Chapter 19
Brain Morphological Abnormalities at the Onset of Schizophrenia and Other Psychotic Disorders: A Review of the Evidence

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Abstract A number of structural brain imaging studies and meta-analytic reviews have shown that multiple subtle brain abnormalities are consistently found in schizophrenia. However, quantitative reviews published to date suggest that structural brain changes found at the onset of the disease may be at least partially different from those found in patients with chronic schizophrenia. Some abnormalities seem to characterize schizophrenia at all stages; others seem more specific to the initial phases of the disease. These findings support the hypothesis of different patterns of involvement of various cerebral areas over the time course of schizophrenia. This suggests a complex scenario in which late cerebral changes, possibly related to the disease course and treatment, may complicate other early abnormalities, probably predating the disease onset. The specificity of such brain abnormalities to schizophrenia or the possibility that they may also be relevant to other psychotic disorders is a matter of debate. In particular, there is evidence for the presence of brain abnormalities in bipolar disorder, partially overlapping those found in schizophrenia. In this case, however, different findings have been reported in first-episode and chronic cases, raising the issue of converging trajectories of brain pathomorphology in these disorders, from a more specific pattern of abnormalities at onset, to a higher degree of overlap in chronic cases. In this chapter, the nature and meaning of these components of brain abnormalities, and how they affect the neurodevelopmental versus neurodegenerative hypotheses of psychoses are discussed.

Keywords Schizophrenia · Bipolar disorder · Psychosis · Brain morphology · Magnetic resonance imaging · First-episode · Meta-analysis

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Abbreviations

BD	Bipolar disorder
CT	Computed tomography
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
MRI	Magnetic resonance imaging
ROI	A region of interest
STG	Superior temporal gyrus
VBM	Voxel-based morphometry

Introduction

The occurrence of multiple brain abnormalities in schizophrenia and other psychotic disorders has been shown by many CT and MRI studies performed in the last 40 years, and confirmed by a series of meta-analytic reviews [1–4], demonstrating that psychotic disorders are characterized by several cortical and subcortical brain abnormalities. The investigation of cerebral morphology at different stages of the illness and, in particular, in patients with a first-episode psychotic disorder, is a matter of particular interest for several reasons: (i) patients with chronic psychoses have been exposed for long periods to various potential confounders that can affect brain structures, such as illness duration and cumulative intake of antipsychotic medications; (ii) the possible detection of brain morphologic abnormalities in the first phases of the illness, compared with those found in chronic cases, may provide useful information about the potential progression of changes in the brain after the onset of the disease; (iii) brain abnormalities at illness onset may represent the core and primary pathologic changes in the disorder, and (iv) the identification of specific patterns of morphologic alterations in the brain in the first stages of the disease may provide a useful tool for earlier recognition or diagnosis. Thus, investigation of brain anatomy in patients at the onset of the disease represents a means to get more insight on the nature of brain abnormalities detected in functional psychoses and their role in the pathophysiology of these diseases.

Schizophrenia

Several MRI studies have examined different cortical and subcortical regions of the brain in patients with first-episode schizophrenia using either ROI method or VBM approach. Some ROI studies have demonstrated a similar pattern of brain abnormalities as that reported in samples of patients with chronic schizophrenia, with a reduction in total grey matter volume [5–11], lateral and third ventricular enlargement [10–17], reduction in frontal lobe volume [18–23] and temporo-limbic abnormalities [20, 24–26, 22, 27–30]. The results of these studies, however, have

been put somewhat into question by others that have reported non-significant changes in brain structures such as cerebral ventricles [31–36], temporal lobe [18, 19, 33–35, 37] and temporo-limbic structures [7, 38–40] in similar samples of patients with first-episode schizophrenia.

A lower number of VBM MRI studies, with a more extensive survey of grey matter abnormalities than the manually drawn ROI analyses, has been conducted to compare brain morphology in patients and healthy controls. Investigations of grey matter volume in patients with first-episode schizophrenia using VBM have shown decreased volume of the mediodorsal thalamus and ventral and medial prefrontal cortices [41], prefrontal cortex [42], right medial frontal lobe, left middle temporal gyrus, left postcentral gyrus and the left limbic lobe [43], anterior cingulate cortex [43, 44], left STG, and bilateral anterior cingulate gyri and insula [45]. Three studies that recruited never-medicated subjects [46–48] reported reduction in grey matter volume in fronto-striato-thalamic and parahippocampal regions as well as smaller volume of the caudate [46, 47] and middle STG [48].

The presence of specific brain abnormalities in patients with first-episode schizophrenia has also been confirmed by a number of meta-analyses, which have shown the occurrence of multiple subtle brain abnormalities at the onset of schizophrenia. In particular, two studies have been performed on ROI MRI. The analysis by Vita et al. [49] included 21 cross-sectional studies and indicated that patients with schizophrenia, compared with healthy controls, showed significant overall effect sizes for increase of lateral and third ventricular volume (left ventricle $P \leq 0.001$, right ventricle $P \leq 0.001$, lateral ventricles $P = 0.02$, third ventricle $P \leq 0.001$, respectively), and for reduction of whole brain ($P = 0.002$) and hippocampal volume in both cerebral hemispheres (left hippocampus $P \leq 0.001$, right hippocampus $P \leq 0.001$), but not for temporal lobe, amygdala and total intracranial volume. In line with Vita et al. [49] results, the quantitative review conducted by Steen et al. [50], which considered 52 studies in a cross-sectional analysis of first-episode schizophrenia, demonstrated a reduction of whole brain and hippocampal volume (both $P \leq 0.0001$) and an increase of ventricular volume ($P \leq 0.0001$) relative to healthy controls. Moreover, the more recent meta-analysis of VBM imaging studies conducted in patients with first-episode schizophrenia by Ellison-Wright et al. [51] reported decreases in grey matter volume in the thalamus, the left uncus/amygdala region, the insula and the anterior cingulate bilaterally.

DTI makes it possible to assess microstructural abnormalities of brain white matter. In addition, the probable trajectories of fiber tracts can be calculated and visualized, allowing tract-specific measurements. As reported in the review by Peters et al. [52], DTI studies have produced some evidence of widespread white matter abnormalities in patients with first-episode schizophrenia [53–62], but the findings are not unequivocal. Some studies have shown no differences between patients and healthy controls [63–68], whereas others found no FA abnormalities but did identify abnormalities with other diffusion indices [64, 69, 70]. Overall, the most positive findings come from VBM studies, whereas 6 out of 15 fiber tracking or ROI analyses showed no abnormalities [60, 63, 65–68].

Bipolar Disorder

A large number of studies have been performed to date on brain morphology in patients with BD. These are reviewed by Kempton et al. [2] in a recent meta-analysis, which included up to 98 studies. The most significant anatomical abnormalities in BD were enlargement of the third and lateral ventricles, reduction of the cross-sectional area of the corpus callosum and an increased rate of deep white matter hyperintensities. A relatively small number of studies have considered brain morphology in patients with BD at the illness onset.

ROI MRI studies on first-episode BD have demonstrated a pattern of brain abnormalities similar to those detected in samples of patients with chronic BD, that is, enlargement of the ventricular system [71], smaller area of the corpus callosum [72], and the presence of brain white matter hyperintensities [73]. On the other hand, other MRI studies have reported various cortical and subcortical brain abnormalities at illness onset not detected consistently in patients with chronic BD, such as a reduction of neocortical grey matter [74], smaller amygdala volume [75] and larger than normal striatum [76].

VBM MRI studies conducted on first-episode BD showed decreased volumes of frontal lobe and temporal gyrus grey matter [77], and of cingulate gyrus grey matter [77, 78].

DTI studies of brain white matter abnormalities in the early course of BD showed lower FA in the left anterior frontal white matter, left posterior thalamic radiation, left cingulum and bilateral sagittal striatum [79] and superior frontal white matter [80].

The presence of specific brain abnormalities in patients with first-episode BD has also been confirmed by a recent meta-analysis of ROI MRI studies [81], where a significant reduction in total intracranial ($P = 0.022$) and white matter volume ($P = 0.029$), but not in grey matter and whole brain volume, was demonstrated in patients with first-episode BD compared with healthy controls.

Schizophrenia Compared with Affective Psychoses

The evidence so far indicates a consistent association between brain structural abnormalities and schizophrenia and BD in the early phases of these illnesses. Given the evidence of a significant anatomic overlap between the findings of brain morphologic changes across different diagnostic groups of functional psychoses, the specificity of brain structural abnormalities in schizophrenia and affective psychoses at illness onset could be better addressed by means of studies that directly compare patients with a diagnosis of schizophrenia, patients with a diagnosis of affective psychosis, and healthy comparison groups.

A few cross-sectional MRI studies on this topic have been performed but have led to heterogeneous results. Takahashi et al. [82] investigated the STG subregions in patients with schizophrenia and schizoaffective disorders and subjects with a diagnosis of affective psychosis compared with healthy subjects. They reported that

patients with first-episode schizophrenia had significantly less grey matter in the Heschl gyrus, planum temporale, and caudal STG bilaterally compared with all other groups, but that there were no differences between controls and the affective psychosis, schizophreniform disorder, for any STG subregions. The STG white matter volume did not differ between groups. This finding seems to indicate that morphologic abnormalities of the STG grey matter are specific to schizophrenia among psychotic disorders. The cross-sectional investigation conducted in patients with schizophrenia and affective psychosis at their first hospitalization by Kasai et al. [83] found that a bilateral volume reduction in insular cortex grey matter was specific to patients with first-episode schizophrenia. In contrast, both first-episode psychosis groups showed a volume reduction in left temporal pole grey matter and an absence of normal left-greater-than-right asymmetry. The evaluation of the presence of white matter hyperintensities in a large sample of people with first-episode psychosis conducted by Zanetti et al. [73] reported no difference between the whole group with psychosis and controls for the prevalence or severity of these lesions, independent from their brain localization. Similarly, no statistically significant differences in the frequency and severity scores were identified when comparing patients with affective psychosis (psychotic BD or unipolar depression), non-affective psychosis (schizophrenia or schizophreniform disorder) and control subgroups. Nonetheless, as pointed out by the authors, it is possible that white matter hyperintensities could be a feature related to illness chronicity and this might explain why no group differences emerged in the early course of the illness.

In some studies, including both chronic and first-episode cases, schizophrenia and BD have been studied together as a generic psychosis category, with diagnostic categories analyzed post hoc. For example, Janssen et al. [84] found left medial frontal grey matter deficits in both disorders, and left middle frontal deficits only in schizophrenia. Others have compared schizophrenia and bipolar groups separately with normal controls and reported extensive grey matter deficits in the fronto-temporal-thalamic and cerebellar regions in schizophrenia, and no significant grey matter abnormalities in the bipolar group [85]. Most recently, Ellison-Wright and Bullmore [51] performed a meta-analysis with the newly developed anatomic likelihood estimation to compare the grey matter differences in each condition relative to controls. They found that in BD, reductions in grey matter were present in the anterior cingulate and bilateral insula and that these substantially overlapped with areas of reduction in grey matter in schizophrenia, except for a region of the anterior cingulate where the reduction in grey matter was specific to bipolar disorder.

Schizophrenia Compared with Schizophrenia Spectrum Disorders

A limited number of studies have directly compared brain morphology between patients with schizophrenia and a schizophrenic spectrum disorder. In the ROI MRI study performed by Takahashi et al. [82], patients with first-episode schizophrenia revealed significantly less amount of grey matter in the Heschl gyrus, planum

temporale, and caudal STG bilaterally compared with patients with schizophreniform disorder and healthy controls. On the other hand, no differences between controls and patients with schizophreniform disorder were demonstrated for any STG subregion. White matter volume of the STG did not differ between patients with first-episode psychosis and healthy subjects. Another MRI study by Crespo-Facorro et al. [86] investigating patients with schizophrenia and schizophreniform disorder showed an increase in cortical cerebrospinal fluid volume and a decrease in total brain tissue in psychotic patients at illness onset compared with healthy controls. However, the finding of larger lateral ventricular volume and a reduction in thalamic volume was limited to patients with schizophrenia. The VBM study of Pagsberg et al. [87] reported a reduction in white matter volume in the frontal lobe and an enlargement of lateral ventricular volume in patients with both first-episode schizophrenia and schizophrenia spectrum disorder compared with healthy controls, but the two clinical groups did not differ from controls for grey matter volume.

Trajectories of Brain Abnormalities and Specificity of Brain Morphologic Changes in Schizophrenia and BD

Looking at the literature on this issue, it appears that some of the regions of reduced grey matter in BD overlap with those in schizophrenia. This is consistent with the finding that the genetic risk for schizophrenia may be associated with grey matter deficits in the bilateral fronto-striato-thalamic and left temporal regions, whereas the genetic risk for BD may be associated with grey matter deficits in more limited regions of the right anterior cingulate gyrus and ventral striatum [88].

In agreement with these findings, there is increasing convergence toward dimensional constructs, as opposed to purely categorical ones, in the interpretation of the biologic substrate of schizophrenia and BD. Diagnostic classifications, making a priori assumptions about the illnesses as discrete entities, may be obstacles to our understanding of the aetiology and biology of psychosis. Typically, groups of patients with BD or schizophrenia are compared with healthy controls using classification systems such as the DSM IV. However, both conditions are intimately related, with shared genetic determinants [89].

Meta-analytic estimations of the extent to which BD, schizophrenia or both conditions contribute to brain grey matter differences compared with controls, statistically addressed with the so-called anatomic likelihood estimation [51], indicate substantial overlap in the regions affected in schizophrenia and BD including grey matter deficits in frontal, temporal, cingulate and insular cortex and thalamus. BD and schizophrenia contributed together to clusters of grey matter deficits, but schizophrenia was associated with additional grey matter deficits, especially in the left hemisphere, involving limbic and neocortical structures that go beyond the regions affected in BD [51]. On the other hand, a region of the anterior cingulate where the reduction in grey matter was specific to BD was reported [51]. Common

biologic mechanisms may therefore explain the neuroanatomic overlap between the two disorders, but an explanation of why brain differences are more extensive in schizohphrenia remains challenging.

Therefore, current pattern of results indicates that schizophrenia and BD appear not to be completely distinct entities at the level of the neuroanatomic phenotype. This observation is necessarily simplistic, but has lent support to the argument that they share biologic dimensions. The challenge for the future will be to identify whether the reductions in grey matter in BD and schizophrenia may be related to specific genetic factors [90] and whether common susceptibility genes contribute to the overlap in regional brain changes. The shared prefrontal cortical grey matter deficits observed may well contribute to core common cognitive dysfunctions related to negative functional outcomes in both disorders [91, 92].

Some more specificity of neuroimaging findings emerges, however, when only first-episode patients are considered.

The results of the main meta-analyses conducted on schizophrenia [49, 50, 93] confirm the presence at the onset of the illness of some of the brain abnormalities observed in chronic patients, i.e. enlargement of the ventricular system, and reduction in the volume of whole brain and the hippocampus. On the other hand, changes in the volume of the temporal lobe or amygdala do not appear in patients with first-episode schizophrenia compared with healthy controls, at variance with what was found in chronic patients. This pattern of results would support the hypothesis of an earlier involvement of the hippocampus in the cerebral pathomorphologic trajectory of schizophrenia, followed by a later involvement of the amygdala and other grey matter regions of the temporal or frontal lobe.

On the other hand, the main finding of a recent meta-analysis of patients with first-episode BD [94] was the presence, at the onset of the disease, of a significant reduction in intracranial volume and total white matter volume, at variance with the findings of meta-analyses of brain morphology conducted mainly on chronic patients [2]. Even if it is not possible to exclude the possibility that diagnostic shifts could arise over time for some patients enrolled in the original studies of first-episode BD (i.e. some of the patients classified as BD at disease onset could be re-diagnosed later as suffering from other types of psychoses and so are less represented in samples of chronic patients), some morphologic abnormalities appear early in the course of BD and other (especially lateral ventricular enlargement, grey matter changes and white matter hyperintensities) occur later and possibly increase with age.

The presence of definite brain abnormalities early in the course of schizophrenia and BD supports the hypothesis of a neurodevelopmental nature, even though their aetiology remains unclear. Even more important to the present discussion, it indicates that, at onset, a higher degree of specificity of brain morphologic changes in each of these two disorders is detectable. At a later stage, when the diseases progress, adjunctive, possibly progressive abnormalities appear, reducing the differences in the patterns of abnormalities between the two disorders, as is typically seen in more chronic cases.

Among the many possible explanations for the differences between data found at the onset and those reported in chronic patients, the most convincing are those related to the effects of medications and duration of illness. For example, chronic consumption of antipsychotics has been associated with changes in grey matter volume over time in a number of studies reviewed in [93, 95, 96], with substantial differences between the effects of typical and atypical antipsychotics, pointing towards the possibility of morphologic changes in the brain during the course of the disease, solely as a result of the amount and type of drug treatment received. There is also evidence that antidepressants, lithium or mood stabilizers may affect cerebral structure, as well as function [97], and this may occur in opposite directions for different classes of drugs. On the other hand, some authors have reported significant correlations between length of illness and grey matter volume in schizophrenia [36, 98] and in BD [99, 100]. Changes in grey matter volume over time have been reported in a few longitudinal MRI studies on patients with first-episode schizophrenia and chronic schizophrenia [101, 102] and BD [75, 103]. It would be very informative to perform new analyses on patients with schizophrenia and affective disorder using computational methods to take into account the known or hypothetical effect of drugs and chronicity in order to better understand whether a component of later structural changes in the brain is still demonstrable, and whether a higher specificity of brain pathomorphology could also be demonstrated in chronic cases after separating out the effects of treatment and chronicity.

Conclusions and Future Directions

In conclusion, the finding of different brain abnormalities in chronic versus first-episode schizophrenia and BD supports the notion of different pathophysiologic trajectories of specific brain morphologic characteristics over the course of these diseases. Some of the abnormalities occur early, probably predating the clinical onset, and show some specificity for schizophrenia and BD. Other changes occur later, in the course of the disease and after pharmacological treatment, and may be more similar for psychotic disorders, leading to an increasing overlap of findings in chronic cases, at least for grey matter changes. Whether this later and possibly progressive component of brain abnormalities is just an epiphenomenon of the disease course, treatment or other environmental events, or may be already embedded in the pathophysiologic trajectory of these diseases, possibly under some degree of genetic control, is still a matter for research and discussion. To shed more light on these crucial issues, there is still a need for longitudinal studies conducted on first-episode cases, aimed at specifically addressing the issues of the time of appearance and course of individual brain abnormalities in psychotic disorders, taking into account the effects of several confounders. Such studies may lead to a better understanding of the biologic meaning of brain abnormalities in both schizophrenia and BD and, through this, of the pathogenesis of these diseases.

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