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## **Biomarkers of bipolar disorder: specific or shared with schizophrenia?**

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### **1. ABSTRACT**

Kraepelin's observations of the differences in the course and outcome of dementia praecox and manic depression fundamentally influenced thinking about bipolar disorder (BP) and schizophrenia (SZ) for over a century. In modern times, there is increasing awareness that a greater understanding of the similarities between these two highly prevalent and disabling conditions can teach us as many lessons about the pathophysiology of severe mental disorders as does the pursuit of differentiating factors. We review publications on developmental, genetic, epidemiological, and outcome research that challenges the Kraepelinian dichotomy. We highlight the increasing evidence of the overlap in genetic susceptibility. Neuro-developmental studies provide evidence of shared early pathological processes, whilst neurophysiological investigations also suggest that different genes may have a role in the development of both phenotypes. There is also evidence of overlapping neurocognitive phenotypes. It has become increasingly clear that a simple binary classification of these disorders represents an oversimplification. It may be more apposite to think in terms of genetic influences on six continuous symptom dimensions: neurobiological, cognitive, positive, negative, depressive and manic symptoms.

### **2. INTRODUCTION**

"It is becoming increasingly obvious that we cannot satisfactorily distinguish these two diseases (dementia praecox and manic depression)." Emil Kraepelin, 1920.

Schizophrenia (SZ) and bipolar disorder (BD) are frequently occurring conditions that are recognized as leading causes of lifetime disability (1). Both disorders are characterized by abnormalities of thought, behaviour, cognition and mood. Based on careful clinical observations of differences in the clinical course and outcome of psychiatric cases presenting to asylums over a century ago, Kraepelin distinguished dementia praecox from manic depression. The separation of these two major mental disorders has cast a long shadow over psychiatry that has continued to shape but also to distort views about the classification of mental disorders up to the present day (2). However, what is often overlooked is that Kraepelin was also the first 'scientist-practitioner' to recognize the overlap and similarities in the presentation and clinical course in many cases of SZ and BD- an observation that we will discuss in the following review.

There are several well-established arguments that have been used to continue the support of the traditional Kraepelinian dichotomy. For example, clinical descriptions indicated distinct phenomenology's and treatment outcomes such as the recurrent nature of affective disorders and the evidence of efficacy of antidepressants in depression and mood stabilizers in BD, compared with SZ, which is characterized by specific positive and negative symptoms, cognitive decline and response to treatments such as antipsychotics (which are mainly efficacious for positive symptoms).

Some research also suggests that there are differences between SZ and BD on structural and functional neuro-imaging and neurocognitive assessment batteries (3) (4) (5). However, diagnostic classification systems are clearly inspired by the Kraepelinian dichotomy, and so for the most part, researchers have approached the disorders as distinct entities with assumed different aetiologies. Insel and others (6) have promoted the need to rethink investigative approaches and examine evidence of deficits or abnormalities in different research domains (eg cognitive, neuro-endocrine, neuro-imaging studies) to build a dimensional picture of clinical presentations. This strategy helps clinicians identify similarities as well as differences between disorders and is in keeping with emerging research such as the family genetic studies of Lichtenstein and colleagues (7). This review highlights important overlaps between SZ and BD that suggest the need to reflect on the utility of the Kraepelinian dichotomy in contemporary clinical and research practice.

### **3. THE KRAEPELINIAN DICHOTOMY REVISITED**

Several observations challenged the Kraepelinian dichotomy such as diagnostic instability in both disorders, frequency of schizo-affective cases, familial co-aggregation and efficacy of new antipsychotics in both disorders. In addition, dissatisfaction with the Kraepelinian dichotomy in research has also been growing and recent evidences from developmental, genetic, cognitive, neuro-imaging suggest that the two diseases have much more in common than was previously thought. Finally, the “outcome” criteria that was supposed to discriminate between SZ and BD has been challenged by recent follow up studies that show that poor prognosis is not constant in SZ patients (8) and that for BD is not as good as previously thought (9).

#### **3.1. Family, high risk and twin studies**

Family, high-risk, and twin studies provide evidence for the existence of both shared and specific vulnerabilities to SZ and affective psychosis (10) (11) (12).

With regard to family studies, the Roscommon study showed clear co-aggregation of the two disorders suggesting that the familial vulnerability to SZ was at least in part a liability to develop psychosis in general (13). The Mainz study showed an increased risk of unipolar depression in the relatives of schizophrenic patients (14). A Danish population-based study (2.1 million subjects) showed that the risk of BD was associated with a history of BD (OR=13.6) as well as SZ or schizo-affective disorder (OR=4.2) in parents or siblings (15), again suggesting the existence of both shared and specific vulnerabilities to SZ and BD. However, the architecture of familial risk factors remains complex. Indeed, relatives of SZ patients have an increased risk for both disorders with a higher risk for SZ (10%) than for BD (8%) and relatives of BD patients have an increased risk for both disorders with a much higher risk for BD (10%) than for SZ (3.5%) (15). This is also illustrated by a recent family study that examined the prevalence of psychiatric disorders in the first-degree relatives of a sample of 103 inpatients with severe and chronic BD and in a matched control sample of 84 healthy individuals. The relative risks were 14.2 for BD and 4.9 for SZ. Furthermore, the presence of more than one patient with BD in a family increased the risk for SZ nearly fourfold (relative risk 3.5). Altogether, these results suggest that BD, characterized by a high familial loading, is associated with increased risk of SZ in the relatives (16). Perhaps the most important study to date was published by Lichtenstein *et al* (2009) (7) who identified more than 9 millions individuals in more than 2 million nuclear families in Sweden and investigated (1) the risks for SZ, BD for biological and adoptive parents, offspring and (2) the genetic and environmental contributions to liability for SZ and BD. Shared genetic effects for SZ that were in common with BD accounted for 52% of the genetic variance in SZ and for 69% in BD. Finally, the Roscommon family study also showed that the relatives of probands with nonpsychotic BD did not have an increased risk for SZ (13).

A 25-years follow up study of high risk subjects indicated that the risk of SZ (and related psychosis) and affective psychosis was increased both in subjects at risk for SZ and in subjects at risk for affective disorder (17). However, the risk of non-psychotic affective illness was not elevated by comparison with the control group and not different in the two high-risk groups.

Twin studies also provide important evidence for both common and syndrome-specific genetic contributions to the variance in liability to SZ and BD. Indeed, the Maudsley Study that included all psychotic twins for over four decades also suggested the existence in such individuals of a predisposition to psychosis in general, as well as specific genetic factors for each syndrome (18). The study of this cohort also indicated that vulnerability to schizo-affective disorder was shared with SZ and BD showing a degree of overlap in the genetic and non genetic familial factors contributing to both disorders (19).

The interpretation of family and twin studies remains difficult due to heterogeneity of the groups compared in terms of the number of the family members available, their age at interview, other not controlled disease risk factors, and the correlations between measurements (due to the family members being related to each other) that influence the calculation of a morbid risk. Although many studies use sophisticated statistical approaches to minimize biases, these analyses performed in the context of diagnostic uncertainties and diagnostic instability between SZ and BD, mean that co-aggregation studies in SZ and BD could provide spurious evidence for familial co-aggregation (20) (21).

#### **3.2. Molecular Genetic studies**

The evidence obtained of this strong family heritability in SZ and BD, much work has been done to identify susceptibility genes (22). Several well-established linkages have emerged in both disorders (for review (23)). Recent findings emerging from molecular genetic studies show increasing evidence for an overlap in genetic liability across the traditional binary classification. Indeed, linkage studies and Genome Wide Association Studies (GWAS) have identified several overlapping regions of interest in both SZ and BD, including several regions on chromosome 1q, 13q, 22q, 6q, 8p and 18 (24) (12) (25). Interpretation of overlaps in linkage studies of different syndromes are sometime difficult due to the size of the overlapping region identified by the linkage signal and statistical evidence for significant co-occurrence remain difficult to obtain. Interpretations of GWAS are also difficult with regard to the “common liability” hypothesis as these studies may identify single nucleotide polymorphisms (SNPs) that turn out to be associated to both syndromes or may reveal the existence of different SNPs in the same gene to be associated with each disorder.

Despite those methodological issues, additional evidence validates shared genetic susceptibility with genetic analyses of schizo-affective disorder which identified similar regions that SZ and BD have in common (26) suggesting that the pathophysiological processes involved in schizo-affective disorders correlate with those involved in both SZ and BD. The candidate gene approach provided a major contribution to this debate as polymorphisms of genes located in these “common” regions showed replicated association with both syndromes as well as association with schizo-affective disorder. Current evidence supports such hypothesis for DAOA (G30/G72) gene on chromosome 13q22-34, DTNBP1 gene on chromosome 6p22, NRG1 gene on chromosome 8p12, DISC1 gene on chromosome 1q42, COMT gene on chromosome 22q11 and to a lesser extend the BDNF gene on chromosome 11p13.

Consistent association and linkage results have been obtained between DAOA gene polymorphisms and SZ, BD and schizo-affective disorder (27) (28) (24) (29) (30), but the data as they stand do not support that variations on DAOA increase the susceptibility to these syndromes per se. Instead, DAOA/G30 influences susceptibility to major mood episode across the classical SZ and BD diagnostic categories (31). Similarly, DAOA/G75 seems to be associated with psychotic symptoms in both categories (32) (33). A quite similar picture has been obtained with the DTNBP1. This gene polymorphism has been associated with psychotic features (34) and with negative symptoms rather than with the full syndrome (35). Strong evidence for linkage and association with the NRG1 gene polymorphism has been obtained in SZ (review (36)). Of interest is the fact that association between this gene polymorphism and BD has been reported, in particular in the subgroup of patients with psychotic features, as well as in the subgroup of schizophrenic patients who experienced mania (37). Recent studies reported association of two NRG1 haplotypes with SZ and BD in a Scottish case-control sample, but those findings need further studies since it wasn't wholly replicated in a second sample (38) (39).

The DISC1 gene shows the strongest evidence for influencing the susceptibility to both SZ, BD and schizo-affective disorder (40) (41) (42) (43) (44). In addition, association studies and gene expression analyses of the DISC1-interacting molecules, pericentrin 2 (PCNT2) and DISC1-binding zinc finger protein (DBZ), showed association with both SZ and BD (45). Further, GWAS analysis in SZ and BD found significant association evidence for polymorphisms in CACNA1C gene (46) (47). Findings with CACNA1C gene polymorphism suggested that the subphenotype of BD with psychosis may represent a clinical manifestation of shared genetic liability between BD and SZ (48).

Results obtained with the COMT gene polymorphism show evidences for association and linkage with SZ and BD (24) (28) (26) (49). But these results do not support a simple role for this gene and an effect on the bipolar and schizophrenic phenotype (“phenotype modifier”) rather than on the susceptibility to these disorders is likely. Indeed, an association between the functional Val/Met polymorphism of this gene and cognitive frontal lobe function have been reported and has been recently replicated in the two syndromes showing an association between the functional Val (158)Met polymorphism and working memory performance, with a particular vulnerability of SZ but not for BD subjects (50). In addition, the shared phenotype between SZ and BD associated with this gene is not yet identified, however a study found that the COMT Val allele was associated with greater positive symptomatology in SZ, whereas Met homozygosis was associated with greater positive symptomatology in BD (51). These findings support that the COMT Val158Met polymorphism is conferring vulnerability for different clinical phenotypes in SZ and BD. Association and linkage with the BDNF gene polymorphism have also been reported, in particular with depression in SZ as well as rapid cycling in BD (52) (53). Evidence of an association between BDNF and BD and SZ has been recently confirmed (54).

Results favouring the implication of common genetic variants in the susceptibility to BD and SZ emerged from disease-specific genome-wide association study (GWAS) but also from meta-analysis in pooled samples. Mühleisen *et al* found that a common variation in the gene neurocan (NCAN, rs1064395), which confers risk for BD, was significantly over-represented in SZ patients (55). Moreover, association between ZNF804A gene (encoding zinc-finger protein 804A) and both SZ and BD was found (56). Finally, the frontotemporal lobar degeneration risk gene progranulin (GRN) was analysed in both BD and SZ patients showing that GRN variability decreases the risk to develop both disorders (57).

Although both disorders are complex and multifactorial models to test the contribution of polygenic variations have not been published until recently. Of interest is the recent work performed by the ISC (International Schizophrenia Consortium, (58)) that provide evidence for a common polygenic component in SZ and BD.

Beyond molecular genetics, the field of biomarkers in psychiatry has been enriched by approaches using molecular non-genetic markers. This approach aims at the identification of distinct molecular signatures in peripheral blood of patients and has particularly focused on peripheral gene expression or serum-based biomarkers (59) (60). The objective is to increase knowledge of the pathophysiological determinants of SZ and BD targeting molecular alterations that are thought to reflect the interaction between the underlying genetic predisposition and the environmental influences. For example, multiplex immunoassay analyses were carried out using serum from BD and SZ within 1 month before first symptoms of both disorders, and found shared but mostly distinct serum alterations in SZ and BD (60).

In summary, molecular genetic findings strongly support genetic factors conferring susceptibility across a BD-SZ continuum. Results indicate that these polymorphisms may act as common vulnerability factors for the syndromes or as phenotype modifiers. None of the genes presented in this review has a specific risk variant replicated but potential effect on different aspects of psychopathology is likely. It also turns out that some genes may have a predominant effect on the “BD” phenotype (such as DAOA and BDNF), other on the “SZ” phenotype (such as DTNBP1) or on a “schizo-affective” phenotype (such as DISC1 or NRG1). Then, this is probably the very beginning of the story and the data should be interpreted with caution both for the implication on psychiatric nosology and to elucidate the pathophysiological pathways of these syndromes. But it has become increasingly clear that the genetic data showed an overlap between the two diseases and are not compatible with a simple dichotomy of disorders.

### 3.3. Neuro-developmental studies

Several lines of evidence support the neuro-developmental hypothesis of SZ and BD where both diseases can be considered as pathophysiological processes starting early in life and resulting in pathological conditions during adulthood. This field of research also provided evidences of shared early pathological processes. As reviewed previously, the implication of common genetic vulnerability factors that may act early during development, event during foetal life, is consistent with this hypothesis. These common risk factors may have unspecific effects on the vulnerability to both syndromes. Developmental risk factors such as prenatal maternal nutritional deficiency (61), season of birth (62), urbanity (63) and obstetrical complications (64) (65) have long been demonstrated in SZ. Of interest is that the implication of these factors has also been suggested in BD such as prenatal malnutrition (66), neurological soft signs (67) (68), urbanity (69), pregnancy and obstetric complications (70) (71) and the same deviation on season of birth as the one observed in SZ (71). Most of these studies also indicate a gradient of severity of these development risk factors with a smaller effect size in BD by comparison with SZ, suggesting a continuum of severity between non affected and SZ, BD being an intermediate pathological condition (71) (69) (72) (73). Birth cohort studies also indicate that premorbid functioning during childhood was impaired in both disorders, but again the effect size was larger in SZ by comparison with affective disorders (67) (68). The neurodevelopmental models of SZ and BD also include specific hypotheses regarding disruption of foetal development by prenatal maternal infection. A number of studies have suggested that exposure to infections, such as toxoplasma gondii or herpes simplex virus, as a risk factor for the development of both SZ and BD (74–76).

The classical Kraepelinian view suggesting that SZ was associated with a poorer outcome by comparison with affective disorder have also been revisited and recent studies show that poor outcome is not a rule during SZ (77) and that significant proportion of BD patients have a poor outcome (9). However, it should be acknowledged that many of the studies purporting to study BD often included significant proportions of cases with affective psychosis. This means that studies that show shared risk factors for the development of SZ of BD (eg research on obstetric complications), need to be reviewed carefully to ascertain whether they are reporting risk for psychotic symptoms or shared risk for different diagnostic syndromes.

### 3.4. Neuro-imaging studies

#### 3.4.1. Structural neuro-imaging studies

There is compelling evidence for the existence of brain structural abnormalities in both SZ and BD (78). Recent meta-analysis of De Peri *et al.* shows significant overall effect sizes for intracranial, whole brain, total grey and white matter volume reduction as well as for an increase of lateral ventricular volume at disease onset for both BD and SZ. This study is important as it suggests overlapping brain abnormalities are already present at the onset of both diseases (78). However, both disorders may present neurodevelopmental specificities as whole grey matter volume deficits and lateral ventricular enlargement that appear to be more prominent in first-episode SZ, whereas white matter volume reduction seems more prominent in first-episode BD (78). BD in comparison with SZ is associated with smaller lateral ventricular volume and enlarged amygdala volume (79). SZ seems to be characterized by progressive global cortical losses (80) (81) whereas in BD, cortical volume losses are more focused and mostly located in prefrontal cortex and cingulate (82). Genetic risk for BD and SZ are associated with specific grey matter but generic white matter endophenotypes that confirm a more complex picture than a simple Kraepelinian dichotomy (83).

Regarding subcortical structures, structural studies tend to show a decreased volume of the striatum, thalamus, hippocampus, parahippocampus, and amygdala in SZ (84) (82). These modifications are usually not observed in BD in which

some structures implicated in mood regulation such as the limbic system may be increased in volume. More specifically, the pattern of amygdala volume increase seems specific to adult BD patients (85).

For white matter, patients with SZ exhibit a fronto-temporal anatomical disconnection when studied by diffusion tensor MRI (86), while BD is characterized by abnormalities in prefrontal-subcortical networks (87) (88). But, while genetic risks for SZ and BD are associated with different grey matter changes, they share common white matter endophenotypes (83).

Altogether, the existence of both shared and specific anatomical biomarkers is likely. The interpretation of these data remains difficult due to the possible confounding effect of medication. Indeed, increased volume of some brain regions has been reported with the use of antipsychotics, which are prescribed in both diseases (89). Psychotic BD may also be a confounding factor but most of the grey matter structural differences between BD and SZ persist even if the bipolar group is restricted to patients with psychotic features (90).

### **3.4.2. Functional neuro-imaging studies**

The studies investigating resting blood flow in psychiatric patients using PET produced conflicting results, in particular with regard to the level of activation of the frontal cortex, both in SZ (91) (92) (93) (94) and BD (95) (96) (97). Thus, these studies failed to provide consistent evidence of differential (or similar) patterns between the two syndromes. Some data indicate that frontal blood flow may represent a state marker, with hypofrontality being associated with non-specific dimensions of depression and/or psychomotor retardation (98). Whilst most resting state PET studies in SZ indicated hypofrontality (99), studies in BD demonstrate discrepant results depending on the thymic state of patients: altered frontal blood flow in depression and subcortical increased blood flow in mania (100). Overall, uncontrolled clinical state as well as difficulties in controlling for cognitive activity during the assessment may account for these inconsistencies.

Functional studies undertaken during cognitive activation have produced more consistent findings. Despite the fact that there are very few direct fMRI comparisons between BD and SZ (due to the difficulty to design an activation task relevant for both disorders), fMRI studies of executive functions report large prefrontal activation deficits in SZ (101) (102) with more disparate findings in BD, depending on the clinical state: prefrontal hypoactivation is reported in euthymic BD and relative increases in BD depression (103).

Using facial emotion processing tasks, fMRI studies show a pattern of prefrontal cortical hypoactivation common in SZ and BD (104) (105). Subcortical hypoactivations are also observed in such studies (105), but patients with BD usually show subcortical, limbic hyperactivations (104).

Of interest is a recent study of Hulshoff *et al.* that investigated whether BD and SZ twins display overlapping abnormalities in brain structures and whether these are caused by shared genetic or environmental influences (106). Authors found that higher genetic liabilities for SZ and BD were associated with smaller white matter volume, thinner right and left parahippocampus, thinner right orbitofrontal cortex, and thicker temporoparietal and left superior motor cortices (106). Such a study helps demonstrating that brain structures are likely to reflect the influence of genetic liabilities and neurodevelopmental factors to determine a shared vulnerability between SZ and BD.

In summary, brain imaging studies remain inconclusive mainly because they have not been designed to specifically compare common or specific features of SZ and BD, but usually compare cases to controls. Most of our knowledge relies on the comparison of the results of studies of BD patients to studies of SZ patients. Another difficulty relies on the fact that brain imaging biomarkers appear to be largely influenced by several confounding factors such as the clinical state, medication, duration of the disease and age at assessment, IQ, that are difficult to control for (107).

### **3.5. Neurophysiological studies**

The existence of neurophysiological deficits in SZ has been the subject of substantial research efforts for last decades. Most of these deficits have been also demonstrated in unaffected relatives of SZ patients and frequently occur before the onset of the disease. Of interest, is that most of these deficits have also been evidenced in bipolar patients and their unaffected relatives. In particular, several abnormalities in information processing have been associated with the two potential biomarkers: Smooth Eyes Movement abnormality (SEM), P300-evoked response latency (108) and amplitude (109) P50 auditory-evoked response suppression (110) (111), prepulse inhibition (112) and a mismatch negativity paradigm (113). In addition, preliminary data suggest linkage between some neurophysiological biomarkers and genetic vulnerability factors. Altogether it represents a very encouraging area of research for the identification of valid endophenotype biomarkers shared by SZ and BD.

Smooth Eyes movement abnormality has long been demonstrated in schizophrenic patients (114) (115) (116) and their unaffected relatives (for review (117)). This abnormality is mainly observed in SZ patients with negative symptoms (118) (119) as well as their unaffected relatives (118). SEM abnormality has also been reported in patients with affective disorders (120) (121) (122) as well as in unaffected relatives of bipolar patients (120) (123). Significant linkages of SEM abnormality have been obtained by two independent studies on chromosome 6p21-23, a common susceptibility region for SZ and BD (124) (125).

Deficit in the inhibition of a positive evoked potential occurring 50msec after a redundant stimulus (named sensory gating P50 deficits) has been the subject of numerous studies in SZ and BD. In SZ a recent meta-analysis clearly demonstrates the existence of sensory gating deficits in patients (28 studies) and relatives (6 studies) (126). They also indicated that between studies differences in effect size may be related to true variability in the participants studied as well as testing procedures (126). Diminished suppression of P50 auditory stimulus response has also been demonstrated in BD patients characterized by psychotic features only (110) (127). Deficits in P50 suppression have also been reported in the relatives of BD probands with psychotic features (128) (129) (130). No significant influence of medications or clinical state on these deficits has been reported (131) (132) (133). After Freedman *et al.* (1997) (134) reported a linkage between P50 inhibition deficits and markers on chromosome 15q14, subsequent associations between polymorphisms (in particular in the promoter region) of the alpha-7 nicotinic cholinergic receptor subunit gene and both SZ (135) and BD (136) was reported. These results are consistent with several physiological (135) and pharmacological (137) (138) studies indicating the implication of low affinity nicotinic receptors in the P50 gating.

The startle reflex is known to be in the normal range in SZ patients, but they generally show a reduced inhibition associated with the prepulse in the prepulse inhibition (PPI) paradigm (for review (139)). Although influenced by drugs, the sensori-motor deficit observed in SZ appears to be a trait marker and is not related to their treatment or their clinical state. In addition PPI impairment has also been evidenced in non-affected first-degree relatives of SZ patients (139). PPI deficits have also been reported in remitted BD patients (140) (141) (142) and in relatives of BD patients (140) (143) (144). However, PPI impairment is possibly aspecific since reported in several other neuropsychiatric diseases such as obsessive compulsive disorder, attention deficit hyperactivity disorder, tic and Huntington disease (for review in (139)). Genetic studies of PPI deficits include several interesting findings. A missense mutation in the NRG1 gene has been associated with PPI deficit in SZ patients as well as in control subjects (145), consistent with the findings in NRG1 KO mice. Although preliminary, other interesting association results have been obtained with polymorphisms in COMT, DRD3 and DAT1 genes (146) (147) (148). In summary, PPI impairment is present in SZ and BP patients and their relatives. Dopamine-related genes (COMT, DRD3 and DAT1) as well as NRG1 gene may play an important role in PPI deficits. The significance of PPI deficits in other pathological conditions remains hypothetical and includes: general psychopathological marker, influence of psychotropic treatment and state marker.

In a classical oddball paradigm, the P300 component of evoked potential (amplitude and latency) has been studied as a potential biomarker of the vulnerability to SZ and BD. Both reduced amplitude and increased latency have been reported in SZ patients (149) (150). Although, this biomarker is influenced by state-related factors and treatments (150), it appears highly heritable (heritability estimates 50-60%) (151) (152) (153) (154), consistent with the finding that relatives of SZ patients also exhibit these deficits (155) (156) (157). Although BD has been less well studied in that regard, bipolar patients and unaffected relatives present with the same patterns of deficits (reduced amplitude and prolonged latency) (158) (159) (109) (160) (161). Only one study reported differences between SZ and BP patients in the topography (109). Of note associations between P300 characteristics and several dopamine-related genes including DRD2, DRD3 and COMT have been reported (162) (163) (164). DISC1 and DISC2 genes have also been implicated in P300 characteristics in patients with SZ or BD (165).

In summary, neurophysiological studies have produced promising results. Several neurophysiological deficits are both observed in SZ and BD. These deficits are stable, independent of state-related factors and also present in unaffected relatives. Most of these neurophysiological biomarkers are heritable and for some of them association with candidate genes have been reported. Thus neurophysiological investigations suggest that numerous genes may have a role in the development of shared endophenotypes between SZ and BD. Those findings are also consistent with a multifactorial origin of both disorders. For example, as previously stated, it can be hypothesized that some genetic factors favor negative symptoms with specific neurophysiological deficits, whereas other underlie psychotic features.

### 3.6. Cognitive studies

We have reviewed evidence suggesting that organization of brain anatomy show neurodevelopmental deficits both in BD and SZ. Genetic influence in both disorders is likely to impact both structural and functional aspects of brain systems in ways that increase risk for the disorders. These may result in a cascade of events that manifest across a wide range of neurocognitive and affective abilities such as attention, executive function, working memory, affect regulation, affect-cognition integration, declarative memory, spatial processing, and psychomotor function (166). Those potential biomarkers may help to uncover vulnerability genes and to resolve questions about the etiology of both disorders. Further, the established heritability of cognitive abilities and the availability of highly reliable procedures to assess cognitive skills highlight the potential for cognitive measures to be appropriate endophenotypes in BD and SZ (167) (168). Many candidate vulnerability markers identified in SZ and BP are neurocognitive and those in common are likely to be useful for future share genetic research (166).

Neuropsychological deficits are recognized as a “generalized deficit” in SZ, thus characterized by impairments in a wide range of cognitive abilities (169) (170). Deficits are present during the first episode of psychosis and do not worsen dramatically during the illness course, even during acute episodes of psychosis (169) (171). For BD patients, cognitive functioning is often impaired even in inter-episode euthymic states (172). Cognitive deficits in BD are characterized by generalized moderate level of neuropsychological impairment with deficits in some specific domains such as attention, executive function, and to a lesser extent verbal memory and spatial working memory (173). Results also show that a subset of these deficits moderately worsens during acute disease states in BD (172). Meta-analysis revealed worse performance for SZ than BD

in 9 of 11 cognitive domains (5). This is particularly true for premorbid and current intelligence quotient and also perhaps attention, verbal memory and executive functions (174). However, shared pattern of deficits has also been suggested (174) (175). In addition, neuropsychological performance appears over time to be less stable in BD compared with SZ (176). Psychiatric symptoms seem to have a larger impact on test performances in BD than in SZ patients, so level of acute psychopathology, number of episodes (especially of mania) and the influence of comorbidities (such as substance misuse) may also influence the level of cognitive performance and nature of long-term deficits in BD (177). This is also consistent with the hypothesis that cognitive deficits are sequelae due to major thymic episodes' neurotoxicity. Additional reports of improved performances (nonverbal memory, executive function, and sustained attention) after clinical stabilization in BD patients support this hypothesis (178) (179) (180). Cognitive deficits in SZ appear to be relatively stable, generalized, long lasting from illness onset and persisting after clinical stabilization in first-episode patients (177). Bora *et al.* provide interesting negative results from a meta-analysis comparing cognitive functioning across SZ, schizoaffective disorder and affective psychosis that did not show clear differences between SZ and other groups (181). Same authors in a supplementary meta-analysis showed that the pattern of cognitive impairments in affective psychosis was relatively more pronounced but common to euthymic patients with BD (182). Lastly, Bora *et al.* concluded that schizophrenic cognitive impairments are not specific and thus cannot differentiate the major psychosis and do not help in discriminating SZ from BD and affective psychosis (183).

Affective and social impairments have long been considered core characteristics of SZ. However, affective and social cognition studies show similar levels of dysfunction between both disorders for response to interpersonal stressors (184) (185) (186) and social activity (187). Poor premorbid social functioning in adolescence is associated with both disorders, with minimal differences for participation in social activities or frequency of social relations after illness onset (188). Studies of social cognition also show shared impairments in social knowledge (189) and social problem solving (190).

However, overall SZ patients display greater levels of dysfunction than BD patients in the expression of anhedonia, when decoding facial expression or emotional cues in the prosody of speech (166). Therefore, these cognitive domains can't be considered as illness-specific phenotypes to date. In addition, in patients with SZ, schizoaffective disorder and BD, differences on physical anhedonia (higher scores in SZ) but not on social anhedonia were found (191) (192) (193). One study found deficits in facial affect matching in BD euthymic sample (194). Further, a recent study compared visual scanning of facial images between SZ and BD probands; which is widely reported to be abnormal in SZ. Emotional perception in SZ and BD showed no difference in eye movements when visually scanning the facial stimuli (195).

Therefore affective and social impairments have long been associated to SZ, several studies suggest deficits in BD too. Thus, even when measuring a dimension widely believed to separate the disorders, such as the nature of affective disturbances, the Kraepelinian dichotomy is less clear than previously assumed.

The neuropsychological differences reported between both disorders could be due to the presence of psychotic features, to environmental factors or to differences during the neurodevelopmental phase (174). On the other hand, the presence of psychotic symptoms may also play a role in determining the severity and stability of cognitive deficits in BD as in SZ (196). Indeed, several recent investigations have reported that psychosis in BD is associated with more severe neuropsychological dysfunction compared with patients with no history of psychosis (166). In addition, subgroups of BD patients with psychotic symptoms displayed a neuropsychological profile qualitatively more similar to the profile of SZ patients (197) (198). Moreover, a similar pattern of cognitive impairment has also been observed in people with psychotic depression with dramatic differences in performance between the patients with psychotic depression and those with nonpsychotic depression (199). There appear to be parallel cognitive impairments in several disorders that can be associated with psychotic symptoms: SZ, schizoaffective disorder, BD, and psychotic major depression (200). A recent study also demonstrates that neurocognitive impairments in memory, executive functioning and language are common in individuals with first-episode psychosis (201). Altogether, these findings point to a marked distinction in neurocognitive function associated with the expression of psychosis and the lifetime presence of psychosis appears to be a key contributor to cognitive dysfunction, which is independent of affective symptoms (166). Early in their course, cognitive deficits are present in all psychotic disorders but are more severe and pervasive in SZ than BD and mania (202). Therefore, some suggest that psychotic disorders should be conceptualized as being on a continuum rather than as a group of categorically distinct illnesses (175). The same authors support the notion that BD and SZ show phenotypic similarity in terms of the nature than severity of their neuropsychological deficits (175). Determining the degree to which the risk for psychosis (with possible shared genetic vulnerability factors) accounts for overlapping patterns of neuropsychological dysfunction across those disorders is a key challenge for the future. As neurocognitive dysfunction is among the strongest predictors of clinical and functional outcomes in patients, efforts to better detect and treat these deficits, which have shown promise in SZ, should be extended to all patients with psychosis (197), even though it is possible there is a different genesis of cognitive deficits in the two disorders. Cognitive dysfunctions in SZ are very likely to be neurodevelopmental as they present in childhood and detectable premorbidly (169). On the other hand, BD (especially non-psychotic BD) shows less impairment premorbidly with clearer deficits emerging over time probably indicative of neuroprogression with the toxic effects of mania being particularly associated with cognitive impairment (203).

Studies of unaffected first degree relatives have been employed to try to minimize the effects of confounding factors such as medication, psychiatric comorbidities or residual symptoms that pollute cognitive measures in euthymic bipolar patients.



First-degree relatives share, 50% of their genes with probands thus it is expected that some unaffected relatives would also present with vulnerability characteristics including neurocognitive impairments. Neuropsychological dysfunction in BD probands and their unaffected relatives share similarities with SZ probands and their unaffected relatives (166). Keri *et al.* (204) observed verbal recall deficit in unaffected siblings of both BD and SZ patients, suggesting a common impairment of the fronto-hippocampal system. Whereas impairments in general intelligence, working memory, verbal fluency, reasoning, or abstraction distinguished the siblings of SZ patients from the siblings of individuals with BD (204), BD patients and their unaffected relatives were comparable to healthy controls on several executive function tests. The only exception may be a possible enhanced susceptibility to interference and reduced inhibition in the relatives of both BD and SZ patients (205). The authors suggest that susceptibility to interference and reduced inhibitory processing could be a transnosographical markers of shared familial vulnerability to both disorders (205). Moreover, similar memory impairments in SZ and BD probands were reported in unaffected relatives (206). A recent study of BD I patients and relatives from families with or without SZ or schizoaffective disorder lead to further explore the links between psychosis proneness and cognitive profile (207). The authors show that impaired psychomotor processing speed and executive functions may represent markers of susceptibility to BD I irrespective of psychopathology within the family (207). They suggest that generalized impairment in verbal memory may be more specifically associated with BD. Performances in attention regulation, working memory, episodic memory, and emotion processing offer potential for identifying shared neurocognitive phenotypes for SZ and BD. However, much less studies have evaluated neurocognitive dimensions in BD unaffected relatives, and systematic investigations of unaffected relatives of both disorders are still needed.

To conclude, evidence for shared neuropsychological deficits between BD and SZ are substantial whereas evidence for the existence of specific dysfunctions in each disorder is relatively sparse. Cognitive dysfunctions in SZ are very likely neurodevelopmental whereas deficits in BD are partly explained by neuroprogression and/or the presence of psychotic symptoms. Available evidence in both disorders (probands or their unaffected relatives) may help to identify shared and illness-specific phenotypes, although evidence for cognitive dysfunction as a marker of familial vulnerability is stronger for SZ than for BD (208). Bora *et al.* suggest the inclusion of cognitive impairment criteria in DSM-V would not provide a major advance in discriminating between both disorders and affective psychoses and propose to consider cognitive impairment as a specifier and to define cognitive impairments as a dimension within a hybrid categorical-dimensional system (183).

#### 4. SUMMARY AND PERSPECTIVE

Hypotheses on a more direct association between related genetic characteristics and biomarkers, such as neurophysiological measures and cognitive processes, compared with the clinical expression, has generated enthusiasm and has stimulated the development of precise, reliable and accurate measures of candidate phenotypes in each disorder. The developing evidence-base has drawn attention to shared aspects of psychopathology, neurobiology, and mechanisms of treatment efficacy across the BD and SZ disorders. Genetic linkage findings offer a further challenge to the traditional Kraepelinian model of two distinct disorders, as they do not fully separate the vulnerability to each disorder. Thus, empirical support for a common pathogeny comes from genetic studies demonstrating shared genetic susceptibility. These shared genetic factors appear to be more common in psychotic BD patients and their family members, suggesting that psychosis-proneness may represent the phenotypic expression of this common physiopathology and symptom dimension. However, as most research is conducted on individuals who have crossed the 'diagnostic threshold' for caseness, these shared markers could of course represent trans-diagnostic predictors of poor outcome. To date, unequivocal support for a shared phenotype approach in psychiatric genetics remains absent and needs further investigation.

The traditional dichotomous classification has formed the foundation of contemporary diagnostic systems. This has profoundly influenced conventional approaches to psychiatric research that usually proceed under the *a priori* assumption that SZ and BD are separate disease entities with different underlying etiologies. However, whilst we of course acknowledge that evidence for important differences exists, this review of the evolving literature shows several key findings, emerging from different research areas that do not support this model. As stated by Craddock and Owen (209), it seems that psychiatry is « (entering) a transitional period of several years during which psychiatry will need to move from using traditional descriptive diagnoses to clinical entities (categories and/or dimensions) that relate more closely to the underlying workings of the brain »

Consequently, it may be more apposite to think in terms of genetic influences on continuous variations in six symptom dimensions: neurobiological, cognitive, positive, negative, depressive and manic symptoms (210). Therefore, rather than classifying patients into dichotomous categories of disorder, each patient can be described as having a unique combination of symptoms, which are the result of the effects of various risk factors operating across a psychosis and affective continuum. Thus both disorders can be integrated in a continuum of clinical expression that may express shared and specific vulnerabilities consistent with a multifactorial origin. Neurobiological and neurocognitive dysfunctions may represent symptom dimensions that spans diagnostic categories, and may reflect shared pathogenic processes. Figure 1 summarizes the possible clinical expressions of the simplified hypothesis of overlap between BD and SZ.

There are several implications of such dimensional models; especially for future research paradigms and future nosology (6). These theoretical models may help the exploration of pathophysiological mechanisms, whilst data on shared

phenotypes may help to resolve questions about the causal chain between gene expression and clinical expression. Gottesman and Gould (2003) proposed the use of endophenotypes (211) as a measurable component with a better phenotype/genotype correlation. It is supposed to have a simpler genetic architecture than clinical diagnoses themselves. Studying common endophenotypes may circumvent the limitation of Kraepelinian diagnostic system posed on BD and SZ. Meanwhile, the conceptualization of common endophenotypes does not contradict the existence of specific phenotypes and vulnerabilities for both disorders.

In conclusion, there is growing evidence that BD and SZ, rather than being wholly distinct disorders as in Kraepelin's earliest observational model, may share genetic risk at several loci. Further, there is growing evidence of similarity in the patterns of neurobiological and cognitive expression, which may be consequences of these common genetic factors. Initial findings of similarities across probands with BD and SZ as well as unaffected family members warrant further investigation as potential intermediate trait markers. Finally, a diagnostic classification system that incorporates dimensional elements of both disorders, and that is more inclusive than what is planned for DSM-V would help in the delineation of modern nosology, better inform the exploration of pathophysiological mechanisms and ultimately lead to advances in translational research with the discovery of new trans-diagnostic treatments and drug discovery.

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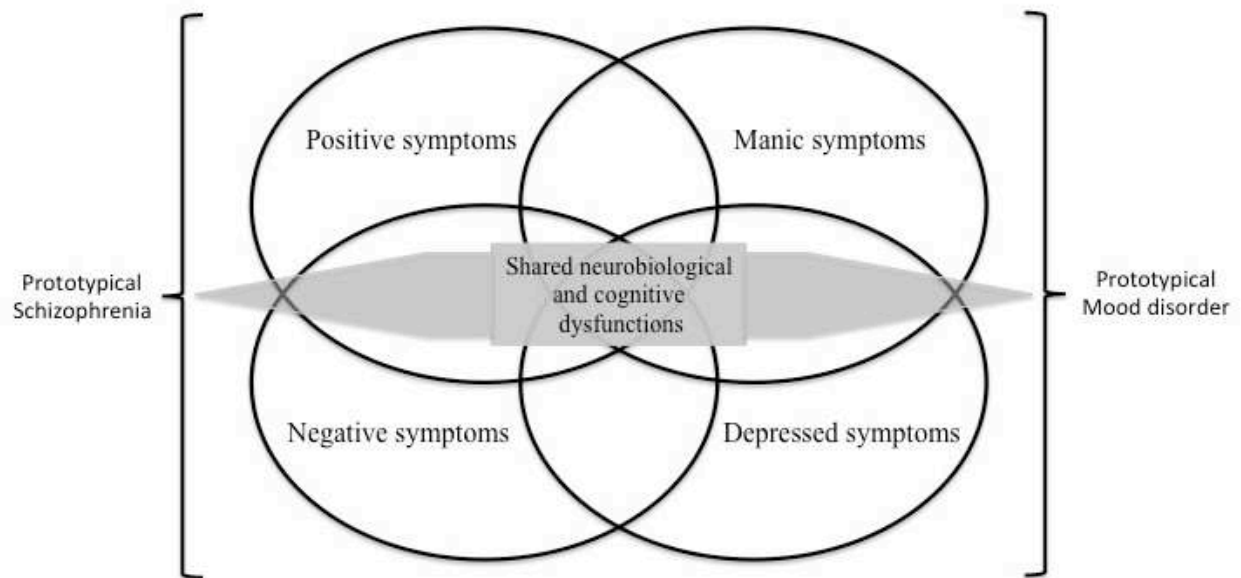
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**Figure 1.** Simplified hypothesis of overlap between Mood disorders and schizophrenia. This model proposes a dimensional approach of the traditional dichotomy between both prototypical mood disorder and schizophrenia based on six phenotypic dimensions: neurobiological, cognitive, positive, negative, manic and depressed symptoms. Most of the neurobiological and cognitive dysfunctions are shared and unspecific.

Running title: Markers in bipolar disorder and schizophrenia