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REVIEW ARTICLE

REVIEW OF EVIDENCE OF THE OVERLAP BETWEEN SCHIZOPHRENIA AND BIPOLAR DISORDER

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ABSTRACT

A basic view of medicine holds that if discrepant symptoms can be explained by one disease instead of two or more, it is likely there is only one disease. The scientific justification for bipolar disorder (BD) and schizophrenia (SZ) as distinctive disorders has been questioned. The diagnosis of schizophrenia rests upon the presupposition that the diagnostic symptoms are disease specific. They are not, since patients with severe mood disorders can demonstrate any or all of the schizophrenic symptoms. Furthermore, there is consistent evidence that genes contribute to the etiology of psychosis. Recent findings from genetic studies provide evidence for an overlap in genetic susceptibility across the traditional psychosis categories. Candidate genes show strong associations with component symptom complexes, such as psychosis, that are not projected directly onto Kraepelinian disease entities. In this paper we will review the literature that describes the possible relationships between bipolar disorder and schizophrenia.

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INTRODUCTION

Schizophrenia and bipolar disorders have been considered as two distinct disorders since Emil Kraepelin (1856–1926) divided psychotic illness into two diagnostic categories (Craddock and Owen, 2005). However, schizophrenia and bipolar disorders have a number of clinical, epidemiological features and shared susceptibility genes in common. So far it is still uncertain whether or not these two major psychoses are separate things or not. The challenge arises due to the presence of overlapping symptoms between schizophrenia and bipolar disorder. We present a review of the literature that describes the possible relationships between bipolar disorder and schizophrenia.

Psychopathological Features

Psychotic symptoms are common in both the manic and depressive phases of bipolar affective disorder.

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More than half of patients with bipolar disorder will experience psychotic symptoms in their lifetime. Grandiose delusions are the most common type of psychotic symptoms, however any kind of psychotic symptoms, including thought disorder, hallucinations, mood-incongruent psychotic symptoms, and catatonia could present as part of a manic episode. More than half of patients with bipolar disorder will experience psychotic symptoms in their lifetime (Keck, 2003).In a survey of symptoms by self-report screening scales, up to 90% of patients indicated that they experienced at least one psychotic symptom in their lifetime (Krishnan, 2005). Pope and Lipinski, 1978, summarized over 18 phenomenological studies and found that psychosis was present in 20% to 50% of patients with acute bipolar disorder. Similarly, Goodwin and Jamison, 1990, reviewed 26 studies of psychotic features in bipolar disorder and estimated that approximately 58% of patients with the illness had a lifetime history of at least one psychotic symptom (more often during manic rather than depressive episode). Importantly, these studies revealed that all types of psychotic symptoms occurred during bipolar mood episodes, including Schneider an first-rank symptoms which were previously believed to occur

exclusively in patients with schizophrenia (Azorin, 2007). Furthermore, Marneros *et al*, 2009 carried out a longitudinal study on 182 patients meeting the DSM-IV criteria for bipolar I disorders over a long period of time (16 years). During the investigated course (mean duration = 16.84 years, SD = 10.91), although 66% of the patients developed mood -incongruent psychotic symptoms at least once, the great majority of episodes did not show any mood -incongruent psychotic symptoms (MIS): Out of 1,539 episodes, 68% did not experience any MIS, whereas 32% did. In the group of patients who had MIS at least once ($n = 120$), when 1,003 episodes were assessed, there was no significant difference between those who did not experience MIS (518 = 52%) and those who experience them (485 =48%).They found that bipolar I patients with mood -incongruent psychotic symptoms differ from patients without mood -incongruent psychotic symptoms in the following domains:

- Gender distribution, 57% of all cases with MIS were found in males and 43% in females. In contrast, bipolar patients not having MIS were most often females (60%).
- Although the frequency of mental illnesses in the families of patients with mood-congruent is nearly the same as that with mood -incongruent psychotic symptoms (57 vs. 56%). The frequency of schizophrenia, however, is higher in families of mood-incongruent psychosis than that in the families of patients with mood-congruent psychotic symptoms. However, the significance is weak.
- It is very rare that the mood incongruent disorder manifests for the first time after the age of 55.
- Additionally, there are significant differences between the two groups regarding prognosis, especially disability and social consequences of the illness. One of the most robust indicators of disability and social consequences is the variable "disability pension" (as it excludes subjective estimations of the patients or subjective impressions of the investigator). Significantly more patients with MIS (63 vs. 48%) had to retire due to the mental disorder and also at a significantly younger age (approx. 37 years vs. approximately 45 years of age) than patients with mood-congruent psychotic symptoms.
- Significantly more bipolar I patients with mood incongruent psychotic symptoms had no stable heterosexual (or in very few cases a homosexual) relationship than patients with mood-congruent psychotic symptoms (45 vs. 24%). In spite of the fact that the mean age at investigation showed a statistically significant difference, albeit a weak one (50.72 vs. 46.4 years), this finding perhaps only relies on the patients' age, as in both groups the youngest patient was 21 or 22 years old i.e. suitable age for starting a relationship(Marneros,2009).

Finally, in his study on in 352 patients with bipolar I disorder participating in the Stanley Foundation Bipolar Treatment Network, Keck *et al*., 2003 reported that: Mood-congruent (grandiose, referential, and persecutory) delusions were the most prevalent presentations of delusional ideation. Mood-incongruent (bizarre and first-rank) delusions occurred in 29% of patients with psychotic features. Among patients with a history of psychosis, hallucinations occurred in 25% and were most commonly auditory or visual. Symptoms of catatonia, grossly disorganized behavior, and negative symptoms occurred in 21% of patients with psychosis. It has been estimated that 48% of patients who were experiencing a manic episode present with at least one delusion, 19% with one thought disorder (defined by the authors as "problems in the ability to attend, abstract, conceptualize, express or continue coherent thought") and 15% with one hallucination.

Risk factors for psychosis in bipolar patients

- Increased severity of the illness, the severer the core manic symptoms, the more prominent, the more bizarre and more frequent are the psychotic symptoms. (Harrow *et al*, 2000).
- Early age at onset of bipolar disorder is associated with a higher incidence of psychosis. However, early onset is not necessarily associated with a poor long-term outcome (Krishnan, 2005). The objective of the current analysis was to further explore the spectrum of psychosis in patients with bipolar mania. In the only study in an epidemiologically derived sample, Carlson *et al*. 2000, found that onset between 15 and 20 years of age of mania was associated with paranoid ideation in 100% of the sample and grandiosity in 74%, as compared with 80% and 74% respectively in the adult-onset group.
- Racial differences in symptom profiles suggest that black patients may demonstrate more severe psychotic symptoms, especially first-rank symptoms, as compared with whites (Strakowski, 1996).
- Family history of psychotic bipolar disorder, schizoaffective disorder or schizophrenia (Canuso, 2008).

Phenomenological Evidence Supporting an Overlap between Schizophrenia and Bipolar disorder

The most marked clinical feature shared by patients with Schizophrenia (SZ) and Bipolar disorder (BD) is psychosis. Psychotic symptoms, such as delusions, hallucinations, disorders of forms of the thought, and grossly disorganized or catatonic behavior, are major components in clinical characteristics of Schizophrenia. Additionally, some schizophrenic patients also present negative symptoms; including anhedonia (loss of interest or pleasure in daily activities) and avolition (lack of desire, or motivation to pursue meaningful goals). The conventional diagnostic criteria for BD are established based upon mood disturbances, i.e., mania and depression. For individuals diagnosed with bipolar affective disorder, their manic episodes may be dominated by psychotic symptoms. Previous studies have estimated that at least 50% of BD individuals have experienced at least one psychotic episode during their lifetime. Additionally, mood components may also be shared by individuals afflicted by SZ and BP (Hafner, 2005). Individuals affected by schizophrenia may also present affective disturbances that mimic depression and mania. Schizophrenic patients may exhibit reduced emotional responses or experience overly active and exultant feelings. Studies reported that the lifetime prevalence of depressive mood (lasting for at least 2 weeks) at first admission for schizophrenia is 83%. Additionally, during the first psychotic episode 71% of schizophrenic patients presented clinically relevant depressive symptoms and 23% were diagnosed with a depressive episode. In addition, anhedonia, one of the negative

symptoms inherent to schizophrenia, is also a symptom in depression. Romney and Candido, 2001, examined clinical symptoms in schizophrenia and major depressive disorder using factor analysis and found that anhedonia pertains to the domain of depression. Hence, differential diagnosis between schizophrenia and Bipolar disorder is required for individuals exhibiting negative symptoms such as anhedonia. Such overlap in symptoms has provided the first line of evidence for shared etiological components in SZ and BD (Lake and Hurwitz, 2006).

Pathophysiology: The thalamus is considered to play a crucial role in the pathophysiology of psychiatric illnesses such as schizophrenia (Andreasen, 1997) and mood disorders (Soares and Mann, 1997). The thalamus forms a variable gate of access for sensory information to reach the cerebral cortex (McCormick and Bal, 1994). Dysfunctional cortico-striato-thalamic connections and abnormal thalamocortical connections associated with schizophrenia were widely demonstrated (Andreasen, 1997; Woodward *et al*., 2012). Furthermore, schizophrenic patients show anatomic (Ettinger *et al*., 2007) and metabolic (Kim *et al*., 2000) thalamic alterations. In contrast to this, no abnormalities in thalamic size have been found in persons with bipolar or unipolar affective disorders (Mamah *et al*., 2010). Nonetheless, functional and neurochemical abnormalities in this brain region have been reported for individuals with bipolar disorders (Deicken *et al*, 2000). Alterations of pre-attentive sensory gating as reported in neurophysiological studies emphasize the central role of the thalamus in the regulation of cortical input. The prepulse inhibition has been shown to be abnormal in patients with schizophrenia and their relatives (Braff, 2010). The findings are not equally consistent for patients with bipolar disorder (Thaker, 2008). However, two studies reported an abnormal prepulse inhibition in patients with bipolar disorder (Perry *et al*., 2001) and their first-degree relatives (Giakoumaki *et al*., 2007), whereas Carroll *et al*. (2007) found no difference in prepulse inhibition between bipolar patients and healthy controls. Despite their advantageous high temporal resolution, electrophysiological studies of possible thalamocortical dysfunction in schizophrenia or bipolar disorder other than the startle response are rare. Later evoked potential phenomena have been studied more often than early ones, i.e., occurring within 50 ms after stimulus application (Shagass *et al*., 1977). However, early evoked potentials are less susceptible to changes by uncontrollable factors such as, attention, and their underlying neurophysiology is better understood than that of the later potentials (Buchner *et al*., 1995).

Finally, the findings of Hagenmuller *et al*., 2014 study suggest that the risk for schizophrenia, in contrast to bipolar disorder, may involve an impairment of early cerebral somatosensory processing. Neurophysiologic alterations in schizophrenia may precede the onset of initial psychotic episode and could therefore serve as indicator of vulnerability for developing schizophrenia. This study is the largest investigation of somatosensoryevoked potentials published to date, and the first in populations at risk for developing psychosis. The heterogeneity among studies and the lack of SEP studies comparing schizophrenia and bipolar disorder as well as the sparse studies comparing these populations on the risk level limit definitive conclusions from the literature to date.

Response to medications

Pharmaceutical managements may reveal the pathological mechanism of a disease. A small number of same classes of pharmaceutical treatments are possibly considered to treat the two disorders. The mechanisms of actions of these treatments may shed some understandings into the molecular basis for these 2 disorders. Atypical antipsychotics that target both the dopamine 2 (D2) and serotonin 5-HT2A receptors can be used to treat SZ. Lately, anti-psychotic agents have been increasingly prescribed to BD patients. The effects of these pharmaceutical combinations on SZ and BD suggest that dopaminergic and serotonic pathways are both involved in the pathogenesis of SZ and BD (Bowden, 2005).

Genetic Evidence supporting the overlap between Bipolar Disorder and psychotic spectra

Psychiatric research, including the search for predisposing genes, has tended to proceed under the assumptions that schizophrenia and bipolar disorder, as defined in Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, and International Statistical Classification of Diseases, 10th Revision, are discrete disease entities with distinct etiology and pathogenesis and that these disease entities can be identified by current "operational" diagnostic conventions. However, recent findings emerging from genetic studies show increasing evidence for an overlap in genetic susceptibility across the traditional binary classification of psychosis (Crow, 2007). The emerging evidence suggests the possibility of relatively specific relationship between genotype and psychopathology. For example, variation in Disrupted in Schizophrenia 1 (DISC1) and Neuregulin 1 (NRG1) may confer susceptibility to a form of illness with mixed features of schizophrenia and mania (Wolfgang Maier, 2008).

Family Studies: Many family studies have demonstrated that schizophrenia and bipolar disorder tend to "breed true". However, some studies have shown statistically significant evidence that bipolar disorder occurs at increased rates in relatives of probands with schizophrenia, and that schizophrenia occurs at increased frequency in relatives of probands with bipolar disorder (Valles, 2000). Moreover, schizoaffective disorder has been shown to occur at increased rates both in families of probands with schizophrenia and in those of probands with bipolar disorder, and both schizophrenia and bipolar disorder have been shown to occur at increased rates in families of probands with schizoaffective disorder. (Owen *et al*, 2007). This is supported by one of the largest family studies to date, which used the Swedish inpatient case register and obtained data on over 13 000 cases of schizophrenia and 5000cases of bipolar disorder. The cross-disorder incidence ratios were robustly increased in siblings and half-siblings for both schizophrenia and bipolar disorder (Ősby, 2001).

Twin Studies: Only one twin study has used an analysis that was unconstrained by the diagnostic hierarchy inherent in

current classification systems (i.e., the principle that schizophrenia "trumps" mood disorder in diagnosis). This study demonstrated a clear overlap in genetic susceptibility to syndromically defined mania and schizophrenia (Cardno *et al*, 2002). In addition to supporting the existence of some susceptibility genes that are specific to schizophrenia and others that are specific to bipolar disorder, it suggested that there are others that influence susceptibility to schizoaffective disorder, schizophrenia, and bipolar disorder. Data from twin studies have supported a genetic relationship between bipolar disorder and psychotic disorders. Cardno and colleagues (2002), applying nonhierarchical diagnostic definitions such that twins could be assigned lifetime diagnoses for more than one of these disorders, reported significant correlations in genetic liability among the three syndromes; the genetic correlations were 0.68 for schizophrenic and manic syndromes and 0.88 for schizoaffective and manic syndromes. The genetic liability to schizoaffective disorder was entirely shared with the two other syndromes. One possibility raised by these studies is that genes actually influence psychosis, a phenotypic feature common to schizophrenia and a subset of probands with bipolar disorder.

Linkage Studies: Genetic linkage studies have identified some chromosome regions that show convergent or overlapping regions of interest in both schizophrenia and bipolar disorder—including regions of 13q, 22q, 6q (Williams *et al*, 2003); and 18 (Berrettini*,* 2003). There are, however, difficulties in interpreting overlaps in linkage findings from different phenotypes because of the poor localization of linkage signals for complex disorders and difficulties assessing statistical evidence for significant co-occurrence. However, the hypothesis that loci exist that influence susceptibility across the schizophrenia-bipolar divide has recently received further support from a genome-wide linkage scan using families selected on the basis of a member with *DSM-IV* schizoaffective disorder, bipolar type. This study demonstrated genome-wide significant linkage at 1q42 and suggestive linkage at 22q11,with evidence for linkage being contributed equally by "schizophrenia "families (i.e., those where other members had predominantly schizophrenia)and "bipolar" families (i.e., those where other members had predominantly bipolar disorder) (Hamshere *et al*., 2005).

A sex chromosomal locus: There is, however, a genetic phenomenon that deserves more attention than it has so far received. This is the same sex concordance effect which was first reported for psychosis by Mott (1910), and is present in affective as well as schizophrenic psychoses. It is, consistent with a sex chromosomal locus, i.e., with X and Y linkage. Same sex concordance arises because when a sex-linked gene is transmitted from a father it travels either on his X chromosome or on his Y. If on the Y, it is transmitted to his sons, whereas if on the X it is transmitted to his daughters. Thus a tendency arises for the gene to be associated within families with sex of probands. If the gene is transmitted from the mother on her X chromosome it may travel either to sons or daughters, indicating that (at least with dominant transmission) same-sex concordance arises from paternal transmission. Although no genes for psychosis have been established through linkage studies, the tendency to concordance by sex for psychosis within families that applies to both affective and schizophrenic illnesses suggests a gene that is present on both X and Y chromosomes (Akiskal, 2007).

Studies of Individual Genes: Linkage studies can only provide at best indirect evidence for shared genetic effects. More direct evidence has come from reports implicating variation in the same genes as influencing susceptibility to both schizophrenia and bipolar disorder. In most cases the gene was first implicated in studies of schizophrenia, and the evidence in most cases is strongest for this phenotype. This could reflect the true contribution to the phenotype or may simply reflect the fact that substantially greater resources and samples have been used to date on studies of schizophrenia (Craddock *et al*, 2006). We will consider the evidence for each gene in turn.

NRG1: was first implicated in schizophrenia in the Icelandic population after a systematic study of 8p21-22 revealed association between schizophrenia and a multimarker haplotype at the 5'end of *NRG1*(Stefansson *et al.*, 2002). *NRG1* has notyet been extensively studied in bipolar disorder. However, many studies suggest that *NRG1* plays arole in influencing susceptibility to both bipolar disorder and schizophrenia and that it may exert a specific effect in the subset of functional psychoses characterized by both manic and mood-incongruent psychotic features.

***DISC1 (*Disrupted in Schizophrenia 1)**: *DISC1* is certainlyan interesting candidate gene for mental disorder. DISC1 SNPs Linked to Bipolar and Schizophrenia in Scottish Women. In a study of linkage disequilibrium in a representative sample of the Scottish population across the 510 kb of TRAX and DISC1, SNPs representing each haplotype block were selected for case-control association studies of both schizophrenia and bipolar disorder. Significant association with bipolar disorder in women P=0.00026 was detected in a region of DISC1. Only the association between bipolar women and DISC1 remained significant after correction for multiple testing (Hodgkinson *et al*., 2004).

DTNBP1 *(Dysbindin,* dystrobrevin-binding protein 1): *Dysbindin*was first reported by Straub *et al*, 2002in schizophrenia and now there is quite impressive support from a number of studies reviewed recently. However, Raybould and colleagues, 2005, reported the first study of single-nucleotide polymorphisms (SNPs) from dysbind in bipolar disorder. They found no significant associations in bipolar disorder as a whole but found modestly significant evidence for association in asubset of bipolar cases with predominantly psychotic episodes. This finding suggests that variation in dysbind in confers risk to some aspect of the psychotic syndrome rather than to the *DSM-IV* schizophrenia phenotype per se. Moreover, Breen *et al*, 2006, reported evidence for association with dysbidin SNPs in a small sample of bipolar patients, though no analyses stratified by phenotype were conducted.

G72 (DAOA)/G30: This locus was first implicated in studies of schizophrenia by Chumakov *et al*, 2002, who undertook association mapping in the linkage region on chromosome 13q22-34. This locus has been quite extensively studied in

bipolar disorder, for which it is now arguably the best-supported locus. Support for association with bipolar disorder has been reported from at least 5 independent datasets, and, as for schizophrenia, the presence of association is supported by meta-analysis without clear implication of specific alleles or haplotypes (Detera-Wadleigh *et al*. 2006). No pathologically relevant variant has yetbeen identified, and the biological mechanism remains to be elucidated. The current evidence supports these predictions: Neuregulin 1 and the gene product of G72/G30 (more precisely DAOA) are serving very different neurobiological pathways. Nevertheless, the proteins expressed by the two genes which operate most likely as susceptibility for schizophrenia as well as bipolar disorder have one functional target in common: the glutamatergic NMDA receptor and postsynaptic proteins of the glutamatergic pathway in the hippocampus. This structure and this region are apparently strongly involved in the pathophysiology of schizophrenia and also in bipolar disorder (Owen, 2003).

Post-mortem studies: Another target area is myelinizationand oligodendroglia which are under the control of neuregulin during development, whereas schizophrenia displays a reduced number of oligodendroglia (prefrontal) in post mortem studies, bipolar disorder does not reveal a changed number. However, an under expression of genes involved in myelinization was found for both disorders (Tkachev *et al*, 2003). On a macroscopic level a comparable mixture of similarities and dissimilarities between both disorders emerged from the single volumetric study considering schizophrenia and bipolar disorder compared to controls in the same study (McDonald *et al*, 2004).

One possible explanation of associated genetic markers between both diagnoses is mediation of these associations through the genetic determination of shared symptom patterns. Schulze *et al*. (2005) found that a single symptom "persecutory delusions" is significantly associated with specific genetic markers, but not any other symptoms which are going together with any of both disorders. "Persecutory delusions" are common in schizophrenia as well as bipolar disorders. However, a symptom-related association suffers from a lack of stability due to their reduced reliability and was not replicated by Williams *et al*., 2006.These authors found a cross-diagnostic association of the same genetic markers in the G72/G30 locus to major mood syndromes which are also common in schizophrenia (Lin and Mitchell, 2008). Such findings suggest an overlapin the biological basis of disorders. Current genetic findings suggest that rather than classifying psychosis as a dichotomy, a more useful formulation may be to conceptualize alternative categories ora spectrum of clinical phenotypes with susceptibility conferred by overlapping sets of genes (Craddock and Owen, 2005).

Cognitive functions impairment: Abnormalities in information processing associated with these 2 disorders include P300-evoked response latency and amplitude, P50auditory-evoked response suppression, prepulse inhibition, (Perry *et al*., 2001) facial scan path patterns, and a mismatch negativity paradigm (Loughland, 2002). Additionally, other cognitive function impairments, such as executive deficits, can be demonstrated in psychotic and bipolar disorder (Szoke *et al*. 2008). If an end phenotype is influenced more directly by genetic factors, one may expect to observe a higher heritability of an endophenotypecompared with its end-point disease. Take smooth pursuit eye movement (SPEM) as an example. SPEM refers to the movement of the eyes as they track a slowly moving target, a process that is initiated by visual processing of motion signals. One of the major SPEM sub-measurements, predictive pursuit gain, is highly heritable (heritability estimate = 0.90), (Hong *et al*., 2006) indicating that this trait is under substantial genetic control. Additionally, both schizophrenic patients and their unaffected relatives are more likely than healthy individuals to have deficits in SPEM, suggesting that this trait co-segregates with SZ and that deficits in SPEM are not secondary sequel occurring as a result of SZ. Moreover, individuals affected with BD and their relatives are also more likely to have deficits in SPEM compared with healthy individuals (Kathmann *et al*., 2003). Genetic analysis of SPEM-related phenotypes has provided further insights into shared genetic influences that might cut across different psychiatric diagnoses, including SZ and BD. For example, 2 studies have reported evidence for link age of SPEM phenotype to 6p23-21, suggesting that this chromosomal region may harbor one or more genes influencing variation in SPEM (Matthysse, 2004). Interestingly, the same region also harbors 2 genes previous associated with risk of schizophrenia, *ATXN1* (*SCA1*) and *NOTCH4*.

Endophenotypes and pathogenesis of SZ and BD: Other candidate genes associated with SPEM include dopamine D3 receptor gene (*DRD3*), *DISC1* (Hennah, 2005) and *COMT*. All these genes have also been hypothesized to play a role in the pathogenesis of SZ and BD. Taken together, these findings suggest that the study of common endophenotypes for SZ and BD, such as SPEM, may reveal insights into alleged etiologic factors linking these 2 disorders. Studying common endophenotypes may circumvent the limitation of hierarchical diagnostic system posed on SZ and BD. Meanwhile, the conceptualization of endophenotypes does not contradict the putative hierarchical pathological relationship between SZ and BD. Furthermore, endophenotypes can allow the investigator to examine the genotype-phenotype relationship in the same population. Conventional studies focusing on SZ and BD in different populations separately may produce findings that cannot be transferred to each other. Therefore, deciphering the genetics of common endophenotypesmay serve as an alternative and effective approach to untangling the mechanism of shared genetic liability for these 2 disorders. Goldman and Ducci, 2007 discovered a number of lociwith a greater impact on endophenotypes compared with relatedpsychiatric disorders, such as BD and alcoholism. However, one recent study compared the effects of genetic variants on severalendophenotypes and end-point diseases using the meta-analysistechnique and did not produce supportive evidence for this assumption. The investigators examined 7 different endophenotypes, such as "circadian rhythm" and prefrontal cognitive function, etc., as the endophenotypes for BD, and "spatial and verbal working memory" and "ventricular enlargement," etc., as endophenotypes for SZ. Their findings suggest that genetic contributions of the COMT gene Val/Met polymorphism to endophenotypes were notsignificantly different from those

effects on SZ or BD (Flint, 2007). Therefore, one needs to carefully evaluate the locus-specific genetic effect size of the endophenotype in order to unravel the joint genetic determinants for SZ and BD. Alternatively; investigators can use an endophenotype to selecta more clinically homogeneous subgroup of subjects for genetic studies. SZ and BD characterized by a shared endophenotypic feature may be regarded as subtypes of SZ and BD, respectively. Such an endophenotype-based approach may not only overcome the problem of genetic heterogeneity in each individual disorder but also enhance clinical resemblances for these 2 disorders and hence help identify the shared genetic variant of a possiblylarger effect. This approach may allow investigators to avoidthe concern that an endophenotype is not modulated by less complexgenetic factors than those associated with the risk of SZ or BD (Wolfgang Maier, 2008).

Pharmaco-genetic aspect of the monoamine (MA) neurotransmitters norepinephrine (NE), dopamine (DA) and serotonin (5-HT) play important roles in psychotic disorders. The availability of extracellular NE, DA and 5-HT is limited by presynaptically localized transporters, NET, DAT and SERT, respectively. Polymorphisms in monoamine transporter genes could influence transporter function in a variety of ways. Single nucleotide polymorphisms (SNPs) that substitute one amino acid for another (nonsynonymous) could alter expression levels by producing an unstable protein conformation, resulting in retention in the endoplasmic reticulum via quality control mechanisms, or decreasing the time resident on the plasma membrane surface. Dopamine is a major neurotransmitter and pharmacological evidence suggests that dysfunction of the dopaminergic system could be involved in the etiology of the major psychiatric disorders (Georgieva, 2002).

Dopamine transporter: Dopamine transporter (also dopamine active transporter, DAT, SLC6A3) is a membrane-spanning protein that pumps the neurotransmitter dopamine out of the synapse back into cytosol, from which other transporters sequester DA and NE into vesicles for later storage and release. Dopamine reuptake via DAT provides the primary mechanism through which dopamine is cleared from synapses except in the prefrontal cortex, where dopamine uptake via the norepinephrine transporter plays that role. The dopamine transporter plays a key role in the regulation of central dopaminergic transmission, which modulates cognitive processing. Disrupted dopamine function and impaired executive processing are robust features of schizophrenia and other psychotic disorder (Joober, 2000). The dopamine transporter (DAT) is a member of the family of Na^+- and Cl^--dependent neurotransmitter transporters. The DAT is believed to control the temporal and spatial activity of released dopamine by rapid reuptake of the neurotransmitter into presynaptic terminals. It is therefore an important element in regulating the action of dopamine on locomotion, cognition, affect and neuroendocrine functions (Grünhage, 2000).

The role of polymorphism in DAT gene expression: A large-scale SNP discovery study that examined 106 genes encoding proteins with functions relevant to cardiovascular and neurologic disorders was the first to identify SNPs, six synonymous and one nonsynonymous, in the hDAT gene (Cargill *et al.*, 1999). Another group identified ten SNPs, including two novel nonsynonymous SNPs, in controls and bipolar disorder patients (Grunehage, 2000). Several groups have studied the association between the VNTR polymorphism and some neuropsychiatric disorders, which are thought to be related to dopaminergic neurons such as attention deficit hyperactivity, alcohol abuse, schizophrenia and bipolar disorder. However, the relationship between the DAT1 gene and these disorders remains unclear because some studies have reported no association between the VNTR polymorphism and these disorders (Jonathan, 2005). Genetic association studies have implicated the *DAT1* gene in the development of various neuropsychiatric disorders including attention deficit hyperactivity disorder, bipolar affective disorder, schizoid avoidant behavior, cocaine-induced paranoia. All published studies employed the VNTR polymorphism for testing of the *DAT1* gene (Heinz, 2000). Linkage studies in schizophrenic patient pedigrees from Italy, Rouen, France and the Island of La Reunion and Germany failed to demonstrate positive linkage of the 40-bp VNTR polymorphism in the *DAT1* gene to schizophrenia. Most association studies have reported no significant evidences for association between this *DAT1* polymorphism and bipolar disorder or schizophrenia (Joober, 2000; Greenwood, 2001).

DAT Polymorphisms: Linkage and Association studies in Affective disorder. Association studies of DAT polymorphisms and both bipolar disorder and major depressive disorder (MDD) have met with negative results. However, family-based studies of linkage, that provide a means for removing population stratification due to ethnic or socioeconomic influences, have yielded intriguing results (Greenwood, 2001).

Evidence against an overlap between schizophrenia and bipolar disorder

DSM-IV-TR diagnostic symptoms for bipolar disorder are unique. Bipolar disorder has been validated as a specific disease by consistent genetic (Green *et al*., 2005), pharmacologic (Belmaker, 2004) and epidemiologic data accumulated across 30 years (Berrettini, 2001). The concordance for bipolar disorder in monozygotic twins is approximately 75%, and susceptibility loci for bipolar disorder are established (Green *et al*., 2005). Other clinical evidence supporting mood disorder rather than schizophrenia are the following: Past history of diagnosis or symptoms of a mood disorder; family history of mood disorder or alcoholism; Periods of uncharacteristic and excessive goal-directed activities e.g. Political, religious, legal, sexual, business, criminal, medical, physical, spending, calling, writing, preaching, cleaning, planning, exercise; history of respond to lithium, valproic acid, or other mood stabilizers; Presence of uncharacteristic emotions or conflict e.g. Irritability, anger, violence, conflict with law enforcement, elation, grandiosity (paranoia), sadness, hopelessness, crying, suicidal ideation; Periods of appropriate affect; Mood-congruent delusions and/or hallucinations; Episodes of relatively normal function/remission; and enjoys a friendship, active interactions with spouse and own children, and regular interactions with

others. Bipolar disorder patients compared to schizophrenia patients appear to have more social (rather than withdrawn) premorbid interpersonal function, the presence (rather than absence) of prior depression, and rapid (rather than insidious) onset. Schizophrenia is a severe chronic disorder with poor prognosis. Mood disorders are generally less severe and carry a better prognosis compared to schizophrenia. However, prognosis in schizophrenia is not invariably bad, and in psychotic mood disorders is not always benign. Thus, psychotic mood disorders may represent illnesses which are more severe than non-psychotic mood disorders, but less severe than schizophrenia. Earlier compared to later onset conditions are often considered more severe, perhaps resulting from greater genetic vulnerability.

Consistent with this notion, psychotic symptoms are more prevalent in patients with earlier compared to later onset bipolar disorders (Angst, 2008). Psychosis also appears characteristic of more severe illness when is considered longitudinally. Thus, patients with psychotic compared to non-psychotic first manic episodes have poorer outcome, including markedly higher relapse rates at 4 years. Patients with mood-incongruent compared to those with mood congruent psychotic symptoms may reflect a more obvious psychotic component, may have a long term disturbance that is more consistent with schizophrenic spectrum, and may, hence, carry a more guarded prognosis (Ketter *et al*., 2004). Finally, psychosis is central to schizophrenia but not bipolar disorders.

Conclusion

Epidemiological and genetic studies support the hypothesis that psychosis is a clinical phenotype with multiple etiologies and a genetic component. Psychosis strongly aggregates in families. Twin studies have suggested high heritability estimates for psychosis and a complex mode of transmission. Whole-genome linkages studies have identified chromosomal loci that influence susceptibility to psychosis, independent of diagnostic categories. Detailed studies of linked genomic regions have identified several putative candidate genes *(NRG 1, dysbindin, DISC 1, COMT, G72/G30, BDNF,RGS 4)*, which appear to be involved in schizophrenia and affective psychoses. It is difficult to determine the disease mechanism of each risk gene. Interactions between risk genes add to the complexity of the picture. In addition, environmental factors, interacting with risk genes, contribute to psychosis susceptibility. While originally the candidate risk genes were implicated in schizophrenia, recent findings provide evidence that many show strong associations with symptom dimensions, such as psychosis*(NRG1, DISC1, and dysbindin)* or mood symptoms *(G72/G30, BDNF)*, across the schizophrenia-mood disorder continuum. A growing number of reports suggest that psychosis may be a clinical phenotype with a unique genetic background from categorical diagnoses. Future genetic studies, focusing on the symptom dimensions across the functional psychosis continuum, are needed. Dimensional approach may provide more direct clues to understanding the mechanisms of psychotic illnesses (Elena Ivleva, *et al*., 2008). Genetic studies suggest that psychosis may be conceptualized as a clinical phenotype with specific genetic etiologies. Hypothetically genes or sets of genes, interacting with environmental factors, may predetermine vulnerability to psychosis. Depending on additional syndrome-specific genetic influence and environmental interactions, psychosis may coexist with other clinical phenotypes, e.g. mood symptoms or cognitive dysfunction, composing categorical diagnoses.

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