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Brain change trajectories that differentiate the major psychoses

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Abstract

Background: Bipolar disorder and schizophrenia are highly heritable, often chronic and debilitating psychotic disorders that can be difficult to differentiate clinically. Their brain phenotypes appear to overlap in both cross-sectional and longitudinal structural neuroimaging studies, with some evidence to suggest areas of differentiation with differing

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trajectories. The aim of this review was to investigate the notion that longitudinal trajectories of alterations in brain structure could differentiate the two disorders. *Design:* Narrative review. We searched MEDLINE and Web of Science databases in May 2016 for studies that used structural magnetic resonance imaging to investigate longitudinal between-group differences in bipolar disorder and schizophrenia. Ten studies met inclusion criteria, namely longitudinal structural magnetic resonance studies comparing bipolar disorder (or affective psychosis) and schizophrenia within the same study. *Results:* Our review of these studies implicates illness-specific trajectories of morphological change in total grey matter volume, and in regions of the frontal, temporal cortex, and cingulate cortices. The findings in schizophrenia suggest a trajectory involving progressive grey matter loss confined to fronto-temporal cortical regions. Preliminary findings identify a similar but less severely impacted trajectory in a number of regions in bipolar disorder, however, bipolar disorder is also characterised by differential involvement across cingulate subregions. *Conclusion:* The small number of available studies must be interpreted with caution but provide initial evidence supporting the notion that bipolar disorder and schizophrenia have differential longitudinal trajectories that are influenced by brain maturation.

Keywords: psychosis, schizophrenia, bipolar disorder, magnetic resonance imaging, neurodevelopment, brain maturation, longitudinal, trajectories**;** *Number of words:* 5727

Introduction

Bipolar disorder (BP) and schizophrenia (SZ) are to a large extent debilitating and chronic psychiatric conditions whose clinical expressions overlap while being classified as different disorders within current diagnostic classification systems (i.e., DSM-5, ICD-10). BP is characterized by recurrent and episodic mood alterations, including elated mood (i.e., mania or dysphoria), low mood (i.e., depression, sadness), and alterations in drive. SZ is characterized by altered perception (i.e., hallucinations and delusions), thought disorder, and executive dysfunction with disorganized behavior, but also affective alterations with changes in drive. Current evidence suggests that diagnostic boundaries may misleadingly indicate that BP and SZ are discernible disorders even though they overlap in terms of familial inheritance, psychotic symptoms, dysregulated emotional expression, and altered behaviour [1-3]. There is currently no established pathognomonic feature that allows clinicians to differentiate BP and SZ cross-sectionally. However, there is some evidence suggesting that the longitudinal trajectory of dynamic illness features themselves could separate SZ and BP. This is also consistent with the idea, elaborated below, that potential biomarkers for psychiatric

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disorders are dynamically changing during adolescence and may be more informative when mapped longitudinally [4-6].

BP and SZ share many elements clinically, but have generally been considered to be two different conditions, as first described by Emil Kraepelin (1907/1911)[7, 8]. Kraepelin described manic-depressive illness (bipolar disorder) and dementia praecox (renamed *schizophrenie* by Bleuler in 1911), based on his careful phenomenological characterization and observation of patients' longitudinal course (i.e. trajectory). He considered that the key distinguishing feature between these disorders was the differing long-term outcome, reflecting different trajectories. Thus, he considered that manic-depressive illness had a recurrent episodic course whereas dementia praecox was considered a more deteriorative, progressive and "degenerative" illness. These initial descriptions highlight the importance of characterizing the longitudinal course of psychosis, a notion that was generally ignored until recently [4, 5, 9].

Indeed, the dominant notion has been that schizophrenia is a neurodevelopmental disorder [10, 11], a notion that was used to imply that the disorder had its roots in early development (esp. during foetal development). In fact, the neurodevelopmental notion was proposed much earlier by Sir Thomas Clouston [12], a contemporary of Kraepelin, who characterized a condition resembling severe forms of psychosis from the perspective of the development of the nervous system. Clouston coined the term "developmental insanity" to describe what we today regard as SZ [13].

Kraepelin's century-old dichotomy is still evident in modern diagnostic systems but the neurodevelopmental perspective was brought to the fore again almost 30 years ago in research on the etiopathogenesis of SZ [10, 11, 14]. These early notions focused on a possible 'hit(s)' during early (gestational) neurodevelopment, the effects of which become unmasked during later maturation [15]. These theories were limited in that the effects of morphogenesis beyond the first few years of life were not considered; recent data highlights the importance of brain maturation extending into early adulthood [16-19]. More recent conceptualizations include the importance of genetically determined and late neurodevelopmental (brain maturational) processes in SZ [9] and BP [20, 21]. While the concept of SZ as an evolving condition has been long established, recent reconceptualizations of BP also highlight the need for a longitudinal perspective that takes neurobiological trajectories into account [22]. Thus,

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the maturational context relevant to the peak time for development of these disorders (adolescence and early adulthood) provides an important backdrop to elucidate the pathophysiology of SZ and BP. Mapping longitudinal trajectories of emerging psychotic illnesses may help to distinguish the disorders, help inform pathogenesis, and provide predictive markers of diagnosis, treatment response and prognosis [4, 23].

The psychosis continuum

There has been longstanding debate surrounding the distinction between SZ and BP (see [24] for review). These disorders were originally conceptualized as a *unitary psychosis* by Guislain, and later extended by Zeller whereby all psychotic syndromes were believed to be underpinned by different stages of a single pathological process, a notion that has been recently reconceptualised as a pluripotential state [25]. While Kahlbaum differentiated between two major groups of mental illnesses, which he termed *vecordia* (alterations of mood) and *vesania* (frank insanity), Kraepelin is credited as the first to posit a clear dichotomy between dementia praecox (i.e. SZ) and manic-depressive insanity (i.e. BP) as distinct and unrelated disease entities on the basis of causation, symptoms, course and outcome [26]. Crow reignited the debate and argued for a continuum of psychosis, extending from pure affective disorder to SZ [27, 28]. This argument was based on several lines of evidence which were purported to cast doubt on Kraepelin's dichotomous model. Firstly, Crow cited work by Kendell and co-workers who failed to demonstrate separation of these disorders on the basis of symptoms using discriminant function analysis, and instead classified most patients in the mid-point between the two disorders [27, 29]. Secondly, Crow suggested an underlying shared aetiology as a result of shared season of birth and illness onset [30], as well as similar treatment responses [31, 32]. Lastly, findings from family studies indicating a propensity for individuals with SZ to not only descend from parents with SZ, but also from those with an affective psychosis [33], and for schizoaffective disorder to equally occur in the relatives of patients with both SZ and affective disorder, were presented as evidence of a shared genetic contribution rather than two unrelated diatheses [34, 35]. Rather than suggesting a single aetiology, McDonald et al. [36] contend that several genetic and environmental aetiologies underlie these disorders. These authors suggest some common genetic liability; but that patients with SZ are subject to additional genetic (i.e. risk alleles) and environmental factors that impair neurodevelopment [37, 38]. Lichtenstein et al. [1] found evidence that SZ and BP partly share a common genetic basis. They report that all biological relatives of individuals with BP had an increased risk for SZ and the genetic

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correlation between the two disorders was 0.60. The estimated heritability for SZ was 64%, whereas the estimated heritability for BP was 59%. These findings were recently replicated and point to considerable overlap in genetic risk and familial lineage between the two conditions [3]. Recent genome-wide associations studies have also identified loci of single-nucleotide polymorphisms that implicate such shared (*ZNF804A, ITIH3–ITIH4, ANK3, CACNA1C)* and non-shared genetic determinants of SZ (*MIR137, VRK2, PCGEM1, MHC, MMP16, CSMD1, LSM1, CNNM2, NT5C2, AMBRA1, NRGN, CCDC68, TCF4*) and BP (*ODZ4, NCAN*) [39, 40]. Thus, it is also clear that a considerable proportion of genetic variance is not common between the two disorders. An alternative and more recent view is that these disorders may emerge from a pluripotential state to develop into one or other of these conditions [41]. While this represents an appealing notion, it remains unclear whether patients can move between diagnostic categories in a fluid manner, or whether patients in an early, less differentiated phase of illness already have a predetermined biologically driven path. Examining the overlap of these disorders at the phenotypic and neurobiological levels may help to address such questions.

Diagnostic stability in schizophrenia and bipolar disorder

SZ and BP are hard to differentiate clinically, and particularly so during the earlier phases of either disorder, which is also reflected in an initial diagnostic instability. Evidence of diagnostic instability has been suggested to reflect an early undifferentiated state of psychosis that may later differentiate into either SZ or BP as the illness progresses [41]. If so, it is likely that the neurobiology at the earliest stage of psychosis overlaps but that differences emerge over time as these disorders progress. This is also consistent with clinical observation and practice, namely, that diagnosis can only be truly clarified when a patient's illness is considered longitudinally. As such, examining the disorder phenotypes at later stages may be informative about differences, whereas examination early in their course may provide evidence of overlap; while, longitudinal studies are required to assess differences in trajectories between these diagnostic outcomes.

Diagnostic stability at the early stages of illness can be assessed by examining incident cases, as well as individuals at high risk for the disorder. Persons at ultra-high risk for developing psychosis are those between 15-30 years that have attenuated psychotic symptoms, brief intermittent psychotic symptoms, and display risk factors for psychosis. Over a decade, 34.9% of such individuals develop psychosis; two thirds do so within the first 2

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years of prodrome-onset, and increased age, decreased global functioning, and longer symptom duration are positively associated with the transition to psychosis [42, 43]. Several studies have examined diagnostic stability in psychosis [44-48]. The available evidence suggests that, while there is a high level of diagnostic stability (>80%) reported in first-episode psychosis samples over long-term follow-up [45], a changed diagnosis occurs in a significant proportion. Schimmelman et al. [46] reported relatively high diagnostic stability over an 18-month follow-up period in a representative sample of 492 first-episode patients. Over the 18-month period, the most consistent diagnoses were SZ (97.3%), schizoaffective disorder (94.1%), and BP (83.2%), while the least stable was schizophreniform disorder (40.0%). A shift to SZ spectrum disorders from non-SZ spectrum disorders was uncommon (6.8%). The most frequent diagnostic changes were seen in those with an initial diagnosis of schizophreniform disorder, resulting in a follow-up diagnosis of either SZ or schizoaffective disorder. Naz et al. [47] similarly reported a high level of diagnostic stability over a two-year period in 162 first-episode patients who were within 6-months of illness onset. They showed that the majority of patients with schizophreniform disorder were diagnosed with SZ spectrum disorder (61.1%) at follow-up, and only a small proportion were re-diagnosed with other disorders including depressive disorder (5.8%), BP (5.8%) or schizoaffective disorder (8.3%). Over a longer follow-up period of five years, Chang et al. [48] demonstrated an overall diagnostic consistency of around 80% in a first-episode sample. One hundred percent consistency was observed in BP diagnosis over that period, and 95.8% consistency in SZ diagnosis, whereas acute and transient psychotic disorders and delusional disorder were the least stable baseline diagnoses. In a recent longitudinal study of diagnostic stability in 64 adolescent patients with BP, 63.6% remained diagnosed with BP (type I) at follow-up after a mean period of 8 years, while 18.2% were re-diagnosed with SZ and 18.2% with schizoaffective disorder [49]. Taken together, comparing the diagnostic stability of the psychotic disorders, an initial diagnosis of SZ appears to be most stable, followed by less stability of BP diagnosis in the majority of patients, regardless of the time these patients were followed-up, whereas an initial diagnosis of schizophreniform disorder is the least stable. This lends support to the notion that BP and SZ remain separate diagnostic entities over time even though they are difficult to differentiate at single time-points. This further implicates the importance of understanding illness specific trajectories to establish biomarkers of BP and SZ. The dynamic features of schizophreniform disorder could be interpreted as a greater overlap between disorders at an early time in the psychotic illness, thereby indicating a pluripotent stage with an ongoing differentiation into specific psychotic disorders. While the clinical

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features and diagnoses may evolve over time, the similarities and differences in neurobiological measures are also informative across these stages, as well as examining how such measures change from pre-illness onset to chronic illness.

Structural neuroimaging in schizophrenia and bipolar disorder

In a recent volumetric mega-analysis of subcortical structures in 1,745 BP patients and 2,613 healthy controls, Hibar et al. [50], showed that BP is associated with increased lateral ventricular size, and decreased amygdala, hippocampus and thalamus volumes. In a methodologically similar study of SZ, van Erp et al. [51], showed close to an identical anatomical pattern of differences when comparing 2,028 patients with SZ and 2,540 healthy controls, with the exception of ventral striatum (nucleus accumbens) volume, which was decreased in SZ but not in BP. The effect-sizes also showed a tendency of being more pronounced in SZ when compared with BP. One earlier comparison of SZ and BP is largely consistent with this pattern, but instead identified an enlargement of the amygdala in BP compared to SZ [52]. Other studies also confirm that ventricular enlargement appears greater in SZ compared to BP [52]. Thus, there appears to be an overlapping anatomical pattern of differences in the disorders compared to controls, with more pronounced alterations in SZ.

Regional morphology studies also suggest an involvement of the insular, cingulate, frontal, and temporal cortices in SZ and BP [53-55]. So-called WM hyperintensities (small bright regions within WM on T2-weighted MR images probably reflecting vascular disease or demyelination) may be more prevalent in BP than in SZ whereas other WM metrics show heterogeneous results [56].

Broadly, cross-sectional studies of brain structure in SZ and BP across the life span show differences compared to healthy controls in both lateral and medial aspects of the frontal and temporal lobes, different regions of the cingulate cortex, and ventricular CSF volume [52, 56]. Thus the available cross-sectional evidence suggests an anatomical overlap between the two conditions, especially in GM abnormalities, with more extensive involvement in SZ. Previous findings also suggest differences at different illness stages [57]. These findings highlight the importance of examining longitudinal studies as a way to potentially differentiate the two conditions.

The relatively few available longitudinal structural neuroimaging studies of BP and SZ

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suggest progressive changes in both disorders [58, 59]. In BP over time, there is evidence for decreased GM in the prefrontal cortex, subgenual region of the cingulate cortex, and temporal lobe, in particular the hippocampus and amygdala [20, 60]. In SZ, there is a progressive decrease in whole brain GM volume [61], however, in a recent meta-analysis such changes may predominantly involve the left lateral temporal cortex [62]. Further, progressive structural changes are most pronounced during early phases of the illness. Interestingly, in a study by Sun and colleagues [63, 64] that examined neocortical changes in first-episode SZ over time, significant progressive change was observed in frontal regions, which represented an amplification of normal neurodevelopmental processes. When the changes were examined across the whole neocortex, the two-fold accentuation of grey matter thinning observed in frontal regions was also seen across the whole neocortex. This suggested that in SZ, the changes are more global; it was speculated that frontal regions reached significance because these regions are the areas showing the most dynamic maturational changes in later adolescence and early adulthood. That is, the significant findings in the frontal regions can be understood by placing the findings within a neurodevelopmental context [9, 65] as has also been observed with neurocognitive data [66]. It is unclear whether this is also relevant to BP, although studies that examine trajectories of structural and functional brain changes from childhood to adulthood may be informative (see below).

In summary, despite a number of reviews on available cross-sectional and longitudinal investigations of neuroimaging metrics in BP and SZ, no consensus has been reached with regard to longitudinal between-group comparisons that might differentiate these disorders. The aim of this narrative review was to investigate the current evidence that supports the notion of illness-specific trajectories in alterations of brain structure that differentiate BP and SZ over time.

Search method

We searched the MEDLINE and Web of Science databases in May 2016 using the terms: *longitudinal, magnetic resonance imaging, psychosis, bipolar disorder,* and *schizophrenia*. Our search retrieved 20 hits in MEDLINE, and 35 hits in Web of Science. Only English-language articles that comprised longitudinal structural magnetic resonance studies comparing bipolar disorder (or affective psychosis) and schizophrenia within the same study were considered. This resulted in 5 publications from MEDLINE, and 5 publications from Web of Science. In total this yielded 7 unique publications. We also searched the reference lists of included

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publications for additional studies and identified 3 further articles. A quantitative meta-analysis was not possible due to the heterogeneity of the available studies and limitations in their methodology (i.e., no consistent reporting of anatomical coordinates in standard space, differing neuroimaging metrics, region-of-interest versus regional voxel-based analyses). In this narrative review, we discuss the 10 articles that fulfilled our criteria.

Results

Study descriptives

Search results with study descriptives are reported in Table 1. The retrieved articles were published between 2005-2016. The number of patients across all studies at baseline was 467 (SZ, n=249; BP, n=218), and 342 (SZ, n=183; BP, n=159) at follow-up. However, data in several (n=5) papers appear to have been collected at one study site [67-71], indicating that the same sample was used in several publications. This was also corroborated through personal communication with corresponding authors, which confirmed a partial overlap across at least three studies [67, 69, 70]. The age range across all studies was 13-40 years. The mean follow-up time ranged from 13-36 months. The majority of participants were first-episode psychosis patients except for one cohort that contained patients at ultra-high risk for psychosis [72]. All images were acquired using 1.5 Tesla MRI scanners and varying voxel dimensions in the tomographic images. One study used more than one scanning site, and between scanner effects were not accounted for in the analyses [61]. Studies used either a region-of-interest (ROI), or a voxel-based morphometry (VBM) approach. Most ROI studies used user-dependent, manual tracing methods. VBM is a user-independent and automated method, which allows for assessment of finer regional changes in brain structure at a more detailed resolution beyond ROI based volumetry, and determines local GM volume/concentration or local shape alterations. In general, early studies were ROI studies (n=8) focusing on particular structures or tissue compartments such as gray matter (GM), white matter (WM), or cerebrospinal fluid (CSF). More recent studies examined regional differences in morphology within tissue compartments based on VBM (n=4).

Gross measures over time in schizophrenia versus bipolar disorder

Two whole-brain studies showed that progressive GM volume loss was more pronounced in SZ than BP [69, 73]. One of those studies, by Nakamura et al., showed confinement of such tissue loss to neocortical GM, while also showing lateral ventricle enlargement over time in SZ compared to BP, but no between-group differences in sulcal CSF

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or WM [69]. The absence of significant WM between-group differences was also evident in one other study by Dickey et al. [67]. Thus, there is evidence from volumetric studies of gross measures such as cerebral tissue classes that suggest more pronounced GM loss and lateral ventricle enlargement in SZ.

Region-of-interest measures over time in schizophrenia versus bipolar disorder

Four studies have investigated the temporal lobe [69-72], and two of these showed that progressive volume loss was more pronounced in SZ than BP with regard to whole temporal lobe volume [69] and left Heschl's gyrus [70], with no differences regarding the temporal pole [71]. The involvement of the superior temporal regions is also corroborated by Takahashi et al. [72], who showed a progressive volume decrease of the Heschl's gyrus as subjects at ultra-high risk of psychosis developed manifest psychotic disorder, although no statistically significant differences were identified when the sample was stratified according to either affective psychosis (incl. BP) or SZ.

In a longitudinal study, Nakamura et al. found that progressive frontal lobe volume decreases were more evident in SZ than in BP, while a progressive increase of parieto-occipital lobe volume was observed in BP compared to SZ [69]. However, in a relatively small study examining prefrontal cortex (PFC) volume over time, Dickey et al. did not find group differences between SZ and BP [67].

A study by Koo et al. [68] focused on differences in cingulate cortex subregions in SZ and BP compared with normal controls. Koo et al. found that in patients with SZ compared with controls, significantly smaller cingulate volumes were found across all subregions examined. In contrast, only the subgenual subregion was significantly smaller in BP compared to healthy controls, although this did not differ significantly from SZ. Longitudinal analysis demonstrated that in SZ, grey matter decreased in all subregions, while in BP this progressive change was limited to the subgenual region and was similar in magnitude to SZ. These findings suggest that in SZ, compared with BP, there is differential involvement of anterior cingulate regions implicated in cognition versus affective functions. This is consistent with other studies of affective psychosis and BP [74-78], including involvement of the subgenual subregion in ultra-high risk for psychosis individuals who develop BP compared with those who develop SZ [74].

The insular cortex has not been highlighted until recently in longitudinal comparisons of

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SZ and BP. The insula is a paralimbic brain region implicated in a broad range of functions such as emotion, movement perception, and interoceptive processing, relevant to both SZ and BP [79]. Cross-sectional studies show decreased insular cortex volume in established BP and SZ [54, 55, 80, 81]. However, longitudinal studies of the early phases of these disorders show that progressive changes are specific to SZ [81, 82], and that progressive changes of total insular cortex volume are greater in SZ compared to BP [71].

Thus, the available five studies examining specific regions using ROI based methods, implicate illness-specific trajectories in fronto-temporal, insular, and cingulate cortices, with greater and more spatially extensive progressive volume loss in SZ compared to BP [69-71, 73, 83]. These regions are heteromodal and play an important role in sensory integration, cognitive functions (e.g. attention, memory, language, planning), emotion and motor behaviour – functional domains affected in both BP and SZ [84], and implicated in a wide variety of psychiatric symptoms in both disorders (e.g. cognitive control, emotional expression) [85]. In one of these five studies, BP patients on the other hand, show a progressive increase of tissue volume in the parieto-occipital cortex [69]. However, as these ROI studies measured large volumes, they do not necessarily preclude the possibility of smaller regional changes. The insula is another important structure in SZ and BP that remains to be fully investigated in longitudinal ROI studies that compare the two disorders.

Voxel-wise measures over time in schizophrenia versus bipolar disorder

The two available VBM studies that have tested for a group x time interaction at the voxel level show contrasting results [61, 86]. Neither study established significant between-group differences when comparing SZ and BP. The study by de Castro-Manglano et al. [86], showed counterintuitive findings, with greater longitudinal changes in controls versus patients as a group, and little change observed in patients. Subdivision of the patient group revealed no volumetric changes in patients with SZ, whereas patients with affective psychoses displayed similar longitudinal reductions to controls. Their findings of potential differences in trajectories between FE SZ and FE affective psychoses are difficult to interpret in light of their overall findings. The larger study of the two, by Arango et al. assessed FE psychosis patients with less than 6 months illness duration followed over 2 years [61]. They identified significant progressive volume reductions in whole brain volume, bilateral frontal and left parietal GM as well as left frontal CSF enlargement, in SZ compared with controls, while BP did not differ from either group. However, there was no significant interaction effect of time by diagnosis.

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Only one study, by Trzesniak et al. [87], has investigated the prevalence and length of cavum septum pellucidum (CSP) and adhesio interthalamica (AI) longitudinally in BP and SZ; signs considered to reflect limbic neural maldevelopment during early gestation. They found that the length of the CSP increased over time in the patient group as a whole, but did not establish any significant between group differences across all groups, and this was not related to progressive ventricular enlargement. While studies suggest that absent or shorter AI may be a developmental marker predictive of both SZ and BP [88, 89], further longitudinal studies are needed to clarify if any progressive brain changes impact these indices, in which case they may not represent stable or true markers of an early neurodevelopmental insult (see also [85]).

----------Table 1 about here----------

Discussion

During the last decade, a great number of studies have shown alterations in brain structure in both BP and SZ (e.g. see meta-analyses and commentary: [53, 55, 90, 91]). The majority of studies on SZ and/or BP are cross-sectional, fewer are longitudinal, and very few studies have examined longitudinal trajectories in neuroimaging metrics in both disorders within the same study, and whether such trajectory differences are predictive of diagnosis. A cautious interpretation of the available evidence from a handful of relevant studies published over the last decade suggests that illness-specific trajectories of SZ and BP primarily involve lateral and medial frontal cortex, lateral temporal lobe, anterior cingulate cortex, and lateral ventricles.

The available data suggests a trajectory in SZ that involves progressive GM loss globally, which predominantly involves anterior cingulate, insula and fronto-temporal cortical regions. A putative trajectory in BP does not support changes at the whole brain level, while involvement of fronto-temporal cortices and insula resemble SZ, but to a lesser extent. By contrast, findings suggest differential involvement of anterior cingulate cortex subregions. Importantly, most of the available studies are in late adolescence or early adulthood, which may have an important bearing on these specific findings, and indicate that conclusions should specifically pertain to that period of development. Further, it is important to highlight that some of the findings described above point to changes in SZ being at the whole brain

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level. For example, in the study by Sun et al. [64], the changes observed are apparent across the whole cortex in relation to controls, however only frontal regions show a significant difference. We have previously suggested that brain maturation may be an important mediating variable to explain these findings [4, 5, 9, 65, 66]. We suggest that stage of brain maturation mediates the impact of the illness on brain structure. That is, the pattern of brain changes is not only influenced by the illness but, rather, the stage of brain development at the time of illness onset (Fig. 1, proposed model for mediation analysis).

----------Figure 1 mediation model here----------

A key question is whether brain maturation (the mediator variable) differentially influences trajectories of brain change in SZ and BP. The studies of SZ and BP commencing in childhood are informative in this regard. In longitudinal studies of childhood-onset SZ (COS) and their unaffected siblings [92, 93], trajectory differences suggested an *age-specific* pattern of parietal and fronto-temporal GM changes [94-96], with the latter being consistent across the adolescent period in COS, while unaffected siblings showed this pattern only around puberty and early adolescence and showed normalisation by mid-adolescence. In a further elaboration of this work, we examined structural covariance as a measure of connectivity in this COS group and their unaffected siblings [97], and showed that abnormal brain connectivity in COS was also seen in unaffected siblings in early adolescence, but that this pattern normalised only in the latter group by mid-adolescence. This pattern suggests firstly that potential endophenotypes may be age (brain maturation) dependent; secondly, that cross-sectional studies will potentially miss important endophenotypes; thirdly, that normalisation of trajectories in unaffected 'high risk' individuals who manifest these changes early suggest the influence of resilience or protective factors; and lastly, that mapping trajectories within a neurodevelopmental context is needed for studies investigating brain structure and function in young people [4, 65, 66, 98].

Gogtay et al. [99] used a similar study design to examine childhood BP. However, in this study they aligned scans by age at first manic episode and showed that the BP-specific dynamic GM changes in the lateral temporal regions, and subregions of the anterior cingulate cortex including pregenual and subgenual areas, were related to the onset of the first manic episode rather than chronological age. This data also supports findings from older BP patients, implicating specific subregions of the cingulate, as described earlier [53, 55]. Such

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findings are in accord with observations in early psychosis patients developing BP [75-78]. Thus, brain maturational stage may be less relevant in BP, than in SZ, in mediating the impact of the illness on brain structural changes; though further studies are needed.

Taken together with the findings in COS, these findings suggest a different trajectory of brain change in BP versus SZ, as well as the importance of placing the observed findings within the context of normal and abnormal brain maturation. No work to date has examined this in detail, though work in children and young adolescents at risk for depression demonstrates the importance of trajectories and relevance of risk as well as protective/resilience factors on brain development and the emergence of depression [100, 101].

Understanding longitudinal trajectories of structural change in psychotic disorders during early adulthood is challenging because of the concomitant variation in neural maturation. Here, we have proposed a mediation model, which may provide testable hypotheses in future longitudinal studies (Figure1). Neurodevelopment refers to the growth, morphogenesis, and maturation of the nervous system and its functions. In brief, this highly coordinated process is initiated prenatally during gestational life and continues into adulthood [102-104]. Neurodevelopment is controlled by genetic factors and their interaction with the environment, and involves both progressive (e.g. synaptogenesis, myelination and dendritic arborization; [105]) and regressive elements (e.g. synaptic pruning; [16, 103]) that are closely related to cognitive development [5, 106]. Cognitive functions and motor behaviour are sensitive to aberrant neurodevelopment. Importantly, different higher-order cognitive abilities and motor functions develop at differing rates during development, which likely reflect the underlying neurobiological changes also occurring with maturation and that influence developmental trajectories [5, 107-109]. Only recently have neuroimaging studies shown that tissue metrics in specific anatomical regions have varying developmental trajectories, and that progressive and regressive brain maturational processes in the frontal and temporal lobes continue into adulthood [110-112]. The understanding of these events poses a challenge to psychosis research in that developmental patterns may confound findings (e.g. neural reorganization, brain maturation). It remains an open issue on how to normalize subjects with respect to neurodevelopment when comparing groups or establishing a baseline in longitudinal comparisons. Two alternative ways of normalizing with respect to development (instead of using chronological age) could be: determination of either

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developmental stage (e.g., Tanner stage, hormonal levels), or developmental timing (e.g., heterochrony). Our group has also highlighted the necessity of increased sampling frequency in order to identify these trajectories, their "shape" or "signatures", expressed in neurobiological markers (i.e. structural neuroimaging metrics) of clinical change (e.g. debut, relapse, progression, refractoriness) in psychotic disorders [4, 5, 9, 23].

The evidence of illness-specific trajectories presented in this narrative review has important limitations. Any general conclusion must take into account that findings could be hampered by methodological bias (e.g., recruitment, sample size, varying outcome measures, image acquisition/analysis), confounded by clinical parameters (e.g., duration of illness, symptom severity, number of episodes), medication (e.g., neuroleptics, mood-stabilizers), and substance use, and that findings may not have been sufficiently replicated. The majority of subjects included in this review are first-episode patients whose brain alterations were assessed at illness inception when many of the abovementioned confounders are reduced or absent. However, there is scope for improving measurement given the innovation and increased availability of neuroimaging technology, and the emerging consensus in processing and statistical analysis of brain images.

The neuroimaging field in psychosis research has yet to advance an understanding of the pathophysiological mechanisms behind the observed structural changes. Further hypothesis testing would benefit from combinations of more specific physiological metrics such as molecular imaging (e.g., receptor density mapping, neuroinflammation indices) and magnetic resonance spectroscopy (e.g., neurotransmitters, oxidative stress markers) in order to understand the underlying pathophysiology of psychotic disorders. Such multimodal imaging approaches should be included in longitudinal studies where possible or should complement other longitudinal imaging [113, 114].

Studies that compare the illness-specific trajectories of brain change in BP and SZ, suggest a plausible relationship between neural maldevelopment and the emergence of these two disorders, and the possibility that SZ in particular is mediated by brain maturation to a greater extent than BP. These studies are a first step towards elucidating the presumably genetically determined pathways that lead to altered neurodevelopment, expressed as BP or SZ. However, the causal relationships between genetic determinants of neural maldevelopment, structural brain changes, and clinical expressions, remain to be elucidated.

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Studies included in this review are not designed to address causation. They are longitudinal observational studies. In order to investigate causal relationships, experimental interventional study designs are required where a specific intervention is applied to divert the course of the trajectory of either SZ or BP. In the absence of experimental evidence of causation, then Hill's classic criteria [115] for inferring biological plausibility of causal relationships may be considered. Accordingly, causal factors leading to neural maldevelopment can be explored using a longitudinal prospective cohort study design to track the temporality of suggested cause and effect relationships; to show reversible association of such a relationship and consistency with cross-sectional studies; and to investigate longitudinal trajectories in structural neuroimaging measures in relation to the dynamic expression of the clinical illness, while controlling for normal brain development, and stratifying for genetic load (e.g. polygenic risk score) [116].

One way to narrow down the search for candidate brain regions with illness-specific trajectories in structure is to observe regions where implicated genes exert their effects in SZ and/or BP, but also when theses genes are expressed during brain maturation. Here, recent advances in genome-wide mapping in relation to brain structure and neurodevelopment can be informative, and address more spatially exact hypotheses while taking brain maturation into account [117, 118]. Such a strategy could use resources such as the The Allen Brain Atlas of gene expression (www.brain-map.org) in particular brain regions, while also consulting the Human Transcriptome Atlas to ascertain when they are putatively expressed during neurodevelopment (hbatlas.org), and to map these changes against brain changes at different developmental stages.

Finally, another plausible hypothesis that would be consistent with the notion of an overlapping phenotype early in these psychotic disorders compared to greater differentiation between them at a later stage, is that onset of disorder during critical times of brain development adversely impact such development [5, 9, 65]. This may be reflected as an impact on the mechanisms underlying brain maturation by any disruptive process, such as onset of either SZ or BP. Such disruption may explain the apparent overlap in heritability of these disorders if such overlap relates to genes coding for neurodevelopment [1], while the genetic profile that suggests non-overlap may be more informative as the trajectory of these disorders becomes better clarified as the illness evolves.

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Conclusion

The available evidence from the handful of longitudinal structural neuroimaging studies of both SZ and BP within the same study cohort must be interpreted with caution. Several studies suggest the possibility that GM changes in fronto-temporal and cingulate subregions can differentiate the two disorders and be predictive of diagnosis, however, cross-sectional studies are clearly inadequate. There is scope for further larger longitudinal comparisons of BP and SZ, incorporating frequent assessments that allow accurate mapping of these disorders as they evolve, in the context of other influences that include environmental and genetic factors that may confer risk or resilience [65, 98].

Disclosures

None relevant to this paper.

Contribution

BL and CP contributed equally to the paper. All authors made a substantial contribution to the conception, design and interpretation of this work. BL and CP drafted the manuscript and all authors critically revised it for important intellectual content. Each author approved the final version of the manuscript. We thank Drs Paul Klauser and Caroline Wachtler for valuable comments on the manuscript.

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Figure legends

Figure 1. The mediation model for how brain maturation influences alterations in brain structure in bipolar disorder or schizophrenia.

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Table. Summary of longitudinal structural neuroimaging studies comparing schizophrenia and bipolar disorder.

Author	N (BP/SZ)	Age (BP/SZ)	Follow-up time (years)	Method	Software	Baseline results	Follow-up results	Time × Diagnosis results
Dickey et al. 2004[67]	10/12	22.9/28.1	1.5	ROI	Manual	SZ < HC: PFC	-	-
						BP=HC: PFC	-	-
						SZ < BP: PFC SZ=BP=HC: WM	SZ=BP=HC (between-group, cross-sectional): PFC and WM	SZ=BP: PFC and WM
Farrow et al. 2005[73]	8/25	17.5/19.7	2.5	VBM, ROI	SPM99	FEP < HC: TBV, GMV, WMV	-	-
						SZ < HC: TBV[a], GMV	-	-
						SZ < HC: Regional GM in frontal cortex (right posteriolateral frontal cortex, bilateral medial frontal gyrus/bilateral anterior cingulate gyrus, bilateral precentral gyrus), temporal cortex (left inferior/middle temporal gyrus), parietal cortex (left postcentral gyrus) right cerebellum.	SZ (within-group, over time): ↓Regional GM in frontal cortex (right precentral/inferior frontal gyrus, left anterior cingulate gyrus), temporal cortex (left inferior postcentral/middle temporal gyrus) and right cerebellum.	-

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						SZ < HC: Regional WM ↓ in left frontal lobe, right posterior temporal lobe and bilateral posterior parieto-temporal junction.	SZ (within-group, over time): ↑Regional WM in right frontal lobe, right temporal lobe, right temporo-parietal junction and bilateral parietal lobe.	-
						BP < HC: WMV[a]	-	-
						BP < HC: Regional GM in frontal cortex (right inferior frontal/precentral gyrus), temporal cortex (bilateral inferior temporal gyrus/uncus, left insula, left posterior inferior/middle temporal gyrus), and parietal cortex (left posterior cingulate gyrus).	BP (within-group, over time): ↓Regional GM in frontal cortex (bilateral anterior cingulate gyrus).	-
						BP < HC: Regional WM in left frontal lobe and bilateral posterior parieto-temporal junction.	BP (within-group, over time): ↑Regional WM in right posterior frontal/parietal lobe, left temporo-parietal junction, right parieto-occipital junction, left parietal lobe and right cerebellum.	-

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						SZ < BP: Regional GM in frontal cortex (left precentral/inferior frontal gyrus, left anterior cingulate/medial frontal gyrus, right superior frontal gyrus, bilateral middle frontal gyrus).	SZ < BP (between-group, cross-sectional): ↓Regional GM in frontal cortex (left precentral/inferior frontal gyrus, bilateral middle frontal gyrus, right medial frontal gyrus, bilateral inferior frontal gyrus).	-
						BP < SZ: Regional GM temporal cortex (left inferior/middle temporal gyrus, right uncus, right anterior superior/middle temporal gyrus).	BP < SZ (between-group, cross-sectional): ↓Regional GM in temporal cortex (left uncus/middle temporal gyrus/amygdala), occipital cortex (right lingual gyrus) and left cerebellum.	SZ vs BP: ↓GMV
Salisbury et al. 2007[70]	21/20[b] 13/11[c]	21.8/24.5[b] 22.1/26.0[c]	1.5	ROI	Manual	SZ < HC: Left Heschl's gyrus	SZ (within-group, over time): Left Heschl's gyrus	-
						BP=HC: Heschl's gyrus	-	-
						SZ < BP: Left Heschl's gyrus	-	SZ vs BP: ↓Left Heschl's gyrus
Nakamura et al. 2007[69]	34/29[b] 21/17[c]	22.1/24.3[b] 23.7/26.0[c]	1.5	ROI	Manual	SZ < HC: NCGM SZ > HC: SCSF, LV	SZ (within-group, over time): ↓TL, ↓FL SZ < HC (between-group, cross-sectional): PO, TL, FL SZ < BP (between-group, cross-sectional): TL, FL	SZ vs HC: ↓NCGM, ↑LV, ↑SCSF[a], ↓TL, ↓FL SZ=HC: PO

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						BP < HC: NCGM BP > HC: SCSF, LV	BP (within-group, over time): ↑PO, ↑TL, ↑FL BP=HC (between-group, cross-sectional): PO, TL, FL	BP vs HC: ↑NCGM BP=HC: LV
						SZ=BP: NCGM, SCSF, LV SZ=BP=HC: CWM SZ=BP=HC: PO, TL, FL	-	SZ vs BP: ↓NCGM, ↑LV, ↓TL, ↓FL BP vs SZ: ↑NCGM, ↑FL, ↑TL, ↑PO SZ=BP: SCSF SZ=BP=HC: CWM
Koo et al. 2008[68]	41/39[b] 18/17[c]	22.8/23.9[b] 22.4/24.6[c]	1.5	ROI	Manual	SZ < HC: L/R TCV, L/R ACC, R PCC, L SGC, L/R ARC, R ADC SZ=HC: R SGC, L ADC	-	SZ vs HC: ↓SGC, ↓ARC, ↓ADC, ↓PCC
						BP=HC: L/R TCV, L/R ACC, L/R PCC, L /R ARC, L/R ADC BP < HC: L/R SGC	-	BP vs HC: ↓SGC
						BP=SZ: L/R TCV, L/R ACC, L PCC, L/R SCG, L/R ARC, L/R ADC BP=SZ=HC: L PCC	-	SZ vs BP: ↓ARC, ↓ADC

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Takahashi et al. 2009[72]	5/7	-	1.8	ROI	Manual	UHRP-SZ=UHRP-BP: All superior temporal subregions	UHRP-SZ (within-group, over time): ↓ All superior temporal subregions at trend level; in 6/6 subregions left-lateralized UHRP-BP (within-group, over time): ↓ All superior temporal subregions at trend level; in 5/6 subregions right-lateralized UHRP-SZ=UHRP-BP: All superior temporal subregions	UHRP-SZ vs UHRP-BP: No difference for all superior temporal subregions
Castro-Manglano et al. 2010[86]	14/8	18.5	3	VBM	SPM2	SZ: ↓GM volume in the angular gyrus, middle frontal gyrus, superior parietal gyrus, and thalamus.	SZ (within-group, over time): No progressive changes	-
						BP: ↓GM volume in precuneus	BP (within-group, over time): No progressive changes	HC vs SZ and BP: ↓GM in the left parahippocampal gyrus, thalamus, superior frontal gyrus, middle frontal gyrus, precentral gyrus, superior parietal lobule, middle occipital gyrus, inferior occipital gyrus, lingual gyrus, angular gyrus, cerebellum. ↑GM precuneus posterior cingulate.
Trzesniak et al. 2012[87]	46/62[b] 31/39[c]	28.3/27.7[b] 30.3/29.5[c]	1	ROI, VBM	Manual, SPM8	SZ < HC: AI length SZ < BP: AI length SZ=BP=HC: CSP prevalence and length SZ=BP=HC: AI prevalence	-	FEP vs HC: ↑CSP length SZ vs BP: No differences AI prevalence and length SZ vs BP: No differences CSP prevalence and length

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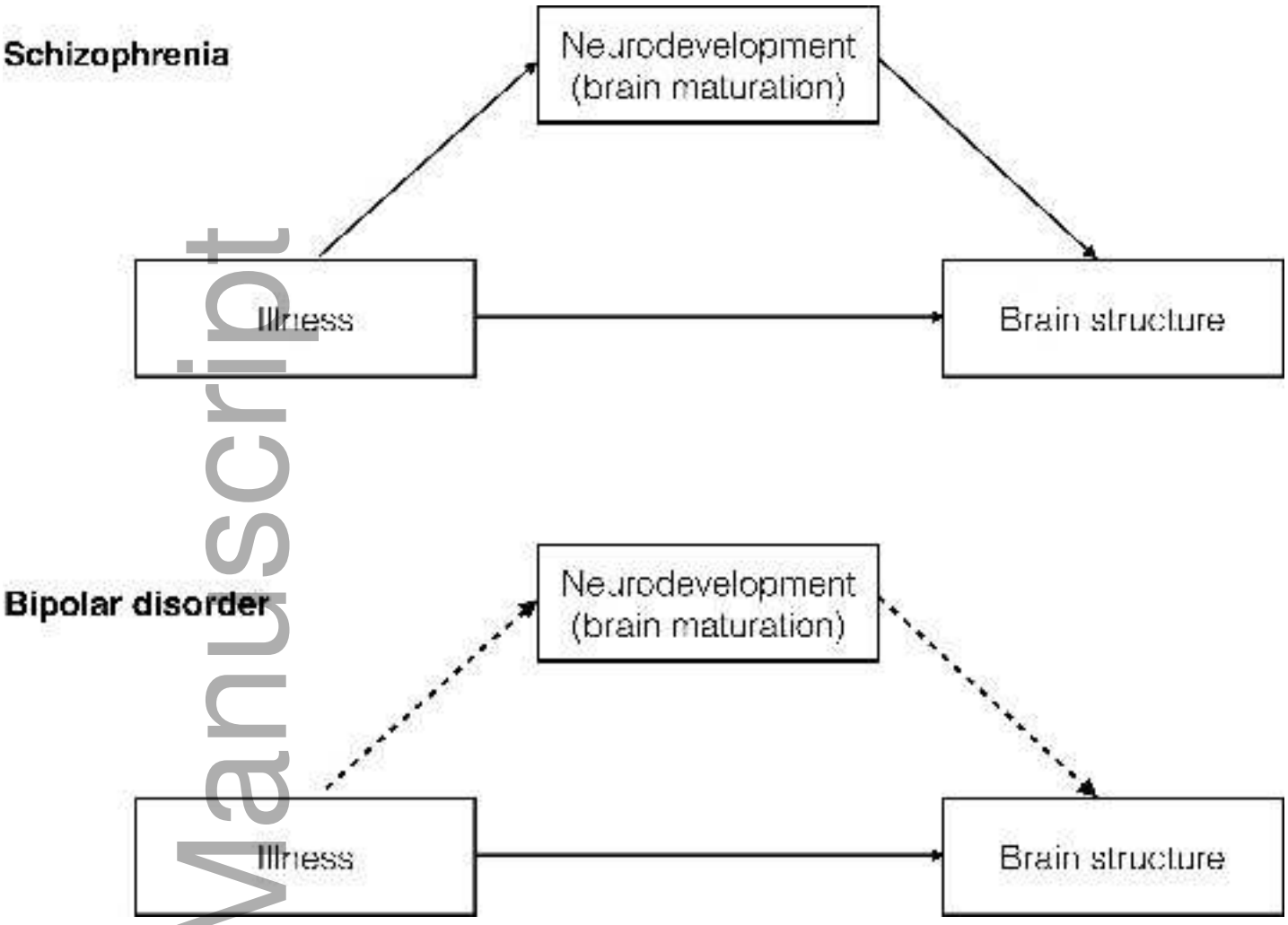
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Arango et al. 2012[61]	16/25	16.6/15.5	2	ROI, VBM	Manual, SPM2	-	-	SZ vs HC: ↓WBGM, ↑Left FCSF, ↓L/R FLGM, ↓Left PLGM BP vs HC: No differences
Lee at al. 2016[71]	23/22	22.7/25.3	1.5	ROI	Manual	SZ=HC: TINS SZ < HC: TP[a] SZ < HC: L TP	-	SZ vs HC: ↓TINS, ↓TP
						BP=HC: TINS, TP	-	BP vs HC: No differences
						SZ < BP: TINS SZ < BP: TP[a] SZ < BP: L TP	-	SZ vs BP: ↓TINS, ↓TP[a]

[a]=trend level (p<0.1), ACC=anterior cingulate cortex, ADC=anterodorsal cingulate cortex, AI=adhesio interthalamica, ARC=anterorostral cingulate cortex, [b]=baseline/timepoint 1, BP=bipolar disorder, [c]=follow-up/timepoint 2, CSP=cavum septum pellucidum, CWM=cerebral white matter, FEP=first-episode psychosis, FCSF=frontal cerebrospinal fluid, FL=frontal lobe, FLGM=frontal lobe grey matter, GM=grey matter, GMV=grey matter volume, HC=healthy controls, LV=lateral ventricles, NCGM=neocortical grey matter, PFC=prefrontal cortex, PLGM=parietal lobe grey matter, PO=parieto-occipital lobe, ROI=region-of-interest analysis, SZ=schizophrenia, SCSF=sulcal CSF, SGC=subgenual cingulate cortex, TBV=total brain volume, TCV=total cingulate volume, TINS=total insula, TL=temporal lobe, TP=temporal pole, UHRP=ultra-high risk psychosis, VBM=voxel-based morphometry analysis, WM=white matter, WBGM=whole-brain grey matter, WMV=white matter volume.

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