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Review Article

The course of neuropsychological impairment and brain structure abnormalities in psychotic disorders

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ABSTRACT

Neuropsychological impairment and abnormalities in brain structure are commonly observed in psychotic disorders, including schizophrenia and bipolar disorder. Shared deficits in neuropsychological functioning and abnormalities in brain structure suggest overlapping neuropathology between schizophrenia and bipolar disorder which has important implications for psychiatric nosology, treatment, and our understanding of the etiology of psychotic illnesses. However, the emergence and trajectory of brain dysfunction in psychotic disorders is less well understood. Differences in the course and progression of neuropsychological impairment and brain abnormalities among psychotic disorders may point to unique neuropathological processes. This article reviews the course of neuropsychological impairment and brain structure abnormalities in schizophrenia and bipolar disorder.

Contents

1. Introduction

Psychotic disorders, including schizophrenia (SCZ) and bipolar disorder (BD) with psychotic features (i.e. psychotic BD), are often chronic, debilitating illnesses that result in lifelong limitations in psychosocial functioning, significant caregiver burden, and substantial economic costs (Wu et al., 2005; Meltzer, 1999; Hegarty et al., 1994; Green et al., 2000; Conus et al., 2014; Sanchez-Moreno et al., 2009). In addition to similarities in clinical symptoms and functional outcome, there is also considerable overlap between SCZ and BD in cognitive impairment, brain structure abnormalities, and genetic vulnerability (Maier et al., 2006). However, emerging evidence indicates there are also differences between disorders in the severity and course of brain dysfunction (Lewandowski et al., 2011). Uncovering similarities and differences between disorders will have important implications for psychiatric nosology, clinical

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management and treatment, and our understanding of the etiology of psychotic illnesses.

This article reviews the trajectories of neuropsychological impairment and brain structure abnormalities in SCZ and BD, primarily psychotic BD whenever possible, focusing in particular on the pre-morbid, early stage, and chronic stages of the disorders. Particular attention is paid to seminal papers and relevant meta-analyses and qualitative reviews. The article begins with a brief overview of normal cognitive and brain development, focusing primarily on the development of cognitive abilities disrupted in psychotic illnesses and macro-level changes in brain structure.

2. Typical neuropsychological and brain development

2.1. Defining neuropsychological phenotypes

The terms "cognition" and "neuropsychology" subsume a diverse array of constructs and abilities that are measured to varying degrees of precision using a wide range of tests. Before reviewing the development of neuropsychological functioning, it is necessary to define the scope of our review by organizing the spectrum of cognitive abilities that are typically assessed in clinical neuropsychology. Even within the field of clinical neuropsychology, it can be challenging to come up with a parsimonious way of classifying the large number of commonly used tests. Quantitative factor analytic methods have a rich history in psychology and have proven very useful for grouping tests into empirically derived cognitive domains. For example, in the first step toward developing a common set of clinical neuropsychological tests to assess cognitive change in treatment trials in SCZ, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative reviewed all empirical factor analysis studies of cognitive function in SCZ (Nuechterlein et al., 2004). The results of this effort revealed seven domains of cognitive function that included Verbal Comprehension, Processing Speed, Attention/Vigilance, Working Memory, Verbal Learning and Memory, Visual Learning and Memory, and Reasoning and Problem Solving. We focus our review on these cognitive domains. It should be noted however that most domains of cognitive function identified in factor analysis studies are not completely independent as they correlate with one another to some extent and are usually related to overall intellectual abilities to some degree (August et al., 2012; Tulsky and Price, 2003). For example, verbal comprehension, working memory, and processing speed, although separate factors, are often subsumed under intellectual abilities (Wechsler, 1997). While the multifactorial nature of many neuropsychological tests compared to experimental cognitive approaches, which focus on isolating relatively specific cognitive abilities, is a drawback, the rigorous standardization they have undergone and abundant data on the developmental trajectories of these constructs in healthy subjects are distinct advantages.

2.2. Developmental neuropsychology

Global cognitive functioning, as measured using standardized tests of intelligence for example, continues to develop well into adulthood (Wechsler, 1997). However, there are marked differences in the development, and subsequent decline with aging, of the various factors comprising intelligence (Wechsler, 1997). For instance, so-called "crystallized" abilities reflecting general knowledge and verbal comprehension show a protracted development, peaking in middle age, and remaining relatively stable into old age. In contrast, fluid reasoning and mental processing speed peak relatively early, in adolescence, and decline in a linear fashion throughout adulthood and into old age (Tulsky et al., 2003). Similarly, new learning and memory for verbal and visual material peaks in late childhood/early adolescence, then decreases linearly from early adulthood through old age (Tulsky et al., 2003).

The developmental course of executive cognitive abilities, including working memory, has attracted considerable attention given the prominent role these abilities play in shaping behavior and psychopathology (Salloway et al., 2001). The term 'executive functioning' is a general descriptor that subsumes a number of conceptually complicated processes such as volition, planning and reasoning, and goal-directed behavior (Lezak, 1995). Measuring these abilities with standardized tests is challenging as these concepts can be difficult to operationally define and many tests of executive functioning are multifactorial. That is, they assess more than one ability. Attempts to fractionate executive functions have generally revealed several dissociable factors, including working memory, inhibition/resistance to distraction, and mental set shifting (Miyake et al., 2000). The development of these abilities is protracted. Mental set-shifting, as commonly assessed with the Wisconsin Card Sorting test for example, continues to improve until about age 20 and remains relatively stable until about the sixth decade of life (Heaton et al., 1993). Working memory on the other hand, reaches adult levels in adolescence then, starting in the third decade of life, begins to decline with the decline accelerating around the 7th decade of life (Tulsky et al., 2003).

2.3. Brain development

Brain development has received considerable attention in the neuroimaging community. Several key findings, focusing on studies from early childhood through adulthood are reviewed here. During normal brain development, total brain volume (TBV) increases rapidly in the first 5–6 years of life in parallel with intracranial volume (ICV) (Kamdar et al., 2009; Sgouros et al., 1999). Then, starting around age 12, TBV and ICV begin to diverge; TBV gradually declines throughout adulthood and ICV remains relatively static (Courchesne et al., 2000; Lenroot et al., 2007). This divergence may have important implications for understanding pathological processes and, possibly, the timing of the onset of neuropathological abnormalities. Specifically, ICV can be considered a proxy of early brain development and discrepancies between TBV and ICV an indicator of later neurodegenerative changes and age-related atrophy (Davis and Wright, 1977). The developmental trajectories of the two tissue classes comprising TBV, gray and white matter, vary. Gray matter volume increases rapidly, peaking between 8 and 12 years of age, then gradually declines over time (Lenroot et al., 2007; Good et al., 2001). White matter on the other hand increases from childhood throughout early adulthood and remains relatively stable thereafter (Lenroot et al., 2007; Good et al., 2001).

Just as the trajectories of overall tissue volumes differ, the developmental trajectories of specific brain structures also varies. Frontal, including anterior cingulate cortex and dorsolateral prefrontal cortex (PFC), and temporal lobes are the last to reach adult levels when it comes to gray matter volume and cortical thickness, which is consistent with evidence that synaptic pruning in these regions extends into early adulthood (Giedd, 2004; Shaw et al., 2008). Frontal lobe white matter is also the last to reach full maturity (Reiss et al., 1996). The prolonged development of the frontal lobes presumably reflects the extended development of the 'higher' cognitive functions supported by this region (Lourenco and Casey, 2013).

3. Neuropsychological impairment in psychotic disorders

Neuropsychological impairment is well-established in psychotic illnesses (Heinrichs and Zakzanis, 1998). However, the

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degree of overlap between SCZ spectrum illnesses and BD remains an active area of investigation. In SCZ spectrum disorders, neuropsychological impairment is characterized by a generalized deficit in overall cognitive ability. Typically, patients perform about 1–2 standard deviation below normal compared to healthy subjects on most neuropsychological measures (Heinrichs and Zakzanis, 1998). Overlaid on generalized cognitive impairment are more severe deficits in specific cognitive domains including executive functioning, mental processing speed, and memory (Dickinson et al., 2004, 2008). For example, SCZ patients with average overall intellectual abilities exhibit impairment in reasoning and problem solving, verbal memory, and processing speed (Weickert et al., 2000; Wilk et al., 2005). While there is overwhelming evidence that SCZ is associated with cognitive impairment, the issue of whether or not it is a core feature of the illness exhibited by all patients, as some have argued, remains a controversial and unresolved issue (see Kahn and Keefe, 2013; Heckers, 2013). On the one hand, there is evidence that a substantial minority of individuals with SCZ, perhaps as many as 30%, do not exhibit cognitive impairment, at least when compared to standard normative data (Palmer et al., 1997). On the other hand, family studies, including discordant twins studies, have found that even patients that perform within the 'normal' range exhibit subtle cognitive deficits when compared to their unaffected family members and pre-morbid expectations based on parental education suggesting that most, if not all, individuals with SCZ exhibit at least some degree of cognitive impairment (Keefe et al., 2005; Goldberg et al., 1990).

Neuropsychological impairment is also prominent in BD and, like SCZ, is characterized by deficits in processing speed, memory, and executive functioning (Mann-Wrobel et al., 2011). However, cognitive impairment in BD is not as severe as SCZ. Specifically, meta-analytic reviews have found that the effect size (ES) for cognitive impairment in SCZ ranges from approximately −1.0 to −1.5, whereas impairment in BD averages between −0.5 and −0.7 (Mann-Wrobel et al., 2011; Heinrichs and Zakzanis, 1998). However, there is growing evidence that cognitive impairment in BD is quite heterogeneous, varying as a function of the presence of psychotic symptoms and illness stage. Specifically, cognitive impairment is greater in BD patients with a history of psychosis (Bora et al., 2010). Indeed, cognitive impairment in chronic BD patients with psychotic features may be virtually indistinguishable from SCZ (Simonsen et al., 2011; Reichenberg et al., 2009).

The following sections focus on neuropsychological impairment in psychotic disorders at three distinct illness stages: pre-morbid, first episode/early stage, and chronic.

3.1. Premorbid neuropsychological functioning

Cross sectional investigations in patients already diagnosed with SCZ have found that pre-morbid functioning, usually estimated using tests that correlate well with intellectual measures but are relatively insensitive to acute brain injury, is impaired in SCZ (Heinrichs and Zakzanis, 1998). However, the best evidence of impaired pre-morbid functioning comes from studies that assessed cognitive functioning in individuals prior to illness onset. Recent meta-analysis of such studies confirmed that pre-morbid intellectual functioning is indeed impaired in SCZ (Woodberry et al., 2008; Khandaker et al., 2011). For example, Woodberry et al. (2008) found that the average ES for pre-morbid intellectual impairment in SCZ derived from 18 studies was approximately −0.5. As discussed earlier, intellectual functioning is a multi-factorial construct reflecting aggregate functioning of a number of abilities. At the broadest level, these abilities are often divided into verbal and non-verbal intellectual abilities (Wechsler, 1997). An obvious question that emerges then is "is pre-morbid intellectual impairment in SCZ due to a selective deficit in verbal (i.e. crystallized abilities) or non-verbal abilities (i.e. fluid reasoning)?" This does not appear to be the case as the meta-analysis by Woodberry et al. (2008) and Khandaker et al. (2011) concluded that verbal and non-verbal abilities were equally affected. Similarly, the available evidence indicates that more specific cognitive abilities, including attention, processing speed, and working memory, are also impaired in individuals who later go on to develop SCZ (Meier et al., 2014).

In contrast to SCZ, considerably less is known about pre-morbid cognitive function in BD, particularly psychotic BP. Generally speaking, premorbid cognitive functioning is relatively intact or only mildly impaired in BD (Gilvarry et al., 2000; Koenen et al., 2009; Mann-Wrobel et al., 2011; Seidman et al., 2013). Moreover, investigations directly comparing pre-morbid cognitive functioning between SCZ and BD often find greater pre-morbid cognitive impairment in SCZ. In a retrospective epidemiological study, Reichenberg et al. (2002), found that patients who went on to develop SCZ as adults performed significantly worse on intellectual and cognitive tests administered during childhood compared to healthy subjects and individuals who subsequently developed BD, which did not differ from one another. Similar results were obtained by Seidman et al. (2013) in a longitudinal investigation of SCZ and psychotic BD. Specifically, SCZ patients assessed at age 7 exhibited deficits in intellectual functioning, academic achievement and most domains of neuropsychological functioning, whereas there were no significant differences between psychotic BD and healthy subjects. However, closer inspection revealed subtle impairment in processing speed and a linear trend in impairment with psychotic BD patients performing intermediate between healthy subjects and SCZ. Moreover, approximately 23% of children that went on to develop psychotic BD were classified as neuropsychologically impaired, defined as having scores that fell below the 10th percentile, compared to 42% in SCZ, suggesting that psychotic BD is associated with subtle pre-morbid cognitive impairment, but less so than that observed in SCZ.

3.2. First-episode/early-stage

It is well-established that cognitive function is impaired at illness onset in SCZ. A meta-analytic review of studies published prior to 2009 concluded that first-episode SCZ patients exhibit widespread impairment that includes prominent deficits in general intellectual ability, processing speed, attention, memory, working memory, and executive functioning (Mesholam-Gately et al., 2009). The severity of impairment in first-episode patients, on the order of ES = −1.0, is approximately double the magnitude of impairment detected in the premorbid phase of the illness, but roughly comparable to that observed in chronic patients (Mesholam-Gately et al., 2009). This suggests that cognitive dysfunction in SCZ is largely in place by the first psychotic episode, but that there is significant cognitive deterioration between pre-morbid and first episode stages of the illness. The results of a recent longitudinal epidemiological study provide compelling support for this hypothesis. Specifically, using the Dunedin Multidisciplinary Health and Development Study cohort, Meier et al. (2014) compared neuropsychological functioning in healthy subjects and individuals with SCZ at ages 7, 9, 11, 13, and 38. They found that intellectual functioning declined markedly between the cognitive assessments conducted at ages 13 and 38 in SCZ, but not healthy subjects. The decline in processing speed was particularly pronounced. In contrast, cognitive functioning in individuals with persistent depression and mild cognitive impairment remained stable indicating that cognitive deterioration was specific to SCZ.

As with the pre-morbid stage, cognitive function in first-episode BD has received considerably less attention than in SCZ, especially in psychotic BD. Nonetheless, two consistent findings have emerged. First, compared to healthy subjects, patients in the early

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stage of psychotic BD exhibit cognitive impairment; however, the pattern and severity of impairment differs across studies (Zanelli et al., 2010; Hill et al., 2009; Barrett et al., 2009; Dickerson et al., 2011). For example, Dickerson et al. (2011) reported deficits in overall cognitive functioning and executive cognitive abilities in a sample of 60 psychotic BD patients examined within 2 years of illness onset. In contrast, a recent population-based investigation of various first-episode psychotic disorders carried out by Zanelli et al. (2010) found that cognitive impairment in psychotic BD was limited to just verbal fluency and verbal memory. The second consistent finding is that cognitive impairment is more severe in first episode SCZ spectrum illnesses than it is in psychotic BD. In the Dickerson et al. (2011) study discussed above, overall cognitive functioning, language abilities, and memory were more severely impaired in SCZ compared to psychotic BD. Similarly, Barrett et al. (2009), Hill et al. (2009), and Zanelli et al. (2010) all found significantly greater cognitive impairment in SCZ compared to psychotic BD.

3.3. Chronic stage

As reviewed above, there is strong evidence for cognitive decline between the pre-morbid and first-episode stages in SCZ. Does this decline mark the onset of degenerative process that continues throughout the illness or is it more consistent static encephalopathy that remains stable over time? The available evidence strongly favors the latter hypothesis. For instance, examining cognitive changes over the first 5 years of illness, Gold et al. (1999) found no significant decline in cognitive functioning. Similarly, a review of the literature concluded that there was little evidence of progressive cognitive decline in SCZ, even out to 10 years after the onset of psychosis (Bozikas and Andreou, 2011).

In contrast to SCZ, emerging evidence, suggests that cognitive function may decline over the course of illness in BD, especially in patients with a history of psychotic features. As noted in the preceding section, neuropsychological impairment is relatively mild in the early-stage of the illness and considerably less severe compared to SCZ (Zanelli et al., 2010). In contrast, there is considerable data indicating that neuropsychological functioning is markedly impaired in chronic BD, especially in patients with a history of psychosis. For example, a large investigation of over 200 psychosis patients found that BD patients demonstrated widespread neuropsychological impairment that was on par with the deficits observed in SCZ and schizoaffective disorder (Simonsen et al., 2011). In contrast, cognitive impairment in BD patients without a history of psychosis was restricted to processing speed highlighting the trans-diagnostic importance of psychosis for cognitive impairment.

4. Brain structure abnormalities in psychotic disorders

Neuropsychological deficits in psychotic illnesses presumably result from abnormalities in brain structure and function. The literature examining brain structure using modern neuroimaging methods is voluminous, especially in SCZ, dating back to the 1970s. The earliest studies used manual tracing methods in which specific brain structures, such as the lateral ventricles, temporal lobes, and hippocampus, were manually traced on brain scans. Reviews and meta-analyses of these studies in SCZ revealed several abnormalities. The most consistent findings include decreased ICV and TBV, enlargement of the lateral and third ventricles, and smaller whole brain gray matter volume due to reductions in the size of frontal, temporal, and sub-cortical brain structures. Reduced volume of the superior temporal gyrus, hippocampus and parahippocampal gyrus, and thalamus are among the most consistent findings (McCarley et al., 1999; Shenton et al., 2001). Although structural brain abnormalities are commonly observed in SCZ, the magnitude of the changes are modest, generally falling within the range of 5–10% for specific structures and <5% for whole-brain volumes (Wright et al., 2000).

Advances in computing power coupled with the development of computational neuroimaging approaches over the past two decades led to an explosion in the use of automated and semi-automated methods for quantifying cerebral morphology. The main advantages of these methods, in addition to being less-laborious, is that they can be used to examine structural changes throughout the brain and investigate morphological features, such as cortical thickness and the shape of structures, that are difficult to assess using manual tracing. The most popular of these approaches is voxel-based morphometry (VBM) which is used to investigate brain structure at the voxel-wise level, typically 1–2 mm. Meta-analytic reviews of VBM studies in SCZ confirmed many of the findings initially reported in manual tracing investigations, such as reduced volume of lateral and medial temporal lobe structures, and reduced thalamic volume (Glahn et al., 2008; Fornito et al., 2009). However, VBM studies also revealed abnormalities in brain structures that had received little attention in manual tracing investigations, including prominent gray matter volume decreases in the anterior insula and medial PFC (Glahn et al., 2008; Fornito et al., 2009). In addition to reduced volume, computational neuroanatomy approaches have also identified widespread cortical thinning in SCZ, involving mainly the frontal and temporal lobes, and abnormal shape of sub-cortical structures such as the hippocampus and thalamus (Rimol et al., 2012; Cronenwett and Csernansky, 2010; Csernansky et al., 2002).

In BD, manual tracing ROI studies revealed a slight reduction in TBV, reduced frontal lobe volume, increased size of the globus pallidus, and lateral ventricular enlargement (Arnone et al., 2009). Recent meta-analyses by Ellison-Wright and Bullmore (2010) and Selvaraj et al. (2012) of VBM studies, which included 14 and 8 studies, respectively, expanded on the gray matter findings reported in manual tracing studies by revealing gray matter volume loss in ventral PFC, anterior insula, and anterior cingulate-key regions involved in emotion and mood regulation (Strakowski et al., 2012). Qualitatively, the brain structure abnormalities observed in BD appear much less severe than what is seen in SCZ. Indeed, a recent meta-analysis of VBM studies by Ellison-Wright and Bullmore (2010) compared BD and SCZ and concluded that gray matter volume reductions in SCZ were more extensive in the cortex, extending to include lateral and medial temporal lobe regions, lateral PFC, posterior cingulate, and sub-cortical structures, including the thalamus.

4.1. First episode/early stage

Fewer investigations have examined brain structure in the earliest stages of a psychotic illness, especially in BD. Nonetheless, a recent meta-analysis of over 40 studies that measured whole-brain volumes revealed a number of similarities and differences between SCZ and BD (De et al., 2012). Specifically, similar to chronic patients, first episode SCZ is associated with smaller ICV and TBV, reduced total gray matter volume, and lateral ventricular enlargement (De et al., 2012). ICV and TBV were also reduced in first episode BD; however, unlike SCZ, gray matter volume was not affected, but white matter volume was reduced compared to healthy subjects. Moreover, lateral ventricular enlargement, while present, was not as severe as that observed in SCZ (De et al., 2012). In brief, the findings in early-stage psychosis appear to recapitulate the main theme in chronic patients that both SCZ and BD are associated with abnormalities in brain structure, but that the changes are more widespread in SCZ.

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4.2. Progressive brain abnormalities and medication effects

As with cognitive function, there is considerable interest in determining if brain structure abnormalities progress over time in psychotic disorders. Generally speaking, progressive changes would implicate neurodegenerative pathological processes, whereas static abnormalities favor neurodevelopmental hypotheses. The dominant etiological models for SCZ are the neurodevelopmental hypotheses which, in the broadest sense, posit that SCZ results from disruption or derailment of normal maturational processes occurring in early life (e.g. Weinberger, 1995). The neurodevelopmental model is supported by a diverse array of data. For example, individuals with SCZ exhibit higher rates of obstetric complications, neurological soft signs, and minor physical anomalies, and demonstrate subtle deficits in motor abilities and cognitive function several years before the onset of florid psychotic symptoms (Rapoport et al., 2012).

Findings from neuroimaging investigations of patients, including reduced ICV, higher incidence of cavum septum pallicidum, and atypical or loss of normal cerebral asymmetry in individuals with established SCZ, and evidence of subtle brain structure abnormalities in at-risk individuals are consistent with atypical neurodevelopment (Wood et al., 2009; Shenton et al., 2001; Trzesniak et al., 2011). However, emerging evidence indicates that there are also progressive brain changes in SCZ. A qualitative review of longitudinal studies in first-episode SCZ, which ranged in duration from 1 to 10 years after illness onset, concluded that the most robust funding was accelerated enlargement of the lateral ventricles compared to healthy subjects (Hulshoff Pol and Kahn, 2008). Increased rate of volume loss of the frontal lobe, lateral temporal lobe (i.e. superior temporal gyrus), thalamus, and whole brain volume were also consistently reported. In contrast, there was little evidence of progressive volume loss of the hippocampus and cerebellum. Recent quantitative meta-analyses confirmed many of these findings, including accelerated lateral ventricular enlargement, and progressive whole brain, frontal lobe gray and white matter, and parietal and temporal lobe white matter volumes (Kempton et al., 2010; Olabi et al., 2011). No progressive changes were reported in medial temporal lobe structures, including hippocampus and amygdala (Olabi et al., 2011). In terms of magnitude, the increased rate of volume loss in SCZ ranges from approximately 0.1% to 0.6% per year (Olabi et al., 2011; Hulshoff Pol and Kahn, 2008). Progressive brain changes have also been linked to cognitive decline, at least in the early stage of the illness (Andreasen et al., 2011).

While the evidence supporting progressive changes in brain anatomy in SCZ is compelling, the interpretation of the finding is controversial. This is due, in large part, to the difficulty disentangling the effects of the illness from the effects of psychotropic medications and deleterious lifestyle choices (e.g. substance abuse). With respect to antipsychotic medications, findings from controlled animal studies are clear: antipsychotics are associated with accelerated brain volume loss (Vernon et al., 2012; Dorph-Petersen et al., 2005). The interpretation of clinical studies is much less straightforward as medication effects are often examined with underpowered post hoc analyses; few controlled clinical trials exist. However, a recent meta-analysis of longitudinal investigations found that gray matter volume loss was inversely correlated with cumulative exposure to antipsychotics, consistent with a neurotoxic effect (Fusar-Poli et al., 2013). However, increased ventricular enlargement was unrelated to antipsychotic exposure suggesting that progressive brain changes in SCZ are not entirely attributable to antipsychotic medication (Fusar-Poli et al., 2013). The issue is further complicated by evidence that antipsychotic drug effects on brain structure vary between typical and atypical antipsychotics. Specifically, a controlled trial comparing antipsychotics found that the typical antipsychotic haloperidol was associated with greater total gray matter volume loss over time compared to olanzapine (Lieberman et al., 2005). A follow-up analysis of this dataset suggested that the reduction in gray matter volume with haloperidol was due to accelerated gray matter density loss in frontal and parietal lobe regions (Thompson et al., 2009).

Evidence that antipsychotics are associated with accelerated brain volume loss does not necessarily mean that these medications are neurotoxic as illness severity and cumulative antipsychotic exposure likely go hand-in-hand. That is, individuals with persistent symptoms may suffer from a more virulent form of psychosis that, in turn, results in higher cumulative exposure to antipsychotics. Recently, using data from the Iowa Longitudinal Study of first-episode SCZ, Andreasen and colleagues (2013) attempted to tease apart illness effects from antipsychotic effects. They found that the duration of relapse, defined as the re-emergence of moderate to severe psychotic symptoms following a 6-month or longer period of mild symptoms, was associated with greater whole brain, total white matter, and frontal lobe volume loss after statistically controlling for the intensity of antipsychotic treatment. Moreover, in contrast to the relatively focal effects of relapse duration on frontal lobe volume, antipsychotic effects were more widespread extending to temporal and parietal lobes, and including ventricular enlargement. As such, a reasonable tentative conclusion is that brain abnormalities in SCZ are progressive and related to relapse, but antipsychotics also exert mild deleterious effects on brain structure.

Compared to SCZ, few studies have investigated brain structure abnormalities in BD over the course of the illness. A recent review of longitudinal studies reported accelerated volume loss mainly in the PFC, primarily dorsolateral PFC, anterior cingulate, and subgenual cortex (Lim et al., 2013). In contrast, no consistent changes were detected in TBV and medial temporal structures, including amygdala and hippocampus. As with SCZ, medication effects are an important confound; many BD patients with a history of psychosis receive long-term treatment with antipsychotics in addition to mood stabilizers. Post hoc, secondary analyses in cross-sectional studies have not found consistent effects of antipsychotics on brain structure (Hafeman et al., 2012). Unfortunately, longitudinal investigations are scarce. A recent study found that duration of treatment with antipsychotics is associated with accelerated total gray matter volume loss (Gildengers et al., 2014). While consistent with findings in SCZ, more research is needed to adequately characterize the effects of antipsychotics on brain structure in BD. In contrast to antipsychotics, mood stabilizers appear to have a normalizing effect on brain structure in BD. In a comprehensive review, Hafeman and colleagues (2012) concluded that a significant number of investigations found that lithium treatment was associated with larger amygdala, hippocampus, anterior cingulate, and subgenual cortex volumes. The results in clinical studies, which are often based on post hoc analyses of uncontrolled studies, are supported by pre-clinical investigations showing that lithium increases brain volumes and in vitro demonstrations of the neurotropic effects of lithium and valproate (Manji et al., 1999; Chen et al., 1999; Vernon et al., 2012).

5. Conclusions

There is considerable phenotypic overlap between SCZ and psychotic BD. Neuropsychological impairment is a central feature of both disorders and a key predictor of functional outcome. However, as reviewed here, the pathway leading to neuropsychological impairment appears to differ between disorders. In SCZ, cognition is mildly impaired well before the onset of psychosis and likely further declines between the pre-morbid phase of the illness and

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onset of florid psychotic symptoms. However, there is little indication that cognitive function worsens after illness onset. In contrast, pre-morbid cognitive functioning is relatively normal in BD and cognitive impairment at illness onset is considerably less severe than that observed in SCZ. However, by the chronic stage, patients with psychotic BD may be virtually indistinguishable from SCZ.

Based on the apparent differences between SCZ and BD in the development and course of cognitive impairment, it is tempting to conclude that the etiology of the disorders also differs. Indeed, the canonical etiological model of SZ posits that it is a neurodevelopmental disorder, whereas etiological models of BD argue that it is a neuroprogressive illness characterized by relatively normal premorbid cognitive development and subsequent deterioration over the course of the illness (Lewandowski et al., 2011; Strakowski et al., 2012). However, there are significant caveats to this interpretation and results from structural brain imaging investigations do not align with strictly neurodevelopmental and neuroprogressive models. Moreover, neurodevelopmental abnormalities and neuroprogression are not mutually exclusive. In the case of psychotic BD, the hypothesis that cognitive function deteriorates over time, while supportive of neuroprogression, is based largely on comparisons between early stage/first episode investigations and studies in chronic patients. Longitudinal studies evaluating first episode patients over several years have yet to be performed. In the case of brain structure, both SCZ and BD are associated with prominent abnormalities, including reduced TBV, localized volume loss in regions of the frontal lobes, and ventricular enlargement. As with the cognitive deficits, brain structure abnormalities are more severe and widespread in SCZ, particularly in the early stage of the disorder which is consistent with neurodevelopmental models of SCZ. Additionally, reduced ICV in SCZ is consistent with atypical early cerebral development. However, progressive brain changes have also been reported in SCZ suggesting that SCZ may involve both neurodevelopmental abnormalities and post-onset changes in brain structure. Moreover, volumetric increases have been reported in BD which runs counter to neuroprogressive models. The interpretation of structural brain changes over time in psychotic disorders is complicated by antipsychotic and mood stabilizing medications that have divergent effects on brain structure. Antipsychotics, particularly typical antipsychotics, have been linked to accelerated brain volume loss, whereas mood stabilizers have been found to increase brain volumes.

In conclusion, there is strong evidence that pre-morbid cognitive functioning differs between SCZ and BD. Emerging evidence also suggests that the trajectory of brain dysfunction following the onset of psychosis differs between disorders; SCZ is characterized by relatively stable cognitive impairment, whereas cognitive function appears to deteriorate over time in BD. This has prompted speculation that the etiopathology of the disorders differs with SCZ being conceptualized as a neurodevelopmental disorder and psychotic BD a neuroprogressive illness. However, key issues remain to be addressed before this hypothesis can be confirmed. Large-scale longitudinal studies including patients with a variety of psychotic disorders will be essential in confirming or refuting this hypothesis as will a better understanding of the effects chronic treatment with antipsychotics and mood stabilizers on brain structure and function.

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