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The psychoses: Cluster 3 of the proposed meta-structure for DSM-V and ICD-11

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The psychoses: Cluster 3 of the proposed meta-structure for DSM-V and ICD-11

Paper 4 of 7 of the thematic section: ‘A proposal for a meta-structure for DSM-V and ICD-11’

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Background. In an effort to group mental disorders on the basis of etiology, five clusters have been proposed. Here we consider the validity of the cluster comprising selected psychotic and related disorders.

Method. A group of diagnostic entities classified under schizophrenia and other psychotic disorders in DSM-IV-TR were assigned to this cluster and the bordering disorders, bipolar (BD) and schizotypal personality disorders (SPD), were included. We then reviewed the literature in relation to 11 validating criteria proposed by the DSM-V Task Force Study Group.

Results. Relevant comparisons on the 11 spectrum criteria are rare for the included disorders except for schizophrenia and the two border conditions, BD and SPD. The core psychosis group is congruent at the level of shared psychotic psychopathology and response to antipsychotic medication. BD and SPD are exceptions in that psychosis is not typical in BD-II disorder and frank psychosis is excluded in SPD. There is modest similarity between schizophrenia and BD relating to risk factors, neural substrates, cognition and endophenotypes, but key differences are noted. There is greater support for a spectrum relationship of SPD and schizophrenia. Antecedent temperament, an important validator for other groupings, has received little empirical study in the various psychotic disorders.

Conclusions. The DSM-IV-TR grouping of psychotic disorders is supported by tradition and shared psychopathology, but few data exist across these diagnoses relating to the 11 spectrum criteria. The case for including BD is modest, and the relationship of BD to other mood disorders is addressed elsewhere. Evidence is stronger for inclusion of SPD, but the relationship with other personality disorders along the 11 criteria is not addressed and the absence of psychosis presents a conceptual problem. There are no data along the 11 spectrum criteria that are decisive for a cluster based on etiology, and inclusion of BD and SPD is questionable.

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BD and affective psychoses (Kendler & Gardner, 1997). These findings are further corroborated by several recent large population-based studies (Mortensen et al. 2003; Laursen et al. 2005). Birmaher et al. (2009) reported on 388 offspring of 233 parents with BD. Of the 52.1% with axis I disorders, most were mood and anxiety disorders and none received diagnoses of schizophrenia and related disorders. However, some studies do show familial co-aggregation of BD and schizophrenia and other related disorders. However, some studies show familial co-aggregation of BD and schizophrenia and related disorders. In the most definitive study, Lichtenstein et al. (2009) analyzed data from over a million nuclear families including more than 75 000 probands with schizophrenia or BD in a national sample from the Sweden registry. About 60% of the variance of each disease is based on genetic effects, and about half of the genetic effect is shared and about half is unique. Owen et al. (2007) provide a model for the genetic deconstruction of psychoses.

Until recently, the evidence for shared candidate genes and chromosomal locations in schizophrenia and BD from linkage and gene association research was considered relatively robust. Meta-analyses supported this view (Badner & Gershon, 2002; Berrettini, 2003; Lewis et al. 2003; Segurado et al. 2003). However, Sullivan (2007) noted that a meta-analysis produces a high number of overlapping genes by chance, and Segurado et al. (2003) did not find overlap in the highest ranking genes for each disorder. Recent genome-wide association studies (GWAS) cast further doubt on the likelihood that leading candidate genes will be useful in testing validity of diagnostic classes and instead suggest that the contribution of any single gene is very small (Wellcome Trust Case Control Consortium, 2007; Sklar et al. 2008).

A shared genetic liability for schizophrenia and BD may be associated with psychopathology common to both disorders (e.g. depression, reality distortion) and may not be relevant for differential diagnosis. Investigators have observed an amplified linkage signal in loci shared by the two disorders when they focused on subgroups of families based on psychosis or affective symptoms (Potash et al. 2001; Hamshire et al. 2005).

In summary, family, twin and genetic studies provide evidence for both shared and non-shared contributions to schizophrenia and BD. However, specific genes are not yet useful in validating diagnoses. The relevance of genetic effects to the question of grouping BD and schizophrenia together depends on whether the focus is on shared or unique genetic effects.

Environmental risk factors and gene–environment interactions

Several environmental factors have been associated with schizophrenia, some of which are also associated with BD. Substance misuse (Henquet et al. 2005, 2006), prenatal factors, particularly preterm birth (Susser et al. 1996; Brown et al. 2000; Clarke et al. 2006; Scott et al. 2006; Laursen et al. 2007), negative life events and childhood trauma (van Os et al. 1998; Hammersley et al. 2003; Read et al. 2005) are reported to be linked to both diagnostic classes. Schizophrenia and BD psychotic episodes are also associated with urbanicity, possibly reflecting a precipitant effect of environmental risks in genetically vulnerable individuals (Krabbendam & van Os, 2005; Kaymaz et al. 2006). BD without positive psychotic symptoms, however, is not correlated with urbanicity (Kaymaz et al. 2006). Advanced paternal age and Toxoplasma gondii are associated with schizophrenia and not known to be risk factors in BD (Laursen et al. 2007; Mortensen et al. 2007; Perrin et al. 2007; Torrey & Yolken, 2007; Torrey et al. 2007; Yolken & Torrey, 2008).

These environmental risk factors are common to many disorders and thus are not determinative of cluster membership. Rather, they may contribute to dimensions of psychopathology across diagnostic categories. Researchers are turning their attention to understanding the complex ways in which nature interacts with nurture to produce psychosis. This genotype × environmental interaction (G × E) approach posits a causal role for synergistic co-participation, where the effect of one is conditional on the other (Leboyer et al. 2008). G × E seems a particularly suitable approach for understanding the development of psychosis across the diagnostic categories in DSM. The psychosis phenotype is known to be associated with environmentally mediated risks, yet people display considerable heterogeneity in their response to those environmental exposures (van Os et al. 2008).

Shared neural substrates

Many neuroimaging studies compare schizophrenia to healthy controls (HC) but fewer examine differences between BD and HC. Fewer still directly compare schizophrenia and BD subjects and, of these, only a subset specifies whether psychosis is present in the BD cases. Neural substrate findings are summarized in Table 1.

Magnetic resonance imaging (MRI)

Structural anatomical abnormalities are reported across the psychosis spectrum. Most commonly, gray
Table 1. Summary of neural substrate findings in schizophrenia (Sz), bipolar (BP) disorder and healthy normal volunteers (HNV)

<table>
<thead>
<tr>
<th></th>
<th>Cross: HNV</th>
<th>Longitudinal: HNV</th>
<th>BP v. HNV</th>
<th>Sz v. BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>↓GM †GM+++</td>
<td>↓GM †GM++</td>
<td>↓GM +</td>
<td>↓GM + (Sz &lt; BP)</td>
</tr>
<tr>
<td></td>
<td>↑WM ↔</td>
<td>↑WM+</td>
<td>↑CSF +</td>
<td>↑CSF + (Sz &gt; BP)</td>
</tr>
<tr>
<td>H-MRS</td>
<td>↑NAA +</td>
<td>↑NAA +</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>↑Glu +</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-MRS</td>
<td>↑PDE +</td>
<td>↑PME +</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>↑FA ↔</td>
<td>Unclear</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>PET receptors</td>
<td>Unclear D₂ receptors</td>
<td>Unclear D₂ receptors</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>DTI</td>
<td>Network differences ++</td>
<td>Network differences +</td>
<td>Two studies suggest network differences</td>
<td></td>
</tr>
<tr>
<td>Post-mortem ultrastructure</td>
<td>↑Neuronal density +</td>
<td>↑Neuronal density +</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>↑Glial density +</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-mortem gene expression</td>
<td>↑GABA markers ++</td>
<td>↑GABA markers +</td>
<td>↑GABA markers + both disorders</td>
<td></td>
</tr>
</tbody>
</table>

MRI, Magnetic resonance imaging; H-MRS, proton magnetic resonance spectroscopy; P-MRS, phosphorus magnetic resonance spectroscopy; DTI, diffusion tensor imaging; PET, positron emission tomography; fMRI, functional MRI; GM, gray matter; WM, white matter; CSF, cerebrospinal fluid; NAA, N-acetylaspartate; Glu, glutamate; PDE, phosphodiester; FA, fractional anisotropy; GABA, gamma-aminobutyric acid; PME, phosphomonoesters. ↓, Decreased; ↑, increased; +, some evidence; ++, some replications; ++++, repeatedly replicated finding.

Matter reductions in multiple regions have been identified in schizophrenia and BD patients, when compared to HC. The magnitude of these effects is larger in schizophrenia but similar to BD in abnormal topography. Meta-analyses document a 3–4% whole-brain volume reduction in schizophrenic probands compared to HC (see e.g. Woodruff et al. 1995; Wright et al. 2000; Steen et al. 2006; for a review, Harrison, 1999) that is not entirely consistent with the pattern of volume loss in BD (Hoge et al. 1999). In both schizophrenia and BD, volume reductions are most consistently reported in cortical gray matter, particularly in frontotemporal regions. Relatives of schizophrenic probands and high-risk individuals also have significant, though smaller, volume reductions compared to HC (Seidman et al. 1999; Lawrie et al. 2001; O’Driscoll et al. 2001; Ho, 2007). Of note, there is a concomitant increase in sulcal and ventricular cerebral spinal fluid in schizophrenic probands. Ventricular enlargement also occurs in BD and may be more severe in patients with multiple episodes (Hauser et al. 2000; Strakowski et al. 2002), but long-term longitudinal studies (comparable to those in early schizophrenia) are lacking. A meta-analysis suggests that right-side ventricular enlargement is the most consistent finding in BD (McDonald et al. 2004). The difficulty in relating imaging findings to the diagnostic grouping issue is illustrated by McIntosh et al. (2005), who report reduced white matter density in the anterior limb of the internal capsule in both syndromes. However, unaffected relatives did not have this reduction and a reduction in frontal subgyral white matter was only observed in cases with a family history of schizophrenia.

Longitudinal changes (mainly gray matter reductions) early in schizophrenia have been repeatedly demonstrated as early as 3 months after treatment (see e.g. DeLisi et al. 1997; McCarley et al. 1999; Rapoport et al. 1999; Lieberman et al. 2001; Ho et al. 2003; van Haren et al. 2003; Theberge et al. 2007). Lieberman et al. (2005) documented global gray matter reductions early in schizophrenia. Early brain volume reduction may stabilize in early adulthood (Woods, 1998) or later (Mathalon et al. 2001), but most evidence suggests progressive changes during the course of schizophrenia (Arango et al. 2008; DeLisi, 2008; Lawrie et al. 2008; Hulsoff Pol & Kahn, 2008; Wood et al. 2008). It is not known whether progressive changes followed by stabilization is the pattern for BD. Epiphenomena such as substance abuse, therapeutic drugs and intense smoking may contribute to these observations (see e.g. Dorph-Petersen et al. 2005; Rais et al. 2008).

Subcortical striatal regions may be enlarged in BD compared to HC (Strakowski et al. 2005) and in schizoaffective disorder (Getz et al. 2002). The available evidence has found increased amygdala in BD and reduced hippocampi in schizophrenia (Altshuler et al. 2005).
One study has followed first-episode psychosis subjects with a baseline and repeat MRI (1.5 years later). Both schizophrenia and psychotic BD subjects had smaller left superior temporal volumes than HC, but only schizophrenia subjects had further volume reductions (McCarley et al. 1999). However, a recent report failed to document gray or white matter differences between BD subjects and non-ill controls (Scherk et al. 2008). Medications may confound relationships between diagnostic cohorts.

Direct comparisons between the first-degree relatives (FDRs) of BD and schizophrenia subjects have revealed prefrontal gray and white matter reductions in schizophrenia relatives but not in BD relatives (McIntosh et al. 2006). Hippocampal volumes were reduced in the schizophrenia subjects but not in their relatives. BD and their relatives had normal brain volume indices (McDonald et al. 2006).

Although these studies highlight broad similarity in the brain systems affected in schizophrenia and BD (i.e. frontotemporal), the data arguably provide the most persuasive evidence for neuroanatomical differences between schizophrenia and BD. Important (and potentially opposite) effects of antipsychotic and mood-stabilizing agents cannot be excluded, but the presence of disease-specific abnormalities in the schizophrenia relatives, but not in the BD relatives, strongly suggests that brain volume deficits are not entirely accounted for by a medication effect in schizophrenia. However, given evidence for neurotrophic effects of mood-stabilizing agents (Sassi et al. 2002) that could increase gray matter volumes in BD subjects, a complex contribution of psychotropic medications (reduced cortical volumes and increased striatal volumes with antipsychotics and increased cortical volumes with mood stabilizers) must be considered in relation to conclusions regarding disease-specific volumetric abnormalities.

**Diffusion tensor imaging (DTI)**

Many studies have examined white matter tract integrity with DTI in schizophrenia/HC comparisons. There have been several reports of reduced white matter integrity in schizophrenia in a variety of regions (Gur et al. 2007). There are fewer reports regarding BD and these are not consistent. Yurgelun-Todd et al. (2007) report increased white matter integrity, whereas Adler et al. (2004) report reduced white matter integrity. No direct comparisons between diagnostic groups are currently available.

**Magnetic resonance spectroscopy (MRS)**

There is abundant evidence of neuronal dysfunction in both schizophrenia and BD. BD is characterized by reduced N-acetylaspartate (NAA), a marker of neuronal viability (Yildiz-Yesiloglu & Ankerst, 2006). However, as in the MRI literature, there are suggestions of neuroprotective effects of lithium, leading to NAA elevations (Brambilla et al. 2005). Direct comparisons between the diagnostic groups are lacking.

Glutamatergic indices are increased in medication-naive schizophrenia probands and those at high risk of the disorder (Theberge et al. 2002; Tibbo et al. 2004; Chang et al. 2007). Glutamate indices are also increased in unmedicated BD (Dager et al. 2004). No study has directly compared these metabolites between schizophrenia and BD.

**Positron emission tomography (PET)/single photon emission computed tomography (SPECT)**

A review of D₂ densities in vivo and post-mortem in schizophrenia is suggestive of increased D₂ receptors (Zakzanis & Hansen, 1998). BD with psychosis is also associated with increased striatal D₂ receptor density comparable to medication-naive schizophrenia probands. This is not found in non-psychotic BD. These studies suggest that psychosis, irrespective of schizophrenia or mood disorder, is related to increased D₂ receptor density. This is consistent with the clinical evidence regarding the efficacy of D₂ blockade for psychotic symptoms regardless of diagnosis. The significance of these pharmacological findings has been explicated in a heuristic model linking excessive dopamine to the development of reality distortion symptoms through its role in reward-based behavior, and the assignment of motivational significance to external stimuli (Kapur et al. 2005; van Os & Kapur, in press). This model provides a means of linking dopamine dysregulation with delusion and hallucination through aberrant associations of salience, and suggests that antipsychotic drugs may serve to ‘detach’ an individual from both aberrant and normal motivational salience. Receptor data are particularly vulnerable to drug effects. Reality distortion symptoms occur in many disorders outside the psychosis cluster.

**Functional MRI (fMRI)**

Functional imaging studies highlight important differences in the activation of frontostriatal networks in schizophrenia and BD patients, depending on task requirements. Working memory performance in schizophrenia has been commonly associated with hypoactivation of the dorsolateral prefrontal cortex (DLPFC), although there is also evidence of hyperactivation in anterior cingulate and frontal pole regions (Glahn et al. 2005). Comparatively fewer studies in BD nevertheless report similar patterns of...
hypoofrontal activation during working memory task performance (see Phillips & Vietta, 2007). Other studies using emotional stimuli have revealed a pattern of increased subcortical striatal and limbic activation alongside reduced prefrontal cortex activity in BD (see Green et al. 2007). This pattern of activity is also evident in pediatric cases of BD (Dickstein et al. 2007; Pavuluri et al. 2008). In schizophrenia, there is a contrasting pattern of decreased limbic activation and hyperfrontality during emotion processing tasks (e.g. Holt et al. 2006). Finally, use of a sentence completion task to study neural correlates of inhibitory control in medicated schizophrenia, BD and HC groups has shown increased activation in the right insula in schizophrenia, whereas BD had reduced activation in this region (McIntosh et al. 2008). Conversely, BD had increased activity in the left DLPFC, whereas schizophrenia subjects had reduced activation in this region. A model including activation of the ventral striatum, middle temporal gyrus, DLPFC and right insula correctly classified 92% of BD and 58% of schizophrenia subjects. Thus, as in other imaging areas, some data suggest similarity and other data suggest important differences between schizophrenia and BD.

**Post-mortem**

Post-mortem studies show both similarities and differences between schizophrenia and BD. Similarities focus mainly on reduced gamma-aminobutyric acid (GABA)ergic indices in the anterior cingulate and hippocampus. There have been several studies describing evidence of decreased glutamic acid decarboxylase (GAD67) mRNA levels in the limbic lobe of both BD and schizophrenia (e.g. Akbarian & Huang, 2006; Benes et al. 2006). Reports from the Stanley Neuropathology Consortium are somewhat consistent with these findings. Evidence of reduced parvalbumin-containing cells in hippocampus layer CA2 (which represent GABAergic interneurons) was found in a direct comparison of both schizophrenia and BD tissue samples compared to HC (Knable et al. 2004). BD and schizophrenia groups shared about 65% of abnormalities in a variety of mRNA and protein markers related to developmental/synaptic and GABAergic systems (Torrey et al. 2005).

Schizophrenia and BD are associated with conflicting glial profiles. Schizophrenia shows increased neuronal density and glial density in prefrontal regions (Selemon et al. 1995) and decreased dendritic spines (Glantz & Lewis, 2000) without neuronal loss or gliosis (Harrison, 1999). This has been interpreted as reduction of the neuropil, with increased neuronal packing in cortical layers III to VI. In contrast to schizophrenia, BD shows reduced glial and neuronal density coupled with glial hypertrophy in these regions (Ongur et al. 1998; Rajkowska et al. 2001). These findings suggest distinct neuropathological substrates in schizophrenia and BD but the samples were small and the potential contribution of medications to these post-mortem findings cannot be dismissed (Dorph-Petersen et al. 2005).

In summary, the neuroanatomy literature contains compelling reports of differences between BD and schizophrenia, but similarities are also observed. There are few direct comparisons between the two groups using MRI (Altschuler et al. 1998; McCarley et al. 1999; Strakowski et al. 1999; McDonald et al. 2006; McIntosh et al. 2006), which all report reduced brain tissue volumes in schizophrenia. Because small effects are expected and the measurement variability with most of these neuroimaging tools is large, concurrent study of both disorders is essential.

**Shared biomarkers**

Several neurophysiological abnormalities are observed in psychotic disorders before the onset of psychosis, are reported to be stable over the course of the illness, and are only mildly affected by psychotic state and medications. Recent data indicate that, in most part, these neurophysiological deficits are independent of each other, and are observed in non-ill relatives of schizophrenia patients and in subjects with schizotypal traits (Light & Braff, 2001; Braff et al. 2007; Gur et al. 2007; Hong et al. 2007; Turetsky et al. 2007). Many of the same endophenotypes are now being studied in BD subjects and their FDRs (Hill et al. 2008; Pearlson & Folley 2008; Thaker, 2008).

**Smooth pursuit and saccadic eye movement abnormalities**

Schizophrenia patients with primary and enduring negative symptoms have impairment in smooth pursuit eye initiation (Hong et al. 2003). Furthermore, pursuit maintenance and, more specifically, predictive pursuit response are abnormal in FDRs of schizophrenia patients and probands, particularly those with schizotypal symptoms (Holzman et al. 1974; Thaker et al. 1998, 2003; Avila et al. 2006; Hong et al. 2008), and are thought to mark psychosis liability (Hong et al. 2006). BD probands and their relatives also show pursuit abnormality similar to the relatives of schizophrenia probands (Rosenberg et al. 1997; Kathmann et al. 2003).

In addition to the smooth pursuit eye movement abnormalities, studies have observed abnormality in saccadic inhibition (anti-saccades) and oculomotor
delayed responses (which assess spatial working memory) in schizophrenia probands and their relatives, and also in persons with affective disorders (see review by Thaker, 2008).

Sensory gating (P50) deficit
Schizophrenia and BD probands with a lifetime history of psychosis show muted inhibition as measured by P50 responses to a paired click paradigm (Perry et al. 2001; Sánchez-Morla et al. 2008). This deficit is not consistently affected by medication status or clinical state. BD without a history of psychosis is not as associated with abnormal P50 suppression (Olincy & Martin, 2005). Abnormalities in P50 suppression have also been noted in FDRs of BD-I probands with psychotic features (Schulze et al. 2007; Hall et al. 2008), and in patients with SPD (Cadenhead et al. 2002).

Prepulse inhibition (PPI)
Patients with schizophrenia show a reduced inhibition of the startle response by a prepulse stimulus (PPI), even when the startle reflex is generally within the normal range (Braff et al. 2001). The deficit is also observed in non-psychotic patients, patients not on medications (Swerdlow et al. 2006), and in FDRs who are clinically unaffected (Kumari et al. 2005).

Similar to schizophrenic probands, impairment in PPI has been consistently observed in BD during acute episodes (Perry et al. 2001), and also in remitted patients (Quraishi & Frangou, 2002; Martinez-Aran et al. 2004; Frangou et al. 2005; Robinson et al. 2006). Three studies have noted PPI deficits in unaffected FDRs of BD probands (Zalla et al. 2004; Frangou et al. 2005; Giakoumaki et al. 2007), suggesting that PPI impairment may mark psychosis liability in both schizophrenia and BD, and is associated with shared genetic predisposition to psychotic symptoms. However, these deficits also occur in disorders of other clusters including co-morbid attention deficit hyperactivity disorder, tic disorders, obsessive–compulsive disorder, and Huntington’s disease (Braff et al. 2001).

P300 evoked potential
BD and schizophrenia have reduced P300 amplitude and increased latency (Souza et al. 1995; Ford, 1999). This deficit is heritable and probably related to the etiology of the two diagnoses as similar impairments are observed in FDRs of both disorder probands (Pierson et al. 2000; Turetsky et al. 2000; van Beijsterveldt et al. 2001; Winterer et al. 2003; Bramon et al. 2005).

Early information processing and mismatch negativity
Abnormalities in mismatch negativity are consistently demonstrated in the auditory modality of schizophrenic probands; however, the findings in their unaffected relatives are less consistent (Michie et al. 2002; Umbricht & Krljes, 2005; Magni et al. 2008). Although not studied extensively, BD patients show unimpaired mismatch negativity (Umbricht et al. 2003).

Neural synchronization deficits
Studies have found abnormality in gamma (30–80 Hz) synchronization in schizophrenia patients (Kwon et al. 1999; Hong et al. 2004) and their FDRs. Similar reductions in the gamma band synchronization are also noted in BD (O’Donnell et al. 2004; Maharaj et al. 2007). The reduced synchrony in the gamma band is correlated to positive symptom ratings such as visual hallucinations, thought disorder, conceptual disorganization, and attention in schizophrenia subjects (O’Donnell et al. 2004; Hermann & Demiralp, 2005).

In summary, although there are extensive data on biomarkers in schizophrenia probands and their relatives, such information is meager in BD. Few studies have directly compared biomarkers in schizophrenia and BD families. The existing data suggest that many of the biomarkers index independent aspects of psychosis risk (Light & Braff, 2001; Hong et al. 2007). Measures of early sensory processing such as smooth pursuit initiation, motion perception and mismatch negativity seem to be unique to schizophrenia liability and tend to be associated with negative symptoms (Hong et al. 2003; Slaghuis et al. 2005; Urban et al. 2008), whereas abnormalities in smooth pursuit maintenance, sensory and sensory-motor gating, the P300 component of evoked potential and gamma-band synchronization mark positive psychotic symptoms and are present in both schizophrenia and BD. Table 2 presents a summary of neurophysiological marker findings.

Shared temperamental antecedents
A strong body of evidence originating in experimental psychology supports the existence of polygenetically inherited variations in temperament and personality factors, which, if inherited in particular combinations, may render an individual vulnerable to the development of psychosis (Green et al. 2008). This view is supported by large population-based evidence of the existence of psychotic-like experiences in ostensibly healthy individuals (van Os et al. 2000, 2009), and considerable evidence of cognitive, perceptual and
psychophysiological characteristics shared by individuals with psychotic disorders, their FDRs and psychosis-prone individuals (Claridge, 1997).

The view that schizotypal characteristics could represent both normal variation in personality and vulnerability to clinical disorders has been difficult to reconcile with the psychiatric notion that these conditions represent distinct classes of ‘illness’, separate from normal function. Although it is beyond the scope of this paper to fully review the evidence in support of this notion, two recent papers have examined whether psychotic-like experiences form a major domain of human variation. Tackett et al. (2008) examined the factor structure of a standard set of abnormal personality scales that was augmented by the inclusion of indices of schizotypal personality in a sample designed to be weighted toward psychosis proneness with the inclusion of FDRs of probands with schizophrenia, schizo-affective and BD diagnoses. Elements of the four-factor structure of abnormal personality that has been discussed extensively as a potential dimensional model for abnormal personality in DSM-V (Widiger et al. 2005) emerged, encompassing domains of emotional dysregulation (neuroticism), introversion, compulsivity and antagonism, augmented by an additional fifth dimension of ‘peculiarity’, primarily reflecting the inclusion of the schizotypy scales. Watson et al. (2008) reported very similar results in a sample of college students who completed a similarly enriched set of indicators of abnormal personality. Of course, the self-report personality indicators in these studies do not constitute diagnosable psychotic disorder per se, but at least some of these personality indicators have shown predictive validity for psychotic disorder diagnosed through structured interviews (Raine, 2006). Studies in this vein generally support a spectrum relationship between schizophrenia and schizotypal personality structure, referring not only to clinical presentation of SPD but also to more broadly defined ‘schizotypal’ personality characteristics within healthy individuals. Some qualities of other cluster A personality disorders may also relate to the peculiarity domain identified in recent factor analytic studies, but the DSM-IV construct that maps best onto this domain is clearly SPD. Endophenotypes, described above as biomarkers, substantiates the relationship between schizophrenia and relatives with schizophrenia spectrum pathology. The relationship between personality and the various other psychotic disorders such as brief reactive psychosis or delusional disorder, has not been a major focus of research.

<table>
<thead>
<tr>
<th>Neurophysiological marker</th>
<th>Schizophrenia/relatives</th>
<th>Bipolar/relatives</th>
<th>Genetic findings</th>
<th>Implicated neurotransmitter</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. SPEM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predictive pursuit</td>
<td>++++/+++</td>
<td>+/+</td>
<td>6p21, COMT</td>
<td>Nicotine, NMDA</td>
</tr>
<tr>
<td>Pursuit initiation</td>
<td>+/+</td>
<td>-/+</td>
<td>15q14/CHRNA7</td>
<td>Nicotine, adrenergic, serotonergic</td>
</tr>
<tr>
<td>2. P50</td>
<td>+++</td>
<td>+/+</td>
<td>22q11, NR1</td>
<td>Dopamine, NMDA, Nicotine</td>
</tr>
<tr>
<td>3. PPI</td>
<td>+++</td>
<td>+/+</td>
<td>4q22, 1q42, DRD3</td>
<td></td>
</tr>
<tr>
<td>4. P300</td>
<td>+++</td>
<td>+/+</td>
<td>4q22, 1q42, DRD3</td>
<td></td>
</tr>
<tr>
<td>5. MMN</td>
<td>+++</td>
<td>-/+</td>
<td>NMDA</td>
<td></td>
</tr>
<tr>
<td>6. Neural synchronization</td>
<td>+++/+</td>
<td>+</td>
<td>GABA, NMDA</td>
<td></td>
</tr>
</tbody>
</table>

SPEM, Smooth pursuit eye movements; PPI, prepulse inhibition; MMN, mismatch negativity; COMT, catecholamine-O-methyltransferase gene; CHRNA7, alpha 7 nicotinic cholinergic receptor gene; NR1, neuregulin 1 gene; DRD2 and DRD3, dopamine receptor D2 and D3 genes; NMDA, N-methyl-D-aspartic acid; GABA, gamma-aminobutyric acid.

a Some evidence; ++, some replications; ++++, repeatedly replicated finding.

* Based on findings in 22q11 deletion syndrome.

b Based on a study in alcoholism.

c Based on findings in (1;11) translocation carriers. Details and appropriate citations are given in the text.

Cluster 3: psychoses

Shared cognitive and emotional processing abnormalities

Cognitive impairment

Cognitive impairments are consistently noted in schizophrenia, BD, SPD (Green, 2006), and schizoaffective disorder (Stip et al. 2005; Torrent et al. 2007). These deficits are thought to underlie functional disabilities (Bilder et al. 1991; Hill et al. 2004; Green, 2006), and may represent candidate endophenotypes for psychotic conditions that may span current diagnostic groups (Arts et al. 2007; Glahn et al. 2007). Cognitive
domains affected in schizophrenia include deficits in sustained attention, visual and verbal episodic memory, working memory, and processing speed (Saykin et al. 1991; Cannon et al. 2000; Green et al. 2000; Egan et al. 2001; Dickinson et al. 2004). In general, the pattern of cognitive deficits in BD is similar to the cognitive profile of schizophrenia, although impairment may be somewhat less severe and state dependent in BD (Egan et al. 2001; Krabbendam et al. 2005; Arts et al. 2007). The FDRs of schizophrenia patients show similar cognitive deficits; although the abnormalities are less salient, this finding supports the heritability of these deficits (Snitz et al. 2006). Some of the available data, in relatively small samples, suggest that cognitive deficits observed in the BD probands also occur in their FDRs (Antila et al. 2007; Trivedi et al. 2008).

In general, cognitive deficits in all domains begin before psychosis and remain stable over the course of schizophrenia (Rund, 1998), whereas deficits in attention and executive function seem to be most stable in BD (Burdick et al. 2006; Mur et al. 2008). However, fluctuating attentional disturbances have been reported in schizophrenia (Dawson et al. 1994). Cognitive impairments in BD tend to vary significantly with clinical state and deteriorate as the illness progresses (Burt et al. 2000). However, subtle impairments in executive function, verbal fluency, attention and episodic memory are observed in BD relatives and patients even during euthymic phases (Deckersbach et al. 2004; Malhi et al. 2004; Pavuluri et al. 2006, 2008; Bora et al. 2008). Comparison of cognitive deficits in BD-I and BD-II revealed more severe deficits in BD-I, consistent with a functional distinction between these groups (Simonsen et al. 2008).

**Emotion**

Patients with schizophrenia often demonstrate a restricted emotional range and diminished ability to experience pleasure (anhedonia) (see, for example, Bleuler, 1911; Kraepelin, 1917; Carpenter et al. 1988). Anhedonia correlates significantly with other negative symptoms of schizophrenia such as affective flattening, avolitional pathology including asociality, apathy, alogia, and is independent of positive symptoms and disorganization (Blanchard & Cohen, 2006). Anhedonia has been thought to be a marker of a genetic liability to schizophrenia (Chapman et al. 1976; Glatt et al. 2006) and may be associated with anhedonia in the general population (Tomppo et al. 2009). By contrast, restricted emotional range and anergia are not commonly associated with BD except when secondary to depression. Anhedonia is not a liability marker for BD (Katsanis et al. 1992; Etain et al. 2007).

**Symptom similarity**

The symptom commonality across the disorders in DSM-IV-TR schizophrenia and related psychoses is based on reality distortion (i.e. hallucinations and delusions). Other criteria A symptoms for schizophrenia are used to differentiate this diagnosis from other psychotic disorders (e.g. disorganization, negative symptoms, psychomotor abnormalities). Reality distortion is associated with many disorders and is not decisive for etiologically based classifications. Bleuler (1911) considered hallucinations and delusions as secondary manifestations and Kraepelin (1917) viewed the combination of avolition and dissociative thought, and the difference between chronic course and episodic course as the defining clinical features that separated dementia praecox from manic-depressive disorder. Schneiderian first-rank symptoms are, however, reality distortion phenomena. DSM-IV-TR criteria for schizophrenia can be met by hallucinations and delusions alone, or even just delusions, if bizarre. What is the affinity of SPD and BD in light of a traditional view of schizophrenia or the current DSM emphasis on reality distortion?

The answer for SPD is clear at a definitional level. If magical ideation and perceptual aberrations reach psychotic severity, the case meets criteria for a psychotic diagnosis. Nonetheless, there is a phenomenological similarity where schizotypal pathology can be viewed on a continuum with psychosis, and similarities reviewed above in other spectrum criteria support a close relationship to schizophrenia.

Comparing psychopathology of BD and schizophrenia supports separateness. Much of the manifest pathology of BD is mood disturbance, often with an episodic pattern. Reality distortion may not occur in BD-II, and is often not present during episodes of BD-I. First-rank symptoms occur in both, but more frequently in schizophrenia. Bizarre reality distortion experiences (Jaspers, 1962) in schizophrenia contrast with the mood-congruent delusions in BD. Thought disturbance is present in both syndromes, but is quite different. Excessive, grandiose and pressured thought and speech is typical in one syndrome whereas disorganized speech with impoverished content is observed in the other. Although depressed affect is present in many cases of schizophrenia, other cases have restricted affect. Excessive affect is typical of BD except in some chronic cases. Avolition defines at least a subtype of schizophrenia and is not associated with BD (Kirkpatrick et al. 2001; Fischer & Carpenter, 2009).

In summary, SPD is separated from the psychoses group by definition although manifestations can be viewed as a mild version of schizophrenia. However,
BD and schizophrenia are differentiated on a symptomatic basis.

**High rates of co-morbidity among disorders as currently defined**

Co-morbidity regarding domains of psychopathology is extensive. Depressive, obsessive, anxiety, attention, social, motor, suicidal, sleep disturbance and other psychopathologies are frequently observed in patients with diagnoses in the psychoses cluster. Overlap with many other disorders (van Os et al. 2000) does not suggest joining the various diagnostic categories in the same grouping. A more meaningful question is whether schizophrenia and other psychotic disorders are co-morbid separate disease entities such as diabetes. Schizophrenia and BD are associated with high prevalence of substance abuse, but this is true of many disorders. Schizophrenia is co-morbid with aspects of the metabolic syndrome including diabetes, but this may relate to lifestyle rather than shared pathology. Co-morbidity at the symptom level can be created by definition as exemplified by the diagnostic category of schizo-affective disorder (Malhi et al. 2008).

**Course of illness**

Schizophrenia does not have a ‘typical’ course (Carpenter & Kirkpatrick 1988; Harding 1988), and the course pattern is variable for BD. Recurrent episodes in schizophrenia tend to be manifestations of symptoms observed previously whereas BD may have distinctive presentations at opposite ends of an affect continuum across episodes. However, more patients with schizophrenia than BD have continuous, rather than phasic, courses. It should be noted that this distinction is based on a proportion of cases rather than unique disorder patterns, and good prognosis cases are often under-represented in long-term course studies.

Both BD affect disturbance and schizophrenia psychosis have typical age-incidence curves with onset in young people (Kennedy et al. 2005b) and both display earlier onset in men (Kennedy et al. 2005a). However, core schizophrenia pathologies (e.g. negative symptoms and cognitive impairment) begin much earlier in most cases. Schizophrenia is associated with a decline in cognition during developmental years and trait-like stability of impairments over time (Woodberry et al. 2008). BD is not generally associated with developmental impairment, prompting the suggestion that the major difference between the two conditions is that schizophrenia, but not BD, is developmental in origin (Murray et al. 2004). The distinct longitudinal patterns of schizophrenia and BD separated the disorders in the original Kraepeliniian concept, but heterogeneity in course is present in each syndrome.

Avalitional pathology begins early and afflicts a minority of cases of schizophrenia. This pathology is rare in the pre-onset and early course of BD. This schizophrenia subgroup is substantially different from BD, but is also distinguished from other schizophrenia subgroups (Kirkpatrick et al. 2001).

**Treatment response**

All antipsychotic drugs reduce the experience of psychosis, regardless of diagnostic category, and may reduce relapse rates. All share a mechanism of action at the dopamine D2 receptor. By contrast, lithium has therapeutic and prophylactic effects for depression and mania in BD patients but is not documented as effective in schizophrenia patients. One study that did examine the effects of lithium in schizophrenia patients found that effects were only evident on mood (Johnstone et al. 1988). Antidepressant drugs have efficacy in BD, but efficacy has not been established in schizophrenia. Although controversial, there are data suggesting that antidepressant drugs may trigger mania in BD but may decrease psychotic relapse in schizophrenia (Siris et al. 1994; Ghaemi et al. 2003). In general, psychopharmacology effects suggest substantial differences in treatment response except with antipsychotic drugs. The latter are not diagnostically specific.

**Conclusions**

The primary argument for grouping several disorders in a psychosis cluster is shared reality testing pathology and the absence of a compelling case for location elsewhere (e.g. psychosis with Alzheimer’s disease). We propose keeping this grouping, incorporating the psychotic disorders already clustered in DSM-IV-TR. There are few data testing the fit between these disorders on the 11 criteria except for similarity in reality distortion symptom criteria. The more challenging issue involves grouping SPD and BD with the psychoses cluster.

The question of adding SPD is cogent because compelling similarities in many of the 11 validating criteria are documented. The main reservation relates to failure of cases to manifest psychotic symptoms and the fact that antipsychotic drugs are not frontline therapy. If psychosis emerges, the diagnosis is changed. A decision on this for DSM-V must also consider how personality disorders are conceptualized.

More complicated is the question of BD. There is substantial overlap in neural substrate, biomarkers, genetic and environmental effects, cognition, and
aspects of symptoms, treatment and course. Yet, in each of these areas there are data supporting unique features. There is no consensus on whether any of the data reviewed above are decisive for validation of cluster membership. An additional consideration involves comparing BD with other mood disorders on the 11 proposed criteria (Goldberg et al. 2009a). Similarities between BD and schizophrenia are extensively based on BD-I with psychosis. It is likely that BD-II will overlap extensively with mood disorders, and the question of splitting BD-I and BD-II will have to be addressed. There may be insufficient evidence to de-link these two forms of BD at present. The fact that many BD patients never manifest psychosis argues against BD joining the psychosis chapter, as does the substantial difference in phenomenology.

Grouping BD and SPD with the current psychoses group could facilitate the identification of shared mechanisms of pathophysiology. The cluster could facilitate investigative focus on crucial issues that distinguish between classes within the cluster and that define the porous boundaries across current classes. This process will be facilitated by DSM-V if key dimensions of pathology associated with the grouping are identified and the paradigm for etiological investigations shifts from diagnostic class/syndrome to pathological dimension (Strauss et al. 1974; Carpenter & Buchanan, 1989) or endophenotypes (Gottesman & Gould, 2003).

There are several limitations in proposing the psychoses cluster based on the 11 spectrum criteria. Five caveats require attention. First, there is insufficient evidence on the etiology and pathophysiology to base group membership on causality. Second, the ultimate determination of group membership for disorders at the border of proposed clusters requires examination of similarities and differences with both clusters. Third, in-depth phenomenology and pattern of illness are not examined in most studies, and state versus trait issues may be crucial. Fourth, psychosis is the main defining feature for grouping these disorders. An alternative is to regard psychosis, especially reality distortion symptoms, as a common manifestation of many disorders and not rare in the general population. Fifth, it is not known whether the 11 spectrum criteria would support the DSM-IV cluster of schizophrenia and related disorders. Groupings would be very different if defined by other trait pathologies of schizophrenia such as avolitional pathology. In summary, the proposed move of BD-I and BD-II from a mood cluster to a psychosis cluster receives only modest support from data relating to the 11 spectrum criteria. This support may be insufficient to overcome tradition and the substantial symptomatic and therapeutic differences with schizophrenia. There is substantial support for SPD, but psychosis as a defining feature may preclude inclusion of a personality disorder in the psychosis cluster.

Declaration of Interest

Dr Carpenter reports European Regional Patent No. 1487998 (6 June 2007) ‘Methods for Diagnosing and Treating Schizophrenia’ with no potential personal financial reward (proceeds pledged to the Maryland Psychiatric Research Center). In the past 12 months Dr Carpenter has been a consultant to Cephalon and Teva. Dr Bustillo is the speaker for CME LCC and reviewed a book chapter for Merck. Dr Thaker has received a research grant from Mitsubishi Tanabe Pharma. Dr van Os is an unrestricted research grant holder with, or has received financial compensation as an independent symposium speaker from, Eli Lilly, BMS, Lundbeck, Organon, Janssen-Cilag, GSK and AstraZeneca. Drs Krueger and Green report no conflicts of interest relating to this paper.

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