2009

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

W. T. Carpenter Jr.
University of Maryland - Baltimore

J. R. Bustillo
University of New Mexico - Main Campus

G. K. Thaker
University of Maryland - Baltimore

J. van Os
Maastricht University

R. F. Krueger
Washington University School of Medicine in St. Louis

See next page for additional authors

Psychological Medicine (2009), **39**, 2025–2042. © Cambridge University Press 2009
doi:10.1017/S0033291709990286

REVIEW ARTICLE

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'

W. T. Carpenter Jr.[1]*, J. R. Bustillo[2], G. K. Thaker[1], J. van Os[3], R. F. Krueger[4,5] and M. J. Green[6]

[1] *Maryland Psychiatric Research Center, University of Maryland School of Medicine, and the Mental Illness Research, Education and Clinical Center, VISN 5 Veterans Administration, Baltimore, MD, USA*
[2] *Department of Psychiatry, University of New Mexico School of Medicine, Albuquerque, NM, USA*
[3] *Department of Psychiatry and Neuropsychology, Maastricht University, Maastricht, The Netherlands*
[4] *Division of Psychological Medicine, Institute of Psychiatry, London, UK*
[5] *Departments of Psychology and Psychiatry, Washington University in St Louis, St Louis, MO, USA*
[6] *School of Psychiatry, Black Dog Institute, University of New South Wales, Sydney, Australia*

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.

Received 22 May 2008; Revised 7 April 2009; Accepted 12 May 2009; First published online 1 October 2009

Key words: Bipolar, DSM-V, meta-structure, psychosis, schizophrenia.

Introduction

DSM-IV is organized into 16 chapters, and ICD-10 manages a similar number of disorders within 10 chapters. The planning for DSM-V and ICD-11 is in progress. The time is propitious for a fresh look at the organization of disorders into groups or clusters. A new organization could reflect both the risk factors and the clinical manifestations of disorders (Andrews *et al*. 2009*a*). Five clusters of disorders are proposed: Neurocognitive (Sachdev *et al*. 2009), Neurodevelopmental (Andrews *et al*. 2009*b*), Psychoses, Emotional (Goldberg *et al*. 2009*b*) and Externalizing (Krueger & South, 2009).

Here we summarize the evidence for including two boundary disorders in the psychosis cluster, schizotypal personality disorder (SPD) and bipolar disorder (BD), applying 11 spectrum criteria recommended by the DSM-V Study Group (Hyman *et al*. personal communication, December 2007).

Shared genetic risk factors and familiality

Early family and twin studies show that familial risks are partly shared among schizophrenia, other non-affective psychoses and SPD, and, to a lesser extent,

* Address for correspondence: Professor W. T. Carpenter Jr., Maryland Psychiatric Research Center, PO Box 21247, Baltimore, MD 21228, USA.
(Email: wcarpent@mprc.umaryland.edu)

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 (Bramon & Sham, 2001; Craddock & Owen, 2005). Cardno *et al*. (2002) report common and specific genetic contributions to liability for schizophrenia and BD, and schizo-affective disorder overlapped with schizophrenia and/or BD. 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; Hamshere *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)*

	Sz *v.* HNV		BP *v.* HNV	
	Cross	Longitudinal	Cross	Sz *v.* BP
MRI	↓GM +++ ↓WM ++ ↑CSF +	↓GM++ ↓WM+ ↑CSF++	↓GM +	↓GM + (Sz < BP) ↑CSF + (Sz > BP)
H-MRS	↓NAA ++ ↑Glu +		↓NAA +	None
P-MRS	↑PDE +		↑PME +	None
DTI	↓FA ++		Unclear	None
PET receptors	Unclear D_2 receptors		Unclear D_2 receptors	None
fMRI	Network differences ++		Network differences +	Two studies suggest network differences
Post-mortem ultrastructure	↑Neuronal density +		↓Neuronal density + ↓Glial density +	None
Post-mortem gene expression	↓GABA markers ++		↓GABA markers +	↓GABA markers + both disorders

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, phosphodiesters; 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*.

1998; Strakowski *et al*. 1999). 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*) *neuroreceptor studies*

A review of D_2 densities *in vivo* and post-mortem in schizophrenia is suggestive of increased D_2 receptors (Zakzanis & Hansen, 1998). BD with psychosis is also associated with increased striatal D_2 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 D_2 receptor density. This is consistent with the clinical evidence regarding the efficacy of D_2 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

hypofrontal 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 (Altshuler *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 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; Magno *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; Maharajh *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

Table 2. *Summary of neurophysiological marker findings*

Neurophysiological marker	Schizophrenia/ relatives	Bipolar/ relatives	Genetic findings	Implicated neurotransmitter
1. SPEM				
Predictive pursuit	+++/++	+/+	6p21, *COMT*	
Pursuit initiation	+/+	−/−		Nicotine, NMDA
2. P50	++/+	+/+	15q14/*CHRNA7*	Nicotine, adrenergic, serotonergic
3. PPI	++/+	+/+	22q11[a], *NR1*	Dopamine, NMDA, Nicotine
4. P300	++/+	+/+	4q22[b], 1q42[c], *DRD2*, *DRD3*, *COMT*	
5. MMN	++/+	−/−		NMDA
6. Neural synchronization	++/+	+		GABA, NMDA

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 D_2 and D_3 genes; NMDA, *N*-methyl-D-aspartic acid; GABA, gamma-aminobutyric acid.

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

[a] 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.

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.

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*. 2005*b*) and both display earlier onset in men (Kennedy *et al*. 2005*a*). 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 Kraepelinian concept, but heterogeneity in course is present in each syndrome.

Avolitional 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 D_2 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*. 2009*a*). 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.

References

Adler CM, Holland SK, Schmithorst V, Wilke M, Weiss KL, Pan H, Strakowski SM (2004). Abnormal frontal white matter tracts in bipolar disorder: a diffusion tensor imaging study. *Bipolar Disorders* **6**, 197–203.

Akbarian S, Huang H-S (2006). Molecular and cellular mechanisms of altered GAD1/GAD67 expression in schizophrenia and related disorders. *Brain Research Reviews* **52**, 293–304.

Andrews G, Goldberg DP, Krueger RF, Carpenter Jr. WT, Hyman SE, Sachdev P, Pine DS (2009*a*). Exploring the feasibility of a meta-structure for DSM-V and ICD-11: could it improve utility and validity? *Psychological Medicine*. doi:10.1017/S0033291709990250.

Andrews G, Pine DS, Hobbs MJ, Anderson TM, Sunderland M (2009*b*). Neurodevelopmental disorders: Cluster 2 of the proposed meta-structure for DSM-V and ICD-11. *Psychological Medicine*. doi:10.1017/S0033291709990274.

Antila M, Tuulio-Henriksson A, Kieseppa T, Soronen P, Palo OM, Paunio T, Haukka J, Partonen T, Lonnqvist J (2007). Heritability of cognitive functions in families with bipolar disorder. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics* **144B**, 802–808.

Arango C, Moreno C, Martinez S, Parellada M, Desco M, Moreno D, Fraguas D, Gogtay N, James A, Rapoport J (2008). Longitudinal brain changes in early-onset psychosis. *Schizophrenia Bulletin* **34**, 341–353.

Arts B, Jabben N, Krabbendam L, van Os J (2007). Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. *Psychological Medicine* **37**, 1–15.

Altshuler LL, Bartzokis G, Grieder T, Curran J, Mintz J (1998). Amygdala enlargement in bipolar disorder and hippocampal reduction in schizophrenia: an MRI study

demonstrating neuroanatomic specificity. *Archives of General Psychiatry* **55**, 663–664.

Avila MT, Hong LE, Moates A, Turano KA, Thaker GK (2006). Role of anticipation in schizophrenia-related pursuit initiation deficits. *Journal of Neurophysiology* **95**, 593–601.

Badner JA, Gershon ES (2002). Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. *Molecular Psychiatry* **7**, 405–411.

Benes FM, Matzilevich D, Burke RE, Walsh J (2006). The expression of proapoptosis genes is increased in bipolar disorder, but not in schizophrenia. *Molecular Psychiatry* **11**, 241–251.

Berrettini W (2003). Evidence for shared susceptibility in bipolar disorder and schizophrenia. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics* **123C**, 59–64.

Bilder RM, Lipschutz-Broch L, Reiter G, Geisler S, Mayerhoff D, Lieberman JA (1991). Neuropsychological deficits in the early course of first episode schizophrenia. *Schizophrenia Research* **5**, 198–199.

Birmaher B, Axelson D, Monk K, Kalas C, Goldstein B, Hickey MB, Obreja M, Ehmann M, Iyengar S, Shamseddeen W, Kupfer D, Brent D (2009). Lifetime psychiatric disorders in school-aged offspring of parents with bipolar disorder. The Pittsburgh Bipolar Offspring Study. *Archives of General Psychiatry* **66**, 287–296.

Blanchard J, Cohen A (2006). The structure of negative symptoms within schizophrenia: implications for assessment. *Schizophrenia Bulletin* **32**, 238–245.

Bleuler E (1911). *Dementia Praecox or the Group of Schizophrenias* (trans. J. Zinkin, 1950). International Universities Press: New York, NY.

Bora E, Vahip S, Akdeniz F, Ilerisoy H, Aldemir E, Alkan M (2008). Executive and verbal working memory dysfunction in first-degree relatives of patients with bipolar disorder. *Psychiatry Research* **161**, 318–324.

Braff DL, Freedman R, Schork NJ, Gottesman II (2007). Deconstructing schizophrenia: an overview of the use of endophenotypes in order to understand a complex disorder. *Schizophrenia Bulletin* **33**, 21–32.

Braff DL, Geyer MA, Swerdlow NR (2001). Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. *Psychopharmacology* **156**, 234–258.

Brambilla P, Stanley JA, Nicoletti MA, Sassi RB, Mallinger AB, Frank E, Kupfer D, Keshavan MS, Soares JC (2005). 1H magnetic resonance spectroscopy investigation of the dorsolateral prefrontal cortex in bipolar disorder patients. *Journal of Affective Disorders* **86**, 61–67.

Bramon E, McDonald C, Croft RJ, Landau S, Filbey F, Gruzelier JH, Sham PC, Frangou S, Murray RM (2005). Is the P300 wave an endophenotype for schizophrenia? A meta-analysis and a family study. *Neuroimage* **27**, 960–968.

Bramon E, Sham PC (2001). The common genetic liability between schizophrenia and bipolar disorder: a review. *Current Psychiatry Reports* **3**, 332–337.

Brown AS, van Os J, Driessens C, Hoek HW, Susser ES (2000). Further evidence of relation between prenatal famine and major affective disorder. *American Journal of Psychiatry* **157**, 190–195.

Burdick KE, Goldberg JF, Harrow M, Faull RN, Malhotra AK (2006). Neurocognition as a stable endophenotype in bipolar disorder and schizophrenia. *Journal of Nervous and Mental Disease* **194**, 255–260.

Burt T, Prudic J, Peyser S, Clark J, Sackeim H (2000). Learning and memory in bipolar and unipolar major depression: effects of aging. *Neuropsychiatry, Neuropsychology and Behavioral Neurology* **13**, 246–253.

Cadenhead KS, Light GA, Geyer MA, McDowell JE, Braff DL (2002). Neurobiological measures of schizotypal personality disorder: defining an inhibitory endophenotype? *American Journal of Psychiatry* **159**, 869–871.

Cannon TD, Huttunen MO, Lonnqvist J, Tuulio-Henriksson A, Pirkola T, Glahn D, Finkelstein J, Hietanen M, Kapiro J, Koskenvuo M (2000). The inheritance of neuropsychological dysfunction in twins discordant for schizophrenia. *American Journal of Human Genetics* **67**, 369–382.

Cardno AG, Rijsdijk FV, Sham PC, Murray RM, McGuffin P (2002). A twin study of genetic relationships between psychotic symptoms. *American Journal of Psychiatry* **159**, 539–545.

Carpenter Jr. WT, Heinrichs DW, Wagman AM (1988). Deficit and nondeficit forms of schizophrenia: the concept. *American Journal of Psychiatry* **145**, 578–583.

Carpenter WT, Buchanan RW (1989). Domains of psychopathology relevant to the study of etiology and treatment of schizophrenia. In *Schizophrenia: Scientific Progress* (ed. S. C. Schulz and C. T. Tamminga), pp. 13–22. Oxford University Press: New York, NY.

Carpenter WT, Kirkpatrick B (1988). The heterogeneity of the long-term course of schizophrenia. *Schizophrenia Bulletin* **14**, 645–652.

Chang L, Friedman J, Ernst T, Zhong K, Tsopelas ND, Davis K (2007). Brain metabolite abnormalities in the white matter of elderly schizophrenic subjects: implication for glial dysfunction. *Biological Psychiatry* **62**, 1396–1404.

Chapman LJ, Chapman JP, Raulin ML (1976). Scales for physical and social anhedonia. *Journal of Abnormal Psychology* **85**, 374–382.

Claridge G (1997). *Schizotypy: Implications for Illness and Health*. Oxford University Press: Oxford.

Clarke MC, Harley M, Cannon M (2006). The role of obstetric events in schizophrenia. *Schizophrenia Bulletin* **32**, 3–8.

Craddock N, Owen MJ (2005). The beginning of the end for the Kraepelinian dichotomy. *British Journal of Psychiatry* **186**, 364–366.

Dager SR, Friedman SD, Parow A, Demopulos C, Stoll AL, Lyoo IK, Dunner DL, Renshaw PF (2004). Brain metabolic alterations in medication-free patients with bipolar disorder. *Archives of General Psychiatry* **61**, 450–458.

Dawson ME, Nuechterlein KH, Schell AM, Gitlin M, Ventura J (1994). Autonomic abnormalities in schizophrenia: state or trait indicators? *Archives of General Psychiatry* **51**, 813–824.

Deckersbach T, Savage CR, Reilly-Harrington N, Clark L, Sachs G, Rauch SL (2004). Episodic memory impairment in bipolar disorder and obsessive-compulsive disorder: the role of memory strategies. *Bipolar Disorders* **6**, 233–244.

DeLisi LE (2008). The concept of progressive brain change in schizophrenia: implications for understanding schizophrenia. *Schizophrenia Bulletin* **34**, 312–321.

DeLisi LE, Sakuma M, Tew W, Kushner M, Hoff AL, Grimson R (1997). Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. *Psychiatry Research* **74**, 129–140.

Dickinson D, Iannone VN, Wilk CM, Gold JM (2004). General and specific cognitive deficits in schizophrenia. *Biological Psychiatry* **55**, 826–833.

Dickstein DP, Rich BA, Roberson-Nay R, Berghorst L, Vinton D, Pine DS, Leibenluft E (2007). Neural activation during encoding of emotional faces in pediatric bipolar disorder. *Bipolar Disorders* **9**, 679–692.

Dorph-Petersen K-A, Pierri JN, Perel JM, Sun Z, Sampson AR, Lewis DA (2005). The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation: a comparison of haloperidol and olanzapine in macaque monkeys. *Neuropsychopharmacology* **30**, 1649–1661.

Egan MF, Goldberg TE, Gscheidle T, Weirich M, Rawlings R, Hyde TM, Bigelow L, Weinberger DR (2001). Relative risk for cognitive impairments in siblings of patients with schizophrenia. *Biological Psychiatry* **50**, 98–107.

Etain B, Roy I, Henry C, Rousseva A, Schürhoff F, Leboyer M, Bellivier F (2007). No evidence for physical anhedonia as a candidate symptom or an endophenotype in bipolar affective disorder. *Bipolar Disorders* **9**, 706–712.

Fischer BA, Carpenter Jr. WT (2009). Will the Kraepelinian dichotomy survive DSM-V? *Neuropsychopharmacology*. Published online: 18 March 2009. doi:10.1038/npp.2009.32.

Ford JM (1999). Schizophrenia: the broken P300 and beyond. *Psychophysiology* **36**, 667–682.

Frangou S, Donaldson S, Hadjulis M, Landau S, Goldstein LH (2005). The Maudsley Bipolar Disorder Project: executive dysfunction in bipolar disorder I and its clinical correlates. *Biological Psychiatry* **58**, 859–864.

Getz GE, DelBello MP, Fleck DE, Zimmerman ME, Schwiers ML, Strakowski SM (2002). Neuroanatomic characterization of schizoaffective disorder using MRI: a pilot study. *Schizophrenia Research* **55**, 5–9.

Ghaemi SN, Hsu DJ, Soldani F, Goodwin FK (2003). Antidepressants in bipolar disorder: the case for caution. *Bipolar Disorders* **5**, 421–433.

Giakoumaki SG, Roussos P, Rogdaki M, Karli C, Bitsios P, Frangou S (2007). Evidence of disrupted prepulse inhibition in unaffected siblings of bipolar disorder patients. *Biological Psychiatry* **62**, 1418–1422.

Glahn DC, Almasy L, Blangero J, Burk GM, Estrada J, Peralta JM, Meyenberg N, Castro MP, Barrett J, Nicolini H, Raventos H, Escamilla MA (2007). Adjudicating neurocognitive endophenotypes for schizophrenia. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics* **144B**, 242–249.

Glahn DC, Ragland JD, Abramoff A, Barrett J, Laird AR, Bearden CE, Velligan DI (2005). Beyond hypofrontality: a quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. *Human Brain Mapping* **25**, 60–69.

Glantz LA, Lewis DA (2000). Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. *Archives of General Psychiatry* **57**, 65–73.

Glatt SJ, Stone W, Faraone SV, Seidman LJ, Tsuang MT (2006). Psychopathology, personality traits and social development of young first-degree relatives of patients with schizophrenia. *British Journal of Psychiatry* **189**, 337–345.

Goldberg DP, Andrews G, Hobbs MJ (2009*a*). Where should bipolar disorder appear in the meta-structure? *Psychological Medicine*. doi:10.1017/S0033291709990304.

Goldberg DP, Krueger RF, Andrews G, Hobbs MJ (2009*b*). Emotional disorders: Cluster 4 of the proposed meta-structure for DSM-V and ICD-11. *Psychological Medicine*. doi:10.1017/S0033291709990298.

Gottesman II, Gould TD (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *American Journal of Psychiatry* **160**, 636–645.

Green MF (2006). Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *Journal of Clinical Psychiatry* **67**, 36–42.

Green MF, Kern RS, Braff DL, Mintz J (2000). Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the 'right stuff'? *Schizophrenia Bulletin* **26**, 119–136.

Green MJ, Boyle GJ, Raine A (2008). Schizotypy personality models. In *The SAGE Handbook of Personality Theory and Assessment* (ed. G. J. Boyle, G. Matthews and D. H. Saklofske), pp. 399–419. Sage Publications: Los Angeles, CA.

Green MJ, Cahill CM, Malhi GS (2007). The cognitive and neurophysiological basis of emotion dysregulation in bipolar disorder. *Journal of Affective Disorders* **103**, 29–42.

Gur RE, Calkins ME, Gur RC, Horan WP, Nuechterlein KH, Seidman LJ, Stone WS (2007). The consortium on the genetics of schizophrenia: neurocognitive endophenotypes. *Schizophrenia Bulletin* **33**, 49–68.

Hall M-H, Schulze K, Sham P, Kalidindi S, McDonald C, Bramon E, Levy DL, Murray RM, Rijsdijk F (2008). Further evidence for shared genetic effects between psychotic bipolar disorder and P50 suppression: a combined twin and family study. *American Journal of Medical Genetics, Part B, Neuropsychiatric Genetics* **147B**, 619–627.

Hammersley P, Dias A, Todd G, Bowen-Jones K, Reilly B, Bentall RP (2003). Childhood trauma and hallucinations in bipolar affective disorder: preliminary investigation. *British Journal of Psychiatry* **182**, 543–547.

Hamshere ML, Bennett P, Williams N, Segurado R, Cardno A, Norton N, Lambert D, Williams H, Kirov G, Corvin A, Holmans P, Jones L, Jones I, Gill M, O'Donovan MC, Owen MJ, Craddock N (2005). Genomewide linkage scan in schizoaffective disorder: significant evidence for linkage at 1q42 close to DISC1, and suggestive evidence at 22q11 and 19p13. *Archives of General Psychiatry* **62**, 1081–1088.

Harding CM (1988). Course types in schizophrenia: an analysis of European and American studies. *Schizophrenia Bulletin* **14**, 633–643.

Harrison PJ (1999). The neuropathology of schizophrenia: a critical review of the data and their interpretation. *Brain* **122**, 593–624.

Hauser P, Matochik J, Altshuler LL, Denicoff KD, Conrad A, Li X, Post RM (2000). MRI-based measurements of temporal lobe and ventricular structures in patients with bipolar I and bipolar II disorders. *Journal of Affective Disorders* **60**, 25–32.

Henquet C, Krabbendam L, de Graaf R, Ten Have M, van Os J (2006). Cannabis use and expression of mania in the general population. *Journal of Affective Disorders* **95**, 103–110.

Henquet C, Murray R, Linszen D, van Os J (2005). The environment and schizophrenia: the role of cannabis use. *Schizophrenia Bulletin* **31**, 608–612.

Hermann CS, Demiralp T (2005). Human EEG gamma oscillations in neuropsychiatric disorders. *Clinical Neurophysiology* **116**, 2719–2733.

Hill SK, Beers SR, Kmiec JA, Keshavan MS, Sweeney JA (2004). Impairment of verbal memory and learning in antipsychotic-naive patients with first-episode schizophrenia. *Schizophrenia Research* **68**, 127–136.

Hill SK, Harris MSH, Herbener ES, Pavuluri M, Sweeney JA (2008). Neurocognitive allied phenotypes for schizophrenia and bipolar disorder. *Schizophrenia Bulletin* **34**, 743–759.

Ho B-C (2007). MRI brain volume abnormalities in young, nonpsychotic relatives of schizophrenia probands are associated with subsequent prodromal symptoms. *Schizophrenia Research* **96**, 1–13.

Ho B-C, Andreasen NC, Nopoulos P, Arndt S, Magnotta V, Flaum M (2003). Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. *Archives of General Psychiatry* **60**, 585–594.

Hoge EA, Friedman L, Schulz SC (1999). Meta-analysis of brain size in bipolar disorder. *Schizophrenia Research* **37**, 177–181.

Holt DJ, Kunkel L, Weiss AP, Goff DC, Wright CI, Shin LM, Rauch SL, Hootnick J, Heckers S (2006). Increased medial temporal lobe activation during the passive viewing of emotional and neutral facial expressions in schizophrenia. *Schizophrenia Research* **82**, 153–162.

Holzman PS, Proctor LR, Levy DL, Yasillo NJ, Meltzer HY, Hurt SW (1974). Eye-tracking dysfunctions in schizophrenic patients and their relatives. *Archives of General Psychiatry* **31**, 143–151.

Hong LE, Avila M, Adami H, Elliott A, Thaker GK (2003). Components of the smooth pursuit function in deficit and nondeficit schizophrenia. *Schizophrenia Research* **63**, 39–48.

Hong LE, Mitchell BD, Avila MT, Adami H, McMahon RP, Thaker GK (2006). Familial aggregation of eye-tracking endophenotypes in families of schizophrenic patients. *Archives of General Psychiatry* **63**, 259–264.

Hong LE, Summerfelt A, McMahon R, Adami H, Francis G, Eliott A, Buchanan RW, Thaker GK (2004). Evoked gamma band synchronization and the liability for schizophrenia. *Schizophrenia Research* **70**, 293–302.

Hong LE, Summerfelt A, Wonodi I, Adami H, Buchanan RW, Thaker GK (2007). Independent domains of inhibitory gating in schizophrenia and the effect of stimulus interval. *American Journal of Psychiatry* **164**, 61–65.

Hong LE, Turano KA, O'Neill H, Hao L, Wonodi I, McMahon RP, Elliott A, Thaker GK (2008). Refining the predictive pursuit endophenotype in schizophrenia. *Biological Psychiatry* **63**, 458–464.

Hulsoff Pol HE, Kahn RS (2008). What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. *Schizophrenia Bulletin* **34**, 354–366.

Jaspers K (1962). *General Psychopathology* (trans. J. Hoenig and M. W. Hamilton). University of Chicago Press: Chicago.

Johnstone EC, Crow TJ, Frith CD, Owens DG (1988). The Northwick Park 'functional' psychosis study: diagnosis and treatment response. *Lancet* **2**, 119–125.

Kapur S, Mizrahi R, Li M (2005). From dopamine to salience to psychosis – linking biology, pharmacology and phenomenology of psychosis. *Schizophrenia Research* **79**, 59–68.

Kathmann N, Hochrein A, Uwer R, Bondy B (2003). Deficits in gain of smooth pursuit eye movements in schizophrenia and affective disorder patients and their unaffected relatives. *American Journal of Psychiatry* **160**, 696–702.

Katsanis J, Iacono WG, Beiser M, Lacey L (1992). Clinical correlates of anhedonia and perceptual aberration in first-episode patients with schizophrenia and affective disorder. *Journal of Abnormal Psychology* **101**, 184–191.

Kaymaz N, Krabbendam L, de Graaf R, Nolen W, Ten Have M, van Os J (2006). Evidence that the urban environment specifically impacts on the psychotic but not the affective dimension of bipolar disorder. *Social Psychiatry and Psychiatric Epidemiology* **41**, 679–685.

Kendler KS, Gardner CO (1997). The risk for psychiatric disorders in relatives of schizophrenic and control probands: a comparison of three independent studies. *Psychological Medicine* **27**, 411–419.

Kennedy N, Boydell J, Kalidindi S, Fearon P, Jones PB, van Os J, Murray RM (2005*a*). Gender differences in incidence and age at onset of mania and bipolar disorder over a 35-year period in Camberwell, England. *American Journal of Psychiatry* **162**, 257–262.

Kennedy N, Everitt B, Boydell J, van Os J, Jones PB, Murray RM (2005*b*). Incidence and distribution of first-episode mania by age: results from a 35-year study. *Psychological Medicine* **35**, 855–863.

Kirkpatrick B, Buchanan RW, Ross DE, Carpenter Jr. WT (2001). A separate disease within the syndrome of schizophrenia. *Archives of General Psychiatry* **58**, 165–171.

Knable MB, Barci BM, Webster MJ, Meador-Woodruff J, Torrey EF (2004). Molecular abnormalities of the hippocampus in severe psychiatric illness: postmortem findings from the Stanley Neuropathology Consortium. *Molecular Psychiatry* **9**, 609–620.

Krabbendam L, Arts B, van Os J, Aleman A (2005). Cognitive functioning in patients with schizophrenia and

bipolar disorder: a quantitative review. *Schizophrenia Research* **80**, 137–149.

Krabbendam L, van Os J (2005). Schizophrenia and urbanicity: a major environmental influence – conditional on genetic risk. *Schizophrenia Bulletin* **31**, 795–799.

Kraepelin E (1917). *Dementia Praecox and Paraphrenia* (trans. R. M. Bradley, 1971). Robert E. Krieger Publishing Co.: New York, NY.

Krueger RF, South SC (2009). Externalizing disorders: Cluster 5 of the proposed meta-structure for DSM-V and ICD-11. *Psychological Medicine*. doi:10.1017/S0033291709990328.

Kumari V, Das M, Zachariah E, Ettinger U, Sharma T (2005). Reduced prepulse inhibition in unaffected siblings of schizophrenia patients. *Psychophysiology* **42**, 588–594.

Kwon JS, O'Donnell BF, Wallenstein GV, Greene RW, Hirayasu Y, Nestor PG, Hasselmo ME, Potts GF, Shenton ME, McCarley RW (1999). Gamma frequency-range abnormalities to auditory stimulation in schizophrenia. *Archives of General Psychiatry* **56**, 1001–1005.

Laursen TM, Labouriau R, Licht RW, Bertelsen A, Munk-Olsen T, Mortensen PB (2005). Family history of psychiatric illness as a risk factor for schizoaffective disorder: a Danish register-based cohort study. *Archives of General Psychiatry* **62**, 841–848.

Laursen TM, Munk-Olsen T, Nordentoft M, Mortensen PB (2007). A comparison of selected risk factors for unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia from a Danish population-based cohort. *Journal of Clinical Psychiatry* **68**, 1673–1681.

Lawrie SM, McIntosh AM, Hall J, Owens DGC, Johnstone EC (2008). Brain structure and function changes during the development of schizophrenia: the evidence from studies of subjects at increased genetic risk. *Schizophrenia Bulletin* **34**, 330–340.

Lawrie SM, Whalley HC, Abukmeil SS, Kestelman JN, Donnelly L, Miller P, Best JJ, Owens DG, Johnstone EC (2001). Brain structure, genetic liability, and psychotic symptoms in subjects at high risk of developing schizophrenia. *Biological Psychiatry* **49**, 811–823.

Leboyer M, Meyer-Lindenberg A, Stefanis N, Rutten BP, Arango C, Jones P, Kapur S, Lewis S, Murray R, Owen MJ, Linszen D, Kahn R, van Os J, Wiersma D, Bruggeman R, Cahn W, Germeys I, de Haan L, Krabbendam L; European Network of Schizophrenia Networks for the Study of Gene-Environment Interactions (2008). Schizophrenia aetiology: do gene–environment interactions hold the key? *Schizophrenia Research* **102**, 21–26.

Lewis CM, Levinson DF, Wise LH, DeLisi LE, Straub RE, Hovatta I, Williams NM, Schwab SG, Pulver AE, Faraone SV, Brzustowicz LM, Kaufmann CA, Garver DL, Gurling HM, Lindholm E, Coon H, Moises HW, Byerley W, Shaw SH, Mesen A, Sherrington R, O'Neill FA, Walsh D, Kendler KS, Ekelund J, Paunio T, Lönnqvist J, Peltonen L, O'Donovan MC, Owen MJ, Wildenauer DB, Maier W, Nestadt G, Blouin JL, Antonarakis SE, Mowry BJ, Silverman JM, Crowe RR, Cloninger CR, Tsuang MT, Malaspina D, Harkavy-Friedman JM, Svrakic DM, Bassett AS, Holcomb J, Kalsi G, McQuillin A, Brynjolfson J, Sigmundsson T, Petursson H, Jazin E, Zoëga T, Helgason T (2003). Genome scan meta-analysis of schizophrenia and bipolar disorder. Part II: Schizophrenia. *American Journal of Human Genetics* **73**, 34–48.

Lichtenstein P, Yip BH, Bjork C, Pawitan Y, Cannon TD, Sullivan PF, Hultman CM (2009). Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet* **373**, 234–239.

Lieberman J, Chakos M, Wu H, Alvir J, Hoffman E, Robinson D, Bilder R (2001). Longitudinal study of brain morphology in first episode schizophrenia. *Biological Psychiatry* **49**, 487–499.

Lieberman JA, Tollefson GD, Charles C, Zipursky R, Sharma T, Kahn RS, Keefe RS, Green AI, Gur RE, McEvoy J, Perkins D, Hamer RM, Gu H, Tohen M; HGDH Study Group (2005). Antipsychotic drug effects on brain morphology in first-episode psychosis. *Archives of General Psychiatry* **62**, 361–370.

Light GA, Braff DL (2001). Measuring P50 suppression and prepulse inhibition in a single recording session. *American Journal of Psychiatry* **158**, 2066–2068.

Magno E, Yeap S, Thakore JH, Garavan H, De Sanctis P, Foxe JJ (2008). Are auditory-evoked frequency and duration mismatch negativity deficits endophenotypic for schizophrenia? High-density electrical mapping in clinically unaffected first-degree relatives and first-episode and chronic schizophrenia. *Biological Psychiatry* **64**, 385–391.

Maharajh K, Abrams D, Rojas DC, Teale P, Reite ML (2007). Auditory steady state and transient gamma band activity in bipolar disorder. *International Congress Series* **1300**, 707–710.

Malhi GS, Green MJ, Fagiolini A, Peselow ED, Kumari V (2008). Schizoaffective disorder: diagnostic issues and future recommendations. *Bipolar Disorders* **10**, 215–230.

Malhi GS, Ivanovski B, Szekeres V, Olley A (2004). Bipolar disorder: it's all in your mind? The neuropsychological profile of a biological disorder. *Canadian Journal of Psychiatry* **49**, 813–819.

Martinez-Aran A, Vieta E, Colom F, Torrent C, Sanchez-Moreno J, Reinares M, Benabarre A, Goikolea JM, Brugue E, Daban C, Salamero M (2004). Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. *Bipolar Disorders* **6**, 224–232.

Mathalon DH, Sullivan EV, Lim KO, Pfefferbaum A (2001). Progressive brain volume changes and the clinical course of schizophrenia in men: a longitudinal magnetic resonance imaging study. *Archives of General Psychiatry* **58**, 148–157.

McCarley RW, Wible CG, Frumin M, Hirayasu Y, Levitt JJ, Fischer IA, Shenton ME (1999). MRI anatomy of schizophrenia. *Biological Psychiatry* **45**, 1099–1119.

McDonald C, Bullmore E, Sham P, Chitnis X, Suckling J, MacCabe J, Walshe M, Murray RM (2006). Regional volume deviations of brain structure in schizophrenia and psychotic bipolar disorder: computational morphometry study. *British Journal of Psychiatry* **186**, 369–377.

McDonald C, Zanelli J, Rabe-Hesketh S, Ellison-Wright I, Sham P, Kalidindi S, Murray RM, Kennedy N (2004). Meta-analysis of magnetic resonance imaging brain morphometry studies in bipolar disorder. *Biological Psychiatry* **56**, 411–417.

McIntosh AM, Job DE, Moorhead TW, Harrison LK, Lawrie SM, Johnstone EC (2005). White matter density in patients with schizophrenia, bipolar disorder and their unaffected relatives. *Biological Psychiatry*. **58**, 254–257.

McIntosh AM, Job DE, Moorhead TW, Harrison LK, Whalley HC, Johnstone EC, Lawrie SM (2006). Genetic liability to schizophrenia or bipolar disorder and its relationship to brain structure. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics* **141B**, 76–83.

McIntosh AM, Whalley HC, McKirdy J, Hall J, Sussmann JE, Shankar P, Johnstone EC, Lawrie SM (2008). Prefrontal function and activation in bipolar disorder and schizophrenia. *American Journal of Psychiatry* **165**, 378–384.

Michie PT, Innes-Brown H, Todd J, Jablensky AV (2002). Duration mismatch negativity in biological relatives of patients with schizophrenia spectrum disorders. *Biological Psychiatry* **52**, 749–758.

Mortensen PB, Nørgaard-Pedersen B, Waltoft BL, Sørensen T, Hougaard D, Yolken RH (2007). Early infections of *Toxoplasma gondii* and the later development of schizophrenia. *Schizophrenia Bulletin* **33**, 741–744.

Mortensen PB, Pedersen CB, Melbye M, Mors O, Ewald H (2003). Individual and familial risk factors for bipolar affective disorders in Denmark. *Archives of General Psychiatry* **60**, 1209–1215.

Mur M, Portella MJ, Martinez-Aran A, Pifarre J, Vieta E (2008). Long-term stability of cognitive impairment in bipolar disorder: a 2-year follow-up study of lithium-treated euthymic bipolar patients. *Journal of Clinical Psychiatry* **69**, 712–719.

Murray RM, Sham P, van Os J, Zanelli J, Cannon M, McDonald C (2004). A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. *Schizophrenia Research* **71**, 405–416.

O'Donnell BF, Hetrick WP, Vohs JL, Krishnan GP, Carroll CA, Shekhar A (2004). Neural synchronization deficits to auditory stimulation in bipolar disorder. *NeuroReport* **15**, 1369–1372.

O'Driscoll GA, Florencio PS, Gagnon D, Wolff AV, Benkelfat C, Mikula L, Lal S, Evans AC (2001). Amygdala-hippocampal volume and verbal memory in first-degree relatives of schizophrenic patients. *Psychiatry Research* **107**, 75–85.

Olincy A, Martin L (2005). Diminished suppression of the P50 auditory evoked potential in bipolar disorder subjects with a history of psychosis. *American Journal of Psychiatry* **162**, 43–49.

Ongur D, Drevets WC, Price J (1998). Glial reduction in the subgenual prefrontal cortex in mood disorders. *Proceedings of the National Academy of Sciences USA* **95**, 13290–13295.

Owen MJ, Craddock N, Jablensky A (2007). The genetic deconstruction of psychosis. *Schizophrenia Bulletin* **33**, 905–911.

Pavuluri MN, O'Connor MM, Harral EM, Sweeney JA (2008). An fMRI study of the interface between affective and cognitive neural circuitry in pediatric bipolar disorder. *Psychiatry Research* **162**, 244–255.

Pavuluri MN, Schenkel KS, Aryal S, Harral EM, Hill SK, Herbener ES, Sweeney JA (2006). Neurocognitive function in unmedicated manic and medicated euthymic pediatric bipolar patients. *American Journal of Psychiatry* **163**, 286–293.

Pearlson GD, Folley BS (2008). Schizophrenia, psychiatric genetics, and Darwinian psychiatry: an evolutionary framework. *Schizophrenia Bulletin* **34**, 722–733.

Perrin MC, Brown AS, Malaspina D (2007). Aberrant epigenetic regulation could explain the relationship of paternal age to schizophrenia. *Schizophrenia Bulletin* **33**, 1270–1273.

Perry W, Minassian A, Feifel D, Braff DL (2001). Sensorimotor gating deficits in bipolar disorder patients with acute psychotic mania. *Biological Psychiatry* **50**, 418–424.

Phillips ML, Vieta E (2007). Identifying functional neuroimaging biomarkers of bipolar disorder: toward DSM-V. *Schizophrenia Bulletin* **33**, 893–904.

Pierson A, Jouvent R, Quintin P, Perez-Diaz F, Leboyer M (2000). Information processing deficits in relatives of manic depressive patients. *Psychological Medicine* **30**, 545–555.

Potash JB, Willour VL, Chiu YF, Simpson SG, MacKinnon DF, Pearlson GD, Depaulo Jr. JR, McInnis MG (2001). The familial aggregation of psychotic symptoms in bipolar disorder pedigrees. *American Journal of Psychiatry* **158**, 1258–1264.

Quraishi S, Frangou S (2002). Neuropsychology of bipolar disorder: a review. *Journal of Affective Disorders* **72**, 209–226.

Raine A (2006). Schizotypal personality: neurodevelopmental and psychosocial trajectories. *Annual Review of Clinical Psychology* **2**, 291–326.

Rais M, Cahn W, Van-Haren N, Schnack H, Caspers E, Hulshoff Pol H, Kahn A (2008). Excessive brain volume loss over time in cannabis-using first episode schizophrenia patients. *American Journal of Psychiatry* **165**, 490–496.

Rajkowska G, Halaris A, Selemon LD (2001). Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. *Biological Psychiatry* **49**, 741–752.

Rapoport JL, Giedd JN, Blumenthal J, Hamburger S, Jeffries N, Fernandez T, Nicolson R, Bedwell J, Lenane M, Zijdenbos A, Paus T, Evans A (1999). Progressive cortical change during adolescence in childhood-onset schizophrenia: a longitudinal magnetic resonance imaging study. *Archives of General Psychiatry* **56**, 649–654.

Read J, van Os J, Morrison AP, Ross CA (2005). Childhood trauma, psychosis and schizophrenia: a literature review with theoretical and clinical implications. *Acta Psychiatrica Scandinavica* **112**, 330–350.

Robinson LJ, Thompson JM, Gallagher P, Goswami U, Young AH, Ferrier IN, Moore PB (2006). A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *Journal of Affective Disorders* **93**, 105–115.

Rosenberg DR, Sweeney JA, Squires-Wheeler E, Keshavan MS, Cornblatt BA, Erlenmeyer-Kimling L (1997). Eye-tracking dysfunction in offspring from the New York

High-Risk Project: diagnostic specificity and the role of attention. *Psychiatry Research* **66**, 121–130.

Rund BR (1998). A review of longitudinal studies of cognitive functions in schizophrenia patients. *Schizophrenia Bulletin* **24**, 425–435.

Sachdev P, Andrews G, Hobbs MJ, Sunderland M, Anderson TM (2009). Neurocognitive disorders: Cluster 1 of the proposed meta-structure for DSM-V and ICD-11. *Psychological Medicine*. doi:10.1017/S0033291709990262.

Sánchez-Morla EM, García-Jiménez MA, Barabash A, Martínez-Vizcaíno V, Mena J, Cabranes-Díaz JA, Baca-Baldomero E, Santos JL (2008). P50 sensory gating deficit is a common marker of vulnerability to bipolar disorder and schizophrenia. *Acta Psychiatrica Scandinavica* **117**, 313–318.

Sassi RB, Nicoleeti M, Brambilla P, Mallinger AG, Frank E, Kupfer DJ, Keshavan MS, Soares JC (2002). Increased gray matter volume in lithium-treated bipolar disorder patients. *Neuroscience Letters* **329**, 243–245.

Saykin AJ, Gur RC, Gur RE, Mozley PD, Mozley LH, Resnick SM, Kester DB, Stafiniak P (1991). Neuropsychological function in schizophrenia. Selective impairment in memory and learning. *Archives of General Psychiatry* **48**, 618–624.

Scherk H, Kemmer C, Usher J, Reith W, Falkai P, Gurber O (2008). No change to grey and white matter volumes in bipolar I disorder patients. *European Archives of Psychiatry and Clinical Neuroscience* **258**, 345–349.

Schulze KK, Hall M-H, McDonald C, Marshall N, Walshe M, Murray RM, Bramon E (2007). P50 auditory evoked potential suppression in bipolar disorder patients with psychotic features and their unaffected relatives. *Biological Psychiatry* **62**, 121–128.

Scott J, McNeill Y, Cavanagh J, Cannon M, Murray R (2006). Exposure to obstetric complications and subsequent development of bipolar disorder. *British Journal of Psychiatry* **189**, 3–11.

Segurado R, Detera-Wadleigh SD, Levinson DF, Lewis CM, Gill M, Nurnberger Jr. JI, Craddock N, DePaulo JR, Baron M, Gershon ES, Ekholm J, Cichon S, Turecki G, Claes S, Kelsoe JR, Schofield PR, Badenhop RF, Morissette J, Coon H, Blackwood D, McInnes LA, Foroud T, Edenberg HJ, Reich T, Rice JP, Goate A, McInnis MG, McMahon FJ, Badner JA, Goldin LR, Bennett P, Willour VL, Zandi PP, Liu J, Gilliam C, Juo SH, Berrettini WH, Yoshikawa T, Peltonen L, Lönnqvist J, Nöthen MM, Schumacher J, Windemuth C, Rietschel M, Propping P, Maier W, Alda M, Grof P, Rouleau GA, Del-Favero J, Van Broeckhoven C, Mendlewicz J, Adolfsson R, Spence MA, Luebbert H, Adams LJ, Donald JA, Mitchell PB, Barden N, Shink E, Byerley W, Muir W, Visscher PM, Macgregor S, Gurling H, Kalsi G, McQuillin A, Escamilla MA, Reus VI, Leon P, Freimer NB, Ewald H, Kruse TA, Mors O, Radhakrishna U, Blouin JL, Antonarakis SE, Akarsu N (2003). Genome scan meta-analysis of schizophrenia and bipolar disorder. Part III: Bipolar disorder. *American Journal of Human Genetics* **73**, 49–62.

Seidman LJ, Faraone SV, Goldstein JM, Goodman JM, Kremen WS, Tommey R, Tourville J, Kennedy D, Makris N, Caviness VS, Tsuang MT (1999). Thalamic and amygdala-hippocampal volume reductions in first-degree relatives of patients with schizophrenia: an MRI-based morphometric analysis. *Biological Psychiatry* **46**, 941–954.

Selemon LD, Rajkowska G, Goldman-Rakic PS, Watson SJ, Meador-Woodruff JH (1995). Abnormally high neuronal density in the schizophrenic cortex. A morphometric analysis of prefrontal area 9 and occipital area 17. *Archives of General Psychiatry* **52**, 805–820.

Simonsen C, Sundet K, Vaskinn A, Birkenaes AB, Engh JA, Hansen CF, Jonsdottir H, Ringen PA, Opjordsmoen S, Friis S, Andreassen OA (2008). Neurocognitive profiles in bipolar I and bipolar II disorder: differences in pattern and magnitude of dysfunction. *Bipolar Disorders* **10**, 245–255.

Siris SG, Bermanzohn PC, Mason SE, Shuwall MA (1994). Maintenance imipramine therapy for secondary depression in schizophrenia. A controlled trial. *Archives of General Psychiatry* **51**, 109–115.

Sklar P, Smoller JW, Fan J, Ferreira MA, Perlis RH, Chambert K, Nimgaonkar VL, McQueen MB, Faraone SV, Kirby A, de Bakker PI, Ogdie MN, Thase ME, Sachs GS, Todd-Brown K, Gabriel SB, Sougnez C, Gates C, Blumenstiel B, Defelice M, Ardlie KG, Franklin J, Muir WJ, McGhee KA, Macintyre DJ, McLean A, Vanbeck M, McQuillin A, Bass NJ, Robinson M, Lawrence J, Anjorin A, Curtis D, Scolnick EM, Daly MJ, Blackwood DH, Gurling HM, Purcell SM (2008). Whole-genome association study of bipolar disorder. *Molecular Psychiatry* **13**, 558–569.

Slaghuis WL, Bowling AC, French RV (2005). Smooth-pursuit eye movement and directional motion-contrast sensitivity in schizophrenia. *Experimental Brain Research* **166**, 89–101.

Snitz BE, MacDonald AW, Carter CS (2006). Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. *Schizophrenia Bulletin* **32**, 179–194.

Souza VBN, Muir WJ, Walker MT, Glabus MF, Roxborough HM, Sharp CW, Dunan JR, Blackwood DHR (1995). Auditory P300 event-related potentials and neuropsychological performance in schizophrenia and bipolar affective disorder. *Biological Psychiatry* **37**, 300–310.

Steen RG, Mull C, McClure R, Hamer RM, Lieberman JA (2006). Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. *British Journal of Psychiatry* **188**, 510–518.

Stip E, Sepehry AA, Prouteau A, Briand C, Nicole L, Lalonde P, Lesage A (2005). Cognitive discernible factors between schizophrenia and schizoaffective disorder. *Brain and Cognition* **59**, 292–295.

Strakowski SM, DelBello MP, Adler C (2005). The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. *Molecular Psychiatry* **10**, 105–116.

Strakowski SM, DelBello MP, Sax KW, Zimmerman ME, Shear PK, Hawkins JM, Larson ER (1999). Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. *Archives of General Psychiatry* **56**, 254–260.

Strakowski SM, DelBello MP, Zimmerman ME, Getz GE, Mills NP, Ret J, Shear P, Adler CM (2002). Ventricular and periventricular structural volumes in first- versus multiple-episode bipolar disorder. *American Journal of Psychiatry* **159**, 1841–1847.

Strauss JS, Carpenter Jr. WT, Bartko JJ (1974). The diagnosis and understanding of schizophrenia. Part III. Speculations on the processes that underlie schizophrenic symptoms and signs. *Schizophrenia Bulletin* **11**, 61–69.

Sullivan PF (2007). Spurious genetic associations. *Biological Psychiatry* **61**, 1121–1126.

Susser E, Neugebauer R, Hoek HW, Brown AS, Lin S, Labovitz D, Gorman JM (1996). Schizophrenia after prenatal famine. Further evidence. *Archives of General Psychiatry* **53**, 25–31.

Swerdlow NR, Light GA, Cadenhead KS, Sprock J, Hsieh MH, Braff DL (2006). Startle gating deficits in a large cohort of patients with schizophrenia: relationship to medications, symptoms, neurocognition, and level of function. *Archives of General Psychiatry* **63**, 1325–1335.

Tackett J, Silberschmidt A, Krueger RF, Sponheim S (2008). A dimensional model of personality disorder: incorporating DSM Cluster A characteristics. *Journal of Abnormal Psychology* **117**, 454–459.

Thaker GK (2008). Neurophysiological endophenotypes across bipolar and schizophrenia psychosis. *Schizophrenia Bulletin* **34**, 760–773.

Thaker GK, Avila MT, Hong E, Medoff DR, Ross DE, Adami HM (2003). A model of smooth pursuit eye movement deficit associated with the schizophrenia phenotype. *Psychophysiology* **40**, 277–284.

Thaker GK, Ross DE, Cassady SL, Adami HM, LaPorte D, Medoff DR, Lahti A (1998). Smooth pursuit eye movements to extraretinal motion signals: deficits in relatives of patients with schizophrenia. *Archives of General Psychiatry* **55**, 830–836.

Theberge J, Bartha R, Drost DJ, Menon RS, Malla A, Takhar J, Neufeld RW, Rogers J, Pavlosky W, Schaefer B, Densmore M, Al-Semaan Y, Williamson PC (2002). Glutamate and glutamine measured with 4.0 T proton MRS in never-treated patients with schizophrenia and healthy volunteers. *American Journal of Psychiatry* **159**, 1944–1946.

Theberge J, Williamson KE, Aoyama N, Drost DJ, Manchandra R, Malla AK, Northcott S, Menon RS, Neufeld RW, Rajakumar N, Pavlosky W, Densmore M, Schaefer B, Williamson PC (2007). Longitudinal grey-matter and glutamatergic losses in first-episode schizophrenia. *British Journal of Psychiatry* **191**, 325–334.

Tibbo P, Hanstock C, Valiakalayil A, Allen P (2004). 3-T proton MRS investigation of glutamate and glutamine in adolescents at high genetic risk for schizophrenia. *American Journal of Psychiatry* **161**, 1116–1118.

Tomppo L, Hennah W, Miettunen J, Järvelin MR, Veijola J, Ripatti S, Lahermo P, Lichtermann D, Peltonen L, Ekelund J (2009). Association of variants in DISC1 with psychosis-related traits in a large population cohort. *Archives of General Psychiatry* **66**, 134–141.

Torrent C, Martinez-Aran A, Amann B, Daban C, Tabares-Seisdedos R, Gonzalez-Pinto A, Reinares M, Benabarre A, Salamero M, McKenna P, Vieta E (2007). Cognitive impairment in schizoaffective disorder: a comparison with non-psychotic bipolar and healthy subjects. *Acta Psychiatrica Scandinavica* **116**, 453–460.

Torrey EF, Barci BM, Webster MJ, Bartko JJ, Meador-Woodruff JH, Knable MB (2005). Neurochemical markers for schizophrenia, bipolar disorder, and major depression in postmortem brains. *Biological Psychiatry* **57**, 252–260.

Torrey EF, Bartko JJ, Lun Z-R, Yolken RH (2007). Antibodies to *Toxoplasma gondii* in patients with schizophrenia: a meta-analysis. *Schizophrenia Bulletin* **33**, 729–736.

Torrey EF, Yolken RH (2007). Schizophrenia and toxoplasmosis. *Schizophrenia Bulletin* **33**, 727–728.

Trivedi JK, Goel D, Dhyani M, Sharma S, Singh AP, Sinha PK, Tandon R (2008). Neurocognition in first-degree healthy relatives (siblings) of bipolar affective disorder patients. *Psychiatry and Clinical Neurosciences* **62**, 190–196.

Turetsky BI, Calkins ME, Light GA, Olincy A, Radant AD, Swerdlow NR (2007). Neurophysiological endophenotypes of schizophrenia: the viability of selected candidate measures. *Schizophrenia Bulletin* **33**, 69–94.

Turetsky BI, Cannon TD, Gur RE (2000). P300 subcomponent abnormalities in schizophrenia: III. Deficits in unaffected siblings of schizophrenic probands. *Biological Psychiatry* **47**, 380–390.

Umbricht D, Koller R, Schmid L, Skrabo A, Grübel C, Huber T, Stassen H (2003). How specific are deficits in mismatch negativity generation to schizophrenia? *Biological Psychiatry* **53**, 1120–1131.

Umbricht D, Krljes S (2005). Mismatch negativity in schizophrenia: a meta-analysis. *Schizophrenia Research* **76**, 1–23.

Urban A, Kremlácek J, Masopust J, Libiger J (2008). Visual mismatch negativity among patients with schizophrenia. *Schizophrenia Research* **102**, 320–328.

van Beijsterveldt CEM, van Baal GCM, Molenaar PCM, Boomsma DI, de Geus EJC (2001). Stability of genetic and environmental influences on P300 amplitude: a longitudinal study in adolescent twins. *Behavior Genetics* **31**, 533–543.

van Haren NEM, Cahn W, Hulshoff Pol HE, Schnack HG, Caspers E, Lemstra A, Sitskoom MM, Wiersma D, van den Bosch RJ, Dingemans PM, Schene AH, Kahn RS (2003). Brain volumes as predictor of outcome in recent-onset schizophrenia: a multi-center MRI study. *Schizophrenia Research* **64**, 41–52.

van Os J, Hanssen M, Bijl R-V, Ravelli A (2000). Straus (1969) revisited: a psychosis continuum in the general population? *Schizophrenia Research* **45**, 11–20.

van Os J, Jones P, Sham P, Bebbington P, Murray RM (1998). Risk factors for onset and persistence of psychosis. *Social Psychiatry and Psychiatric Epidemiology* **33**, 596–605.

van Os J, Kapur S (in press). Schizophrenia – linking biology, epidemiology and pharmacology. *Lancet*.

van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychological Medicine* **39**, 179–195.

van Os J, Rutten BP, Poulton R (2008). Gene–environment interactions in schizophrenia: review of epidemiological findings and future directions. *Schizophrenia Bulletin* **34**, 1066–1082.

Watson D, Clark LA, Chmielewski M (2008). Structures of personality and their relevance to psychopathology: II. Further articulation of a comprehensive unified trait structure. *Journal of Personality* **76**, 1545–1585.

Wellcome Trust Case Control Consortium (2007). Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* **447**, 661–678.

Widiger TA, Simonsen E, Krueger RF, Livesley JW, Verheul R (2005). Personality disorder research agenda for the DSM-V. *Journal of Personality Disorders* **19**, 315–338.

Winterer G, Egan MF, Raedler T, Sanchez C, Jones DW, Coppola R, Weinberger DR (2003). P300 and genetic risk for schizophrenia. *Archives of General Psychiatry* **60**, 1158–1167.

Wood SJ, Pantelis C, Velakoulis D, Yucel M, Fornito A, McGorry PD (2008). Progressive changes in the development toward schizophrenia: studies in subjects at increased symptomatic risk. *Schizophrenia Bulletin* **34**, 322–329.

Woodberry KA, Guiliano AJ, Seidman LJ (2008). Premorbid IQ in schizophrenia: a meta-analytic review. *American Journal of Psychiatry* **165**, 579–587.

Woodruff PWR, McManus IC, David AS (1995). Meta-analysis of corpus callosum size in schizophrenia. *Journal of Neurology, Neurosurgery and Psychiatry* **58**, 457–461.

Woods BT (1998). Is schizophrenia a progressive neurodevelopmental disorder? Toward a unitary pathogenic mechanism. *American Journal of Psychiatry* **155**, 1661–1670.

Wright IC, Rabe-Hesketh S, Woodruff PWR, David AS, Murray RM, Bullmore ET (2000). Meta-analysis of regional brain volumes in schizophrenia. *American Journal of Psychiatry* **157**, 16–25.

Yildiz-Yesiloglu A, Ankerst DP (2006). Neurochemical alterations of the brain in bipolar disorder and their implications for pathophysiology: a systematic review of the in vivo proton magnetic resonance spectroscopy findings. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **30**, 969–995.

Yolken RH, Torrey EF (2008). Are some cases of psychosis caused by microbial agents? A review of the evidence. *Molecular Psychiatry* **13**, 470–479.

Yurgelun-Todd DA, Silveri MM, Gruber SA, Rohan ML, Pimentel PJ (2007). White matter abnormalities observed in bipolar disorder: a diffusion tensor imaging study. *Bipolar Disorders* **9**, 504–512.

Zakzanis KK, Hansen KT (1998). Dopamine D2 densities and the schizophrenic brain. *Schizophrenia Research* **32**, 201–206.

Zalla T, Joyce C, Szoke A, Schurhoff F, Pillon B, Komano O, Perez-Diaz F, Bellivier F, Alter C, Dubois B, Rouillon F, Houde O, Leboyer M (2004). Executive dysfunctions as potential markers of familial vulnerability to bipolar disorder and schizophrenia. *Psychiatry Research* **121**, 207–217.