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Symptoms & Genetic Overlap in Schizophrenia and Bipolar Disorder : A Selective Clinical Review

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ABSTRACT *Following the recent progress mainly in the fields of genetics and neurobiology, the validity of the diagnostic distinction between schizophrenia and bipolar disorder is increasingly challenged.Evidence for basic neurobiological processes common for both disorders is expanding with regard to (a) susceptibility genes, (b) neurodevelopment (for example myelination), and (c) brain functions (for example sensory gating, visuospatial achievement). Recent epidemiological studies also stress communalities.The diagnostic split between schizophrenia and bipolar disorder is unable to define distinct etiological and/or pathophysiological entities. There is considerable ovesrlap in mood and affective features in both disorders with family histories reflecting that both disorders may run concomitantly in families. It is interesting to explore genetic and symptomatic overlap in schizophrenia and bipolar disorder from a clinical point of view to further deepen and unite the nosology of these disorders.*

INTRODUCTION

The debate of symptom overlap in bipolar disorder and schizophrenia is not a new one. However the question remains despite advancements in the biological sciences of mental illness, diagnosis and classification systems as well as treatments. Further, there is anevidence showing the biological overlap between schizophrenia and bipolar disorder challenges the concept of two distinct clinical identities. Symptoms and symptom clusters are the main criteria for diagnosis in nosological as well as in systems of classifications for psychiatric disorders. Despite revolutionary advancements in the field of the biological basis of mental disorders, no definite bio-markers have emerged for any particular disorder. In psychosocial field too, no definite factor or group of factors have been helpful to define any 'pathognomonic' symptom for making a definitive diagnosis [1].

In fact so far neither biological nor psychosocial etiopathological factors form the basis or criteria for diagnosis of any mental disorder. Consequently we are still relying on characteristic symptomatology for diagnosis. This limitation opens up possibilities of some overlap of symptoms between several psychiatric disorders and more specifically between schizophrenia and the mood disorders. This overlap of symptoms has given rise to a thought in retrospect, as to whether some of the syndromes or domains of the disorders itself arise from a common origin. In fact, sometimes this leads to a question regarding schizophrenia and bipolar disorder being two different disordersor one on the same spectrum [2].

The present review examines the categorical diagnostic position and symptom overlapin schizophrenia and bipolar disorder based upon current evidence.We argue that both schizophrenia and bipolar disorder lie on the same spectrum of psychopathology and therefore have significant overlap of symptoms at least in a few domains of the illness. It is likely that overlapping symptoms form the manifestations of a common endophenotype, which may need to be assessed and treated differently [3].Here, we examine the psychopathological and biological evidence in support of the overlap in schizophrenia and bipolar disorder and then discuss the common territories of overlap in symptomatology and psychopathology. Wealso hypothesize that the two illnesses or at least a subgroup of each, are not distinctly different but share a common origin and manifestation. We conclude that both schizophrenia and bipolar disorder share significant common features which are indistinguishable from each other, suggesting a possibility that both these illnesses are probably spectral and continuous and not dichotomous.

Overlapping symptoms IN SCHIZOPHRENIA AND BIPOLAR DISORDER

We first start by trying to explain what we mean by overlapping symptoms for the purpose of this review. Overlapping symptoms are symptoms that may be a part of both schizophrenia and bipolar disorder, though their manner of presentation, phenomenology in the context of the respective disorder and at times neurobiological basis may differ. For example we may see symptoms like crying spells, depressed mood and lack of desire to do anything in both disorders. Socio-occupational non productivity is also common. There is a very thin line between grandiosity which is manic and that which is delusional as seen in schizophrenia. In keeping with the same vein, hyper-religiosity is another feature common to both schizophrenia and bipolar disorder. There are a large number of other symptoms that overlap as well – aggressive behavior, suspiciousness, lack of sleep, anxiousness, hypersexuality and lack of self care along with increase or decrease in appetite that may be a part of both disorders [4]. Though we look at these overlapping symptoms from purely clinical perspective, it is noteworthy that overlap between these disorders is not only symptomatic but also genetic and neurobiological. Various areas have been identified where this overlap occurs. These include neurobiology, genetics, cognitive dysfunction, negative and positive symptoms, affective features, white matter abnormalities and overlap of premorbid risk factors and epigenetics [5].

However the extent to which bipolar disorder is considered separately from schizophrenia and other psychoses varies. For example, schizophrenia usually includes psychotic symptoms such as hallucinations, delusions, and thought disturbances as well as negative symptoms such as flatness of affect, poverty of speech, or loss of motivation. The diagnosis of schizophrenia excludes significant mood disorder in all classifications. In contrast bipolar disorder is characterized by prominent mood symptoms and may or may not involve psychosis [6].

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DIAGNOSTIC DILLEMAS BETWEEN THE TWO DISORDERS

Cross-sectional diagnoses while improved with the advent of defined diagnostic criteria remains a blunt sword. Research has shown that initial diagnoses do not always remain stable over time, though the great majority of those with an initial schizophrenia or mood disorder diagnosis do receive the same diagnosis on reassessment [7]. For example, one study showed that between six months from initial contact, and 24 months, 5% of those initially diagnosed with schizophrenia switched to mood disorder or schizoaffective disorder, while 9% of those initially diagnosed with mood disorder switched to schizophrenia or schizoaffective disorder [8]. In another study, 15 of the 16 patients whose diagnosis changed at later follow-up from affective to non-affective psychosis had mood-incongruent features initially. Diagnostic stability has been particularly poor for schizoaffective disorder. One study showed that only 36% of those initially diagnosed with the disorder received the same diagnosis at a later time point. In addition to the problems with diagnostic stability over time in schizoaffective disorder, investigators have also found a lack of cross-sectional diagnostic reliability for this disorder [9].

EVIDENCES FOR SYMTPOM OVERLAP IN BOTH DISORDERS

BIOLOGICAL PARAMETERS

Finally, as neuroscience has developed, more detailed hypotheseshave emerged to describe the neural substrate from which allpsychiatric disorders ultimately derive. Anatomical studies,functional imaging studies, and more detailed cognitive studieshave begun to piece together the neural mechanisms of emotion [10]. The hippocampal system, for example,connects putative behavioral inhibitory and excitatory systemswith other neural mechanisms in the paralimbic cortex and neocortex,which process complex mental representations of the self andthe social environment. Medications provide yet another usefultool for separating distinct pathologic processes that, froman observational standpoint, might appear identical [11].

Pharmaceutical treatments may reflect the pathological mechanism of a disease. A few same classes of pharmaceutical treatments are arguably considered to treat these two disorders. The mechanisms of actions of these treatments may shed some insights into the molecular basis for these two disorders. Atypical antipsychotics that target both the dopamine 2 (D2) and serotonin 5-HT2A receptors can be used to treat schizophrenia. Recently, anti-psychotic agents have been increasingly prescribed to bipolar disorder patients. The effects of these pharmaceutical compounds on both these disorders suggest that dopaminergic and serotonic pathways are both involved in the pathogenesis of both illnesses[12]. It is of note that these anti-psychotics may have varying affinities for these receptors. The efficacy of these different anti-psychotics may also vary by diagnosis. Possibly, the pathogenesis of these two disorders may be influenced by heterogeneous mechanisms underlying dopaminergic and serotonergic pathways [13].

The most compelling line of support for a common biological pathogenesis shared by schizophrenia and bipolar disorder is provided by genetic studies suggesting that some of the same genes influence risk for both disorders. For example, one study has recently reported altered expressions of oligodendroglia-related genes in multiple brain regions to be associated with both disorders[14]. Linkage studies have provided another line of support. In genome-wide linkage analyses of these disorders, at least 5 distinct genomic regions have been implicated as being linked to susceptibility for both disorders[15]. Among the chromosomal regions identified as possibly harboring putative risk genes for both disorders are 4p (41), 6q, 18p, 13q, and 22q. Candidate gene-based association studies have also implicated several risk genes that may contribute to susceptibility to both illnesses [16]. Among these implicated genes that may influence susceptibility to both disorders are dysbindin (DTNBP1), G72 (DAOA), disrupted in schizophrenia (DISC1), catechol-O-methyl transferase (COMT), and brain-derived neurotrophic factor (BDNF), and others, as reviewed elsewhere [17]. In the next section, we describe some of the epidemiological and statistical genetic approaches for such efforts.

GENETIC Familial Co-Aggregation of SCHIZOPHRENIA AND BIPOLAR DISORDER

Schizophrenia and bipolar disorder are 2 of the most severe mental disorders that still are associated with insufficient clinical response, a chronic relapsing course, and functional disability in a substantial number of patients. Over the past decade, the schizophrenia field has responded to this situation with a push toward early recognition and intervention during the prepsychotic (ie, prodromal) phase of the illness [18].

However, both conditions are intimately related, with shared genetic determinants and common polygenic variants, as confirmed by the International Schizophrenia Consortium (ISC) in a genome-wide association study of 3,322 Europeans [19]. Thus, epidemiological characteristics, family studies, and overlapping genetic linkages together support shared genetic risk factors in bipolar and schizophrenia and there is additional new evidence showing similar changes in gene expression in both conditions [20].

Bipolar disorder shares many of the same brain regions as schizophrenia. However, relative to neurotypical controls, lower gray matter volume in schizophrenia is more extensive and includes the amygdala. Common biological mechanisms may explain the neuroanatomical overlap between these major disorders, but explaining why brain differences are more extensive in schizophrenia remains challenging. There is a substantial overlap in clinical and neuropathological findings between these disorders [21]. Moreover,recent studies have demonstrated that the geneticvulnerability for schizophrenia, bipolar disorder anddepression is shared [22-23].

A common pathological mechanism for two diseases may be reflected by comorbidity in the same individual. However, the current hierarchical diagnostic systems for psychiatric diseases do not allow dual diagnoses for schizophrenia and bipolar disorder in the same individual and thus pose a challenge for assessing shared etiology for both disorders at the individual level [24]. As an alternative, familial co-aggregation, which reflects excessive occurrence of two disorders within the same family, can provide evidence for common genetic pathways for both disorders. Familial co-aggregation and co-segregation differ in that the former indicates that the clustering of two diseases within families, which does not necessarily result in the occurrence of two diseases in the same individual; the latter can lead to the occurrence of two diseases in the same individual [25]. One common approach for testing for the presence of familial co-aggregation is to determine if the risk for one disease (e.g., schizophrenia) is elevated in relatives of an individual affected with a second disease (e.g., bipolar mood disorder)."Excess" familial risk can be assessed either by contrasting disease prevalence of one disease in relatives of case probands with disease prevalence in either the relatives of control probands or with overall population prevalence rates [26]. In familial co-segregation studies, various statistical approaches can be used for the comparisons to take into account such issues as the ages of the family members, other disease risk factors, and the correlations in measurements due to the family members being related to each other [27]. One caveat of co-aggregation studies is that they may provide spurious evidence for familial co-aggregation if the 2 diseases being studied are easily misdiagnosed or can be confused with each other due to resemblances of clinical features of these two disorders.

The clustering of a disease within families alone does not permit one to distinguish between the effects of genetic factors and environmental factors in the etiological pathway of

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disease because relatives who share genes in common are also more likely to share similar lifestyles and/or environmental risk factors [28]. In the same way, the presence of familial co-aggregation of two diseases within the same family alone cannot distinguish between the role of shared genetic factors and environmental factors in a shared etiological pathway. One conventional approach used to clarify the relative impact of genetic variants versus environmental factors on a single disorder is to parse out the variance in trait susceptibility to that attributable to genes and that attributable to non-genetic (or environmental) risk factors using statistical approaches akin to analysis of variance. In such approaches, the variation in the trait due to genetic factors is modeled as a function of trait similarity among related individuals, and the heritability of the trait is defined as the proportion of the total trait variance due to genetic effects [29].

The standard variance decomposition procedures can be extended for the joint study of two diseases to tease apart genetic and environmental influences of two disorders using a bivariate extension of the variance component approach. The shared genetic effects represent effectively the "co-heritability" of the two traits. One can use bivariate variance component method to study the genetic relationship between 2 continuous traits [30].

The analysis of twin studies represents a subtype of family analysis that can be used to differentiate between genetic and environmental contributions to familial aggregation. In principle, one can evaluate whether genes play an important role in susceptibility to disease by comparing disease prevalence in the monozygotic (MZ) twin siblings of affected probands to disease prevalence in the dizygotic (DZ) twin siblings of affected probands. Higher disease prevalence in the MZ twin pairs is generally interpreted to indicate a genetic basis for disease if one assumes that environmental risk factors are shared equally among DZ twin pairs as among MZ twin pairs (an assumption that can be challenged in some situations). [31]. Cardno and colleagues examined genetic correlations between schizophrenia, schizoaffective disorder and bipolar disorder in 77 monozygotic and 89 same-sex dizygotic twin pairs using relaxed diagnostic criteria. They found evidence for both common and syndrome-specific genetic contributions to the variance in liability to schizophrenia and manic syndromes, but the genetic liability to the schizoaffective syndrome was entirely shared in common with the other two syndromes. In contrast, environmental liability to the schizoaffective syndrome was not shared with the other syndromes [32].

IDENTIFYING THE RISK GENES FOR BOTH DISORDERS

Conventional approaches used to identify risk alleles for single disorders include linkage and association studies. Linkage analysis is based on using recombination frequencies to infer physical distance between a genetic marker and target risk locus, while association studies directly measure the correlation between the genetic polymorphism at a locus and the disease endpoint. Association analyses are more powerful to detect causal variants, provided there is linkage disequilibrium (i.e., correlation between a paired of genetic loci) between the genetic marker and disease loci; however, linkage analyses are more powerful in the absence of such disequilibrium [33].

It is possible that approaches such as genome-wide association analysis may identify single nucleotide polymorphisms (SNPs) that will turn out to be associated with both disorders or may even reveal different SNPs in the same gene to be associated with each disorder. Other studies have explored the genetic underpinnings for disorders characterized by a mix of mood and psychotic features, such as schizoaffective disorder [34]. The pathological processes in schizoaffective disorder are thought to be correlated with those in both disorders, although some investigators have questioned the validity of the independent diagnostic entity of schizoaffective disorder [35]. It thus remains to be seen whether susceptibility genes for schizoaffective disorder will turn out to be, at least in part, involved in the shared genetic liability of both disorders.

COMMON ENDOPHENOTYPES OF BIPOLAR DISORDER AND SCHIZOPHRENIA

According to Gottesman and Gould, endophenotype are neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological components associated with the target disorder. From a genetic perspective, endophenotype can be very attractive targets for study if they are easily and reliably measured, co-aggregate with the target disorder within families, and are also present in unaffected relatives [36]. A desirable endophenotype is also one that is more proximal to a causative gene than the end-stage disease state and thus may be more amenable to genetic study than the downstream disease [37].

Many candidate endophenotypes in schizophreneria and bipolar disorder are neurophysiological markers. Other endophenotypes that should be explored extensively include drug response and metabolism, RNA expression, and protein levels [38]. Studies of other neurocognitive functions related to information processing also reveal the biological resemblances of both disorders. For instance, impaired performance in span of apprehension has been shown in both illnesses [39]. Other abnormalities in information processing associated with these 2 disorders include P300-evoked response latency and amplitude, P50 auditory-evoked response suppression,prepulse inhibition, facial scanpath patterns, and a mismatch negativity paradigm.Additionally, other cognitive function impairments, such as executive deficits, can be demonstrated in psychotic and bipolar disorder. These biomarkers related to neurocognitive functions may hence serve as common endophenotype upstream to pathological pathways to schizophrenia and bipolardisorder [40].

Genetic analysis of smooth pursuit eye movement (SPEM) related phenotype has provided further insights into shared genetic influences that might cut across different psychiatric diagnoses. For example, 2 studies have reported evidence for linkage of SPEM phenotype to 6p23-21, suggesting that this chromosomal region may harbor one or more genes influencing variation in SPEM [41]. Interestingly, the same region also harbors 2 genes previous associated with risk of schizophrenia, ATXN1 (SCA1) and NOTCH4. Other candidate genes associated with SPEM include dopamine D3 receptor gene (DRD3), DISC1, and COMT. All these genes have also been hypothesized to play a role in the pathogenesis of SCZ and BMD [42]. Taken together, these findings suggest that the study of common endophenotypes for schizophrenia and bipolar disorder, such as SPEM, may reveal insights into alleged etiologic factors linking these two disorders.

Studying common endophenotypes may circumvent the limitation of hierarchical diagnostic system posed on schizophrenia and bipolar disorder. Meanwhile, the conceptualization of endophynotypes does not contradict the putative hierarchical pathological relationship between the two disorders [43]. Furthermore, endophenotypes can allow the investigator to examine the genotype-phenotype relationship in the same population. Conventional studies focusing on schizophrenia and bipolar disorder in different populations separately may produce findings that cannot be transferred to each other. Therefore, deciphering the genetics of common endophenotypes may serve as an alternative and effective approach to untangling the mechanism of shared genetic liability for these 2 disorders [44].

CONCLUSION

To summarize, the conventional nosological distinction between schizophrenia and bipolar disorder has been challenged by research showing a phenomenological and biological overlap of these two disorders. Genetic research suggesting that common genes may be involved in both dis-

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orders has lent additional support for the presence of shared etiological pathways between these two disorders, although specific genes associated for schizophrenia and bipolar disorders jointly have yet to be identified.

The hierarchical diagnostic system for schizophrenia and bipolar disorder precludes the usual approaches for assessing their being associated with each other because the two diagnoses usually cannot be assigned to the same individual. However, assessment of familial co-aggregation may provide very useful insights into whether these two disorders share common etiologies. Although previous evidence has suggested a number of susceptibility genes shared by both disorders, most of these studies have focused on one disorder at a time in independent populations. Alternatively, mapping genes for schizoaffective disorder, which shares symptoms related to both schizophrenia and bipolar disorder, may help unravel shared genetic mechanisms for these two disorders. Finally, identifying the genes modulating common endophenotypes, such as SPEM, provided that they are influenced more directly by genetic factors, may unveil the shared genetic pathways for SCZ and BMD.

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