures include the amygdala, hippocampus and parahippocampal gyrus, ventral striatum, insula, anterior cingulated (ACC), and orbito frontal cortex (OFC) [149]. Ventricular enlargement and smaller hippocampal volume have also been associated with psychosis in BPD [150]. The majority of the structures associated with the limbic-cortical-striatal-pallidal-thalamic tract have demonstrated structural changes in patients with bipolar disorder [151].

3.3 Neuroendocrine dysfunction

The neuroendocrine dysfunction occurs in bipolar disorder is well established, and recent data reveal that the pituitary gland is small in patients with BPD compared with either patients with unipolar major depression or healthy controls [152]. Likewise disorders of the thyroid gland are associated with mood and cognitive dysfunction, and affective disorders are associated with abnormalities in the hypothalamic-pituitary thyroid (HPT) axis [153]. HPT axis dysfunctions have been reported in (Rapid Cycling Bipolar Disorder) -RCBD. Rapid cycling usually affects about 9 to 20% of all patients with bipolar disorder [154,155]. Among the HPT abnormalities that have been reported in patients with major depression are the following: elevations in thyrotropin-releasing hormone (TRH) in the cerebrospinal fluid (CSF) [156]; chronic reductions in circulating thyroid-stimulating hormone (TSH, thyrotropin) [157,158]; elevations in thyroxine (T4) [159].

Patients with bipolar disorder also have a blunted release of thyrotropin-stimulating hormone in response to administration of exogenous thyrotropin-releasing hormone [160,161]. In a study of first-episode manic and mixed types of bipolar disorder, 33% of the patients in mixed episodes had elevated TSH levels, in comparison with 7% of patients experiencing pure mania [162]. Hypothyroidism is also associated with bipolar affective disorders, depression, or loss of cognitive functions, especially in the elderly [163]. Manic symptoms have been rarely reported in hyperparathyroidism [164,165]. Recent studies also observed that disturbances of the hypothalamic-pituitary adrenal (HPA) axis functioning consistent with bipolar disorder patients and is associated with suicide [166]. Dysregulation of adrenocorticotropic hormone (ACTH) and cortisol response after corticotropin-releasing hormone (CRH) stimulation have been reported in bipolar patients, but altered states of the HPA axis have mostly been demonstrated in patients with depressive or mixed episodes [167,168]. There is a strong evidence of decreased corticotrophin levels following stimulation of CRH in unipolar and bipolar depressed subjects [169-171]. Bipolar patients exhibited significantly higher cortisol concentrations than unipolar patients in acute episodes as well as in remission, and the authors conclude that a higher degree of HPA system dysfunction is present in BPD than in unipolar depression. The severity of the manic episode seems to be highly correlated to the degree of neuroendocrine attention. Anxiety, insomnia, and the intensity of depression were highly correlated with cortisol response [172]. In patients with severe depression, the daily quiet period of the adrenal cycle is interrupted by increased pulsatility which is associated with an elevated mean plasma cortisol concentration [173]. Chronic stress and Nocturnal sleep deprivation is associated with elevated cortisol, are both the depressed and manic phases of bipolar disorder [174-176].
Moreover, recent studies found that the growth hormone system was involved in the psychiatric symptoms of depressed patients [177]. Researchers have demonstrated that disturbances of the hypothalamic-pituitary-gonadal axis are a frequent cause of sexual dysfunction and have also been associated with depression in males [178]. Abnormalities in hypothalamic-pituitary-gonadal hormones, including elevated basal luteinizing hormone; reduced basal follicle-stimulating hormone; and elevated serum testosterone and androstenedione were observed in a sample of 12 women with manic-depressive or psychotic symptoms whose symptoms fluctuated in association with the menstrual cycle [179]. Compared with healthy controls and women with unipolar depression, women with bipolar disorder retrospectively report early-onset menstrual dysfunction more commonly prior to onset of bipolar disorder [180]. Disruption of the pituitary stalk, Shallow and fragmented sleep, prolonged awakening, and interrupted sleep patterns as frequently seen in the elderly, is associated with a dampening of the nocturnal prolactin (PRL) rise, decrease the amplitude of the nocturnal PRL pulses [181,182]. Recent studies demonstrated that increased prolactin concentrations in a patient with bipolar disorder. Finally, patients with bipolar disorders had significantly lower levels and later onset of melatonin secretion [183].

3.4 Neurochemical dysregulation

3.4.1 Dopamine
Dopamine has been proposed to be involved in the pathophysiology of mania, and changes in dopaminergic neurotransmission have been reported as consistent neurobiological abnormalities in BPD [184]. Several studies have identified distinct biological correlates of mania. These include increased dopamine activity [185], hyperpolarization in transmembrane potentials [186], and changes in dopamine sub-3 receptor mechanisms [187]. DAT plays a critical role in the regulation of dopaminergic transmission by mediating the active reuptake of dopamine from the synapse into the presynaptic terminal [188]. The dopamine transporter (DAT) has been implicated as a candidate gene in several disorders including BPD [189,190].

3.4.2 Serotonin
Serotonin promotes sleep, quiet non aroused waking, parasympathetic activation and the anti-stress relaxation response [191,192]. Serotonin is involved in the control (inhibition) of the impulses, in aggression and in the regulation of the sleep-wake cycle [193]. Deakin proposed that impaired function of this serotonergic projection results in mood, low self-esteem, hopelessness, pessimism and reduces stress resilience [194]. There is substantial evidence for abnormalities in 5-hydroxytryptamine (5-HT) functioning in both unipolar and bipolar depressions. Low concentrations of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) have been observed post-mortem in the brain stems of patients who died during unipolar and bipolar depressive episodes [195].

3.4.3 Norepinephrine
In 1967, Schildkraut first implicated NE deficiency as a factor in depression. Later, it was found that changes in the distribution of major NE metabolites in urine roughly correlated with depressed mood [196,197]. The norepinephrine turnover was increased during acute psychotic episodes [198]. NE turnover, in the cortical regions and the thalamus were higher in 10 patients with bipolar disorder than in control subjects [199]. In relation to both bipolar and anxiety disorders, increased amounts of urinary norepinephrine have been found in mania [200].

3.4.4 Gamma (γ)-Amino butyric acid
GABA is a critical neurotransmitter in circuits connecting the prefrontal and limbic cortex. These structures (i.e. amygdala, orbito frontal, anterior cingulate, and medial frontal cortex) are of relevance to impulsivity and related behaviors because of their central importance in behavioral inhibition [201] and affective processing [202]. Dysregulation of GABAergic system and decreased levels of GABA in the patient’s brain with major depression [203,204]. Magnetic resonance spectroscopy studies have observed lower GABA levels in occipital cortex of depressed patients [205]. Similarly GABA concentrations are also lower in the cerebro-spinal fluid and blood plasma in unipolar depressed patients [206]. In healthy women, brain GABA activity decreases through the menstrual cycle, especially the luteal phase. In women with premenstrual depression, brain GABA activity actually increases during the luteal phase [207]. Postmortem studies have provided consistent evidence that a defect of GABAergic neurotransmission probably plays a role in both schizophrenia and bipolar disorder [208].

3.4.5 Glutamate / Glutamine
Glutamatergic neurotransmission is thought to play a role in the pathophysiology and treatment of BPD [209,210]. In most studies an increase in glutamate or glutamine has been reported in...
depressed bipolar patients [211]. Constituent with this finding, a recent analysis of postmortem dorsolateral prefrontal cortex tissue also revealed elevated glutamate levels in the various brain regions in bipolar individuals [212,213,214] and in children [215].

3.4.6 Nitric oxide

Patients suffering from depression have been shown to have a reduced number of nitric oxide synthase (NOS) containing neurons in the hypothalamus [216,217] and hippocampus [218]. In addition, human genetic association studies have repeatedly found an association with NO signaling and psychiatric disorders [219]. A clinical study has demonstrated an increased production of nitric oxide in depressed patients [220,221] and a changed L-arginine metabolism in BPD have been reported [222].

4.0 CREATIVITY IN MANIA:

Creativity as a personal attribute is often measured simply as occupation, raising the question of domain-generality versus domain-specificity of creativity [223], and the distinction between eminent and everyday creativity [224]. The creative process can be partitioned into problem finding, ideation and evaluation [225]. Creative performance is typically operationalized in one of three ways: divergent thinking tasks [226], in sight tasks [227] or external judgments of creative products [228]. Feist’s meta-analysis showed that N is a barrier to creativity in science, but may be positively related to achievement in the arts [229] presumably because of Neuroticism (N) is associated with emotional sensitivity. BPD patients have been reported some advantages of the disease such as increased creativity [230].

Recent creativity studies in BPD have focused on comparing creativity measures among medicated euthymic patients against those of controls, reporting higher creativity in BPD. Peoples with BPD have higher Baron-Welsh Art Scale Scores than healthy controls and comparable to graduate students in creative disciplines [231]. Data from this same cohort revealed that temperament and personality traits contributed to higher creativity in mood disorders [232,233]. Creativity in BPD episodes might be positively influenced by DA levels in the PFC, but may also be dependent on executive function [234]. The DA has also been reported to influence mood and cognition while psychological, neuropsychological as well as functional imaging studies, indicate its potential role in the biology of creativity [235,236]. In a putative hyperdopaminergic state such as mania in which the optimal amount of DA for good executive functioning may be exceeded [237,238], high creativity was observed in those with less compromised executive function. It is possible that to sustain the high creativity associated with high DA, a minimum of executive function is required, and if this optimal level is disrupted creativity then become impaired. It has been estimated that approximately 8% of people diagnosed with bipolar spectrum disorder might be considered creative [239]. Bipolar spectrum patients to have a significantly higher lifetime creative accomplishment than healthy controls on the life time creativity scales [240]. Reviews of biographical material have suggested that BPD is significantly over-represented among samples of authors [241,242], writers, leaders of society [243], poets [244], visual artists, [245]. For example, [246] reviewed biographical material from 1005 eminent individuals. About 8.2% of those in creative professions (including architecture, theatre, expository writing, fiction writing and poetry) appeared to have had experience of mania compared with the general population prevalence of about 1%, multiple studies suggest that some 10% of artists endorse symptoms of BPD [247].

There seems to be a preponderance of the affliction in artists and writers throughout history who were known to have mood disorders of some kind. This perception is borne out by a review of studies investigating the actual percentages in comparison with the population at large. An analysis of seven studies found that the rate of manic-depression and cyclothymia among artists and writers is 10 to 20 times higher than the rate in the general population; the rate of depression is 8 to 10 times higher; and the suicide rate is as much as 18 times higher [248].

Careful review of influential musicians, visual artists and writers reveals that most produce their creative output (whether commercially recognized or not) only after years of practicing their skill with passion supporting this sustained effort [249]. However, there is considerable evidence that people with bipolar disorder are more creative when effectively treated than when they are not treated. Only the early phases of mania appear to contribute to creativity, whereas full-blown mania usually becomes destructive to creativity and productivity [251]. Recent publications have also looked at thought acceleration as a positive feature of mania [252,253]. Similarly manic patients were found to have higher creativity scores, in agreement with previous empirical observation,
although this difference only reached statistical significance when compared with depressive episodes but not with mixed episodes. A few reports of higher creativity production in mania than in depression have emerged from biographical studies and empirical research [254]. Hypomanic traits in healthy samples have been found to predict self-rated creativity, divergent thinking fluency and a biographical measure of spontaneous everyday creative achievement [255,256]. Others argue for a possible transmission in families with genetic susceptibility, showing that children with and at risk for bipolar disorder have higher creativity than healthy controls [257].

5.0 REALISM IN DEPRESSION:

The recent ‘adaptive turn’ in psychology has led to evolutionary explanations being sought for an increasing number of pervasive aspects of human thought and feeling [258,259]. This phenomenon, termed “depressive realism,” has been replicated in numerous subsequent studies, most often employing the contingency judgment paradigm [260,261]. Patients suffering from bipolar disorder spend much more time being depressed than manic, and depression is that phase of BPD which causes greater psychosocial impairment and disability [262,263,264]. It has been repeatedly shown that depressed people are more realistic than the non-depressed in several experiments that measure one’s sense of control [265]. Realism may partly reflect the increased insight of depression [266], and its converse may be decreased insight in mania [267]. Depressed patients showed a more balanced attribution pattern consistent with depressive realism [268]. To the extent that depressive realism is true, therapy might better be directed at denying reality and shoring up efforts at self-deception [269]. Studies by psychologists Alloy and Dobson suggested that depressed people appear to have a more realistic perception of their importance, reputation, locus of control, and abilities than those who are not depressed [270,271]. Specifically, Taylor and others have proposed that depressed individuals exhibit a remarkable degree of realism in their judgments about their personal and social worlds [272]. For example, they avoid overestimating the favorability of impressions they convey to others [273,274]. However, there is research that has shown that the depressed individual may be better able to make certain judgments than non-depressed individuals, a phenomenon referred to as “depressive realism” [269]. Non-depressed participants demonstrate a positive bias in their perceptions of their own performance, but no bias in the perceptions of the performance of others. In addition, mildly depressed participants demonstrate relatively realistic perceptions of their own performance, but a positive bias for their perceptions of others' performance [275]. Severely depressed individuals may be characterized by the negative perceptual and memory biases [276]. Cognitive theory suggests that depression is a consequence of a systematic tendency to misperceive reality in a pessimistic fashion [277]. Beck's theory [278], which formed the basis for cognitive therapy, posits that the depressed effect is heavily influenced by recurrent thoughts with negative content, or automatic thoughts. These thoughts arise from deeply-held dysfunctional beliefs, or schemas, relating to the self, world, and future (e.g., “If I fail, no one will love me”). Beck identified that schemas and automatic thoughts, and the depressed affect that results from them, tend to be self-perpetuating as the depressed person both attends more to negative events in their lives and interprets events that occur after the onset of the depressed mood in light of their own dysfunctional cognitions. A depressed person may experience a significant success, but may minimize the importance of that event as due to chance because they believe that they are a failure. The first evidence for this phenomenon came in the form of studies utilizing what is called the “judgment of contingency task.” In this task, participants are asked to press a button, which results in the illumination of a light a percentage of the time that is predetermined by the experimenter. The dependent variable is the participant-rated contingency between pressing the button and the illumination of the light. As such, there are two factors that the participant needs to attend to: the occurrence of the outcome (i.e. Light illumination) in the presence of the response (i.e. Button press) and the occurrence of the outcome in the absence of the response. Higher positive contingencies result when the outcome occurs at a higher rate in the presence of the response than in its absence (i.e. Button non-press). Negative contingencies are also possible where the outcome is less likely to occur in the presence of the response than in its absence (i.e. If pressed the button suppressed the illumination of the light). Consistent with the depressive realism effect, depressed individuals have been shown to more accurately make these kinds of judgments than non-depressed individuals. The attributional
style of depressive realism seen in patients is associated with abnormalities in fronto-temporal brain regions. Specifically, increased activation to self-serving judgments in these regions may reflect conflict associated with such attributions; this stands in sharp contrast to the increased responses of these same brain regions to non self-serving judgments in controls. Furthermore, as suggested by the preliminary results of the exploratory Psychopathic Personality Inventory (PPI) analysis, these changes may be related to alterations of fronto-limbic connectivity [279].

6.0 CONCLUSION AND FUTURE PERSPECTIVES
BPD has been studied extensively for many decades, and much is known concerning its effects, however, it remains a big challenge to unravel the comprehensive mechanism of action of the brain and its effects on the body. The challenge to biologist in the 21st century is to ensure that a revolution in understanding of the biology of bipolar disorder is translated into a revolution in clinical care. In the future, advances in neuroscience research may provide a better understanding of the underlying neurobiological states of mood disorders that will create a route for the causes of this disorder. Further investigation is needed to ascertain whether these creativity / realism are correlated with hypomania and depression. Identification of genetic mechanisms conferring susceptibility to bipolar disorder will, of course, be a major achievement. However, this will not be an end in itself, but rather the beginning of a path that will lead towards an understanding of the biological underpinnings of bipolar and related mood disorders. Finally, it is my personal belief that BPD may be passes through a horizontal behavior transfer and in those who have a high level of genetic susceptibility risk. Importantly, identification of bipolar susceptibility genes will facilitate identification of environmental factors that confer risk or are protected, both in people who are not genetically susceptible. Once these environmental factors are characterized, it may prove possible to provide helpful occupational, social, and psychological advice to those at genetic risk of bipolar disorder.

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