Review Article

# Neuroimaging in the Field of Psychoses

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## Abstract

**This review looks at the recent findings in the neuroimaging of the psychoses, with a view to clarifying the question of the unitary versus the two-disorder theory of psychosis. Schizophrenia is associated with significantly more cortical grey matter loss than bipolar disorder. The distribution of these losses is different; schizophrenia is characteristically associated with loss of the medial and middle frontal, the superior temporal gyri, and the dorsolateral prefrontal cortex, while bipolar disorder has particular loss in the medial frontal gyrus and the anterior cingulate cortex. Both disorders were associated with extensive white matter deficits. In summary, neuroimaging indicates different patterns of grey matter loss for schizophrenia and bipolar disorder. However, neuroimaging of white matter reveals a good deal of overlap between these two disorders. Thus, neuroimaging does not suggest a unitary psychosis or a two-psychosis model, instead it suggests a two-dimensional psychosis field, on which disorders are located according to two dimensions, the degree of grey matter loss and the degree of white matter abnormality.**

***Keywords:*** *bipolar disorder, magnetic resonance imaging, psychoses, schizophrenia, tomography*

## Introduction

Schizophrenia and bipolar disorder are common, disabling disorders. They were known as "functional" (by which was meant, no organic basis has been demonstrated) as opposed to the "organic" disorders (such as dementia, for which a structural basis can be demonstrated at autopsy). However, the term "functional" says more about the technology of the day than about a particular disorder, and in recent years, neuroimaging has begun to illustrate the structural abnormalities of these disorders.

In 1893, Emil Kraepelin divided the extant single category of psychosis into two (the modern equivalents being schizophrenia and bipolar disorder). His concept has guided much of the psychiatric research and clinical work for the last century. However, there have been repeated calls to return to the unitary theory of psychosis (1). Recent neuroimaging may inform this debate.

Coaxial tomography became available in the 1970s, and was immediately used to demonstrate increased cerebral ventricular size in people with schizophrenia (2), but limited progress was achieved. Magnetic resonance imaging (MRI) then revolutionized neuroimaging. This review will be limited to structural MRI, with some mention of its use in diffusion tensor imaging (DTI; which depends on water diffusing more rapidly in the direction aligned with the internal structure of white matter).

In MRI, voxel-based morphometry (VBM) is a technique in which neuroanatomical differences are detected by comparing voxels across the entire brain. This method has some technical difficulties (3,4). Small abnormalities may go undetected, and perhaps the best use of VBM is the identification of candidate regions (5). In region-of-interest (ROI) MRI, candidate regions are examined in greater detail.

Patient factors also introduce comparison difficulties. Diagnostic criteria may vary, and different disease stages may have different pathological features. Furthermore, some medications are known to alter grey matter volume.

A comprehensive assessment of the literature was conducted in PubMed using "neuroimaging, schizophrenia" and "neuroimaging, bipolar disorder" as the search terms. A selection of papers were examined and reported under these headings: 1) schizophrenia, 2) bipolar disorder, and 3) comparisons of schizophrenia and bipolar disorder.

## Schizophrenia

In a meta-analysis of whole brain volumes in first-episode, medication-naïve patients with schizophrenia, Steen et al. (6) found a 2.7% reduction in comparison with healthy controls. In VBM studies of schizophrenia, reduced grey matter has been described in the frontal, temporal, and thalamic regions. Similar changes have been reported in first-episode and chronic schizophrenia, but the differences are more marked in the latter (7).

In a longitudinal ROI study (8) people with chronic schizophrenia and healthy controls were examined at two points, 4 years apart. The course of the illness was charted using the Brief Psychiatric Rating Scale (BPRS) and periods of hospitalization. People with chronic schizophrenia demonstrated significantly accelerated lateral ventricular expansion and frontal cortical grey matter loss. Rates of loss were greater in patients with higher BPRS scores and longer periods of hospitalization.

Much interest has been directed toward early brain changes. This approach may perhaps avoid complications introduced by medication and the chronic disease process. An understanding of early brain changes may also assist in early diagnosis, and eventually, in prevention. To this end, people at risk of schizophrenia (either by a change in the premorbid mental state, or possible genetic disposition) have been identified and serially investigated.

Pantelis et al. (9) examined young people at increased risk for schizophrenia. In this cross-sectional study, subjects who developed psychosis compared with those who did not, showed less grey matter in the right lateral temporal, medial temporal, and inferior frontal neocortex and in the cingulate cortex bilaterally. Subjects who developed psychosis were re-scanned 1 year later, at which point, there was a loss of grey matter in the left fusiform, parahippocampal, orbitofrontal, and cerebellar cortices. Therefore, some grey matter abnormalities predated the onset of psychosis, and others came later. A similar study (10) found reduced grey matter in posterior and anterior cingulate areas, lateral and medial temporal lobes, and lateral frontal cortex in young patients prior to the development of psychosis in comparison with at-risk individuals who did no develop psychosis and healthy controls.

A recent VBM study (11) compared a group of patients with formal thought disorder with healthy controls. Thought disorder was gauged using the Scale for the Assessment of Thought, Language, and Communication. The severity of thought disorder was negatively correlated with the grey matter volume of the left temporal pole, left superior temporal gyrus, the right cuneus/lingual gyrus, and the right middle orbital gyrus. These findings support an analysis of 15 VBM studies (12) which indicated the left medial temporal lobe the left superior temporal gyrus as key regions of anatomical difference between people with schizophrenia and healthy subjects.

A DTI study of people with schizophrenia (13) revealed significant white matter disruption compared to healthy controls in the uncinate fasciculus, arcuate fasciculus, cingulum, and corpus callosum.

## Bipolar Disorder

Bipolar disorder may feature psychosis, which makes comparison with schizophrenia interesting. The whole brain volume in bipolar disorder appears to be preserved (14). However, moderate ventricular enlargement has been frequently demonstrated (15), suggesting some tissue loss. VBM studies in bipolar disorder have yielded variable findings. Some studies have failed to find grey matter differences in patients relative to healthy controls, suggesting that these changes in bipolar disorder are less pronounced than those found in schizophrenia (16). ROI studies in bipolar disorder have described ventricular enlargement and white matter hyper-intensities as the most robust changes, with grey matter differences generally being small (17). VBM studies of early stage bipolar disorder have been few and contradictory. Janssen et al. (18) found reductions specific to the medial prefrontal cortex. ROI studies of early stage bipolar disorder have also been few and inconsistent. Koo et al. (19) found reduced left subgenual cingulate cortex; however, Fornito et al. (20) reported increased right subgenual cingulate cortex in male patients.

Koo et al. (19) performed a longitudinal study of bipolar disorder, conducting scans at the first episode of psychosis, and again about 3 years later. A reduction was demonstrated in the volume of the anterior cingulate cortex. Moorhead et al. (21) studied people with chronic bipolar disorder for over a 4-year period and found progressive grey matter reduction in the fusiform, hippocampal, and cerebellar cortex, but not in the anterior cingulate cortex.

Savits et al. (22) compared two groups of patients with bipolar disorder (medicated and unmedicated) with healthy controls. The unmedicated patients had significantly smaller

amygdalae and the medicated patients had larger amygdalae (trending towards significance) compared with the healthy controls. The disease process was believed to account for the reduced size of the amygdalae in the unmedicated group, and the medication was believed to account for the increased size of the amygdale in the medicated group.

Heng et al. (23) reviewed 18 DTI studies of the white matter of people with bipolar disorder. They concluded a loss of white matter connectivity (involving prefrontal and frontal regions), projection, associative and commissural fibres was a feature of bipolar disorder.

## Comparisons of Schizophrenia and Bipolar Disorder

Some recent studies have directly compared images of patients with schizophrenia and bipolar disorder, in particular, where there have been psychotic features.

Kasai et al. (24), in a ROI study, compared the grey matter volume of the left superior temporal gyrus of a group of people with first-episode schizophrenia, a group of people with first-episode affective psychosis, and a group of healthy controls, at two points in time, 1.5 years apart. They found progressive loss of the left superior temporal gyrus in schizophrenia in contrast to patients with affective psychosis and controls.

Coryell et al. (25) studied patients with major depressive disorder with psychotic features, patients with schizophrenia, and healthy controls, at two points, 4 years apart. The people with major depressive disorder with psychotic features had significantly smaller grey matter volumes on the left side of the posterior subgenual prefrontal cortex. The volumes of this region for patients with schizophrenia were also smaller than for the healthy controls. Four years later, the relative size relationship was unchanged; however, for the depression group, the size of this region had increased. This suggested (to the authors) that for this disorder, this anatomical deficit is reversible, and that medication may have played a role.

McDonald et al. (26) used VBM to compare the grey and white matter volumes throughout the brain of groups of individuals with schizophrenia, bipolar disorder with psychotic features, and healthy controls. The group with schizophrenia had generalized grey matter loss (predominantly involving frontotemporal neocortex, medial temporal lobe, insula, thalamus, and cerebellum). The group with bipolar disorder did not have regions of significant grey matter loss. The authors observed that the majority of the bipolar patients were on lithium, which may have increased the volume of the grey matter of this group, and hence reduced any differences in grey matter volume, which might otherwise have existed. The pathological groups had anatomically overlapping white matter abnormalities in regions occupied by major longitudinal and interhemispheric tracts (including the superior longitudinal fasciculus, inferior longitudinal fasciculus, and orbitofrontal fasciculus, as well and the anterior and posterior parts of the corpus callosum).

Nakamura et al. (27) conducted a ROI study of the neocortical grey matter of groups at first hospitalization for schizophrenia, first hospitalization for affective disorder with psychosis, and no mental disorder. Patients were scanned at intake and 1.5 years later. At first hospitalization, both the schizophrenia and affective disorder groups demonstrated significantly less neocortical grey matter than the healthy control groups; however, there was no significant volume difference between the pathological groups. Longitudinally, however, the schizophrenia group showed a neocortical grey matter reduction (-1.7%; mainly in the frontal and temporal regions) and the affective disorder group showed a neocortical grey matter increase (+3.6%), which the authors suggested may reflect the neurotrophic effects of mood stabilizers.

Koo et al. (19) studied initial and progressive grey matter volume of cingulate gyrus subregions in patients with first episode schizophrenia, patients with first episode affective psychosis, and healthy controls. Subjects were scanned twice, 1.5 years apart. Patients with affective psychosis, at initial assessment, showed significant loss of the subgenual cingulate, which was progressive. Patients with schizophrenia, on the other hand, had more widespread cingulate deficits, which were less progressive. This suggested (to the authors) that these disorders had different initial grey matter deficits and progression over time. In addition, this group looked at the morphology of the paracingulate sulcus. Cerebral folding occurs during the 2nd and 3rd trimester and is stable thereafter, and consequently, the paracingulate can be used as a marker of neurodevelopment. The authors found less fissuration of the paracingulate sulcus in people with schizophrenia than healthy controls, suggesting neurodevelopmental factors contribute to this disorder.

Janssen et al. (18) conducted an MRI study of early onset first-episode psychosis. For inclusion, onset was prior to 18 years of age and the psychosis

had persisted for less than 6 months. Three diagnostic groups were identified: schizophrenia, bipolar disorder, and other psychiatric conditions. Schizophrenia was associated with grey matter volume loss in the left medial (superior) and left middle frontal gyrus. Bipolar disorder, however, was associated with grey matter volume loss of the left medial frontal gyrus only. The psychotic individuals who at follow-up did not have a diagnosis of either schizophrenia or bipolar disorder displayed different patterns. The authors noted that the schizophrenia and bipolar psychosis both appeared associated with medial frontal gyrus, suggesting some shared pathophysiology.

White matter hyper-intensities had been considered to be a characteristic feature of mood disorder (17). However, Zanetti et al. (28), in a large and well conducted study using MRI, found that white matter hyper-intensities were equally represented in psychotic bipolar disorder and schizophrenia spectrum disorders. Doubt about the specificity of white matter hyper-intensities in bipolar disorder has been recently expressed by Gunde et al. (29). Interestingly, McIntosh et al. (30) demonstrated DTI abnormalities in the uncinate fasciculus in both schizophrenia and bipolar disorder, but Walterfang et al. (31) found MRI differences between the corpus callosum of the first-episode affective psychosis and schizophrenia spectrum patients.

El-Sayed et al. (32) studied young people with early onset schizophrenia spectrum disorders, young psychotic people with mood disorders, and young healthy controls. They found significantly lower total brain volume in those with schizophrenic spectrum disorders compared with the other two groups. They found the schizophrenia spectrum disorder patients had significantly reduced grey matter volume, particularly in the frontal and parietal lobes, but found no difference in white matter volumes.

## Discussion

This paper does not mention every study in the field of neuroimaging in psychosis. However, a good representative sample is presented, with particular attention applied to the most recent studies.

In 1893, Emil Kraepelin divided the psychoses into two categories, schizophrenia and bipolar disorder. However, some still question whether they are two distinct disorders, or a single disorder which is expressed differently (the unitary theory of psychosis). This paper asks whether neuroimaging can contribute to this discussion.

Neuroimaging of schizophrenia finds a significant reduction in whole brain volume (2,6). Grey matter loss has been consistently described in the anterior and lateral prefrontal regions and the medial, lateral surfaces, and the superior gyrus of the temporal lobe (8,10,33). A DTI study in schizophrenia (13) showed significant white matter disruption throughout the brain compared with healthy controls.

Neuroimaging of bipolar disorder finds the whole brain volume to be relatively preserved (14), although there are reports of increased size of the lateral ventricles (15), which can be attributed to white matter loss. In general, grey matter loss has been described as relatively slight (16), and most marked in the medial prefrontal cortex (18) and particularly the anterior cingulate cortex (19). A review of DTI studies (23) in bipolar disorder found extensive white matter deficits.

Direct comparison studies of schizophrenia and bipolar disorder are of particular interest in addressing the question.

El-Sayed et al. (32) found significantly lower total brain volume in people with schizophrenia spectrum disorders compared with people with mood disorders with psychotic features.

McDonald et al. (26) found that schizophrenia was associated with greater grey matter loss (predominantly involving frontotemporal neocortex, medial temporal lobe, insula, thalamus, and cerebellum) compared with bipolar disorder with psychotic features. Similar finding was made by El-Sayed et al. (32). Others (27) conducted a longitudinal study and found that the grey matter in schizophrenia continued to reduce (mainly in the frontal and temporal regions), while in bipolar disorder, neocortical grey matter increased (which they attributed to mood stabilizer effect). Janssen et al. (18) found schizophrenia was associated with grey matter volume loss in the left medial (superior) and left middle frontal gyrus, while bipolar disorder was associated with grey matter volume loss of the left medial frontal gyrus only.

Kasai et al. (24) found progressive left superior temporal gyrus loss in schizophrenia in contrast to patients with affective psychosis. Coryell et al. (25) found significantly greater loss of subgenual prefrontal cortex in major depressive disorder with psychotic features, compared to schizophrenia. Koo et al. (19) made similar findings and concluded that patients with these disorders had different initial grey matter deficits and progression over time.

McDonald et al. (26) found that patients with schizophrenia and bipolar disorder with psychotic

features had similar white matter abnormalities in all regions. McIntosh et al. (30) demonstrated DTI abnormalities in the uncinate fasciculus in people with both schizophrenia and bipolar disorder.

In summary, the evidence suggests that schizophrenia, compared with bipolar disorder, is associated with more extensive grey matter loss, and white matter deficits appear to be a feature of both conditions.

## Conclusion

Neuroimaging indicates different patterns of grey matter loss for schizophrenia and bipolar disorder. However, neuroimaging of white matter reveals a good deal of overlap in these two disorders. Thus, neuroimaging does not suggest a unitary psychosis or a two-psychosis model, instead it suggests a two-dimensional psychosis field, on which disorders are located according to two dimensions, the degree of grey matter loss and the degree of white matter abnormality.

## Authors' Contributions

Conception and design, critical revision of the article, final approval of the article: SP
Analysis and interpretation of the data, drafting of the article: SP, GB

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