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Research report

A voxel based morphometry study investigating brain structural changes in first episode psychosis

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ABSTRACT

Schizophrenia (SCZ) and bipolar disorder (BP) are associated with neuropathological brain changes, which are believed to disrupt connectivity between brain processes and may have common properties. Patients at first psychotic episode are unique, as one can assess brain alterations at illness inception, when many confounders are reduced or absent.

SCZ ($N=25$) and BP ($N=24$) patients were recruited in a regional first episode psychosis MRI study. VBM methods were used to study gray matter (GM) and white matter (WM) differences between patient groups and case by case matched controls.

For both groups, deficits identified are more discrete than those typically reported in later stages of illness. SCZ patients showed some evidence of GM loss in cortical areas but most notable were in limbic structures such as hippocampus, thalamus and striatum and cerebellum. Consistent with disturbed neural connectivity WM alterations were also observed in limbic structures, the corpus callosum and many subgyral and sublobar regions in the parietal, temporal and frontal lobes. BP patients displayed less evidence of volume changes overall, compared to normal healthy participants, but those changes observed were primarily in WM areas which overlapped with regions identified in SCZ, including thalamus and cerebellum and subgyral and sublobar sites.

At first episode of psychosis there is evidence of a neuroanatomical overlap between SCZ and BP with respect to brain structural changes, consistent with disturbed neural connectivity. There are also important differences however in that SCZ displays more extensive structural alteration.

1. Introduction

The diagnostic division between schizophrenia and bipolar affective disorder remains controversial [1,2]. Both are believed to share a genetic disposition to psychosis [3] and reflect anatomical disconnection between components of large-scale neurocognitive networks [4]. Theoretical models of the functional anatomy have implicated overlapping neural systems. For example both appear to involve cortical and subcortical structural deficits [5–7] although these appear more widespread in schizophrenia. Nonetheless it remains unclear how symptomatology and neuropsychological function are related to underlying neuropathology in these conditions.

Schizophrenia is associated with a variety of subtle cortical and subcortical structural abnormalities particularly gray matter (GM) changes [9,12]. The degree to which these changes may be present at illness onset is still under investigation [20]. Brain changes associated with bipolar disorder are less extensively researched; findings from recent region of interest (ROI) meta-analyses are conflicting and non-specific [10,11]. However another meta-analysis of whole brain voxel-based morphometry studies found evidence of consistent medial temporal lobe abnormality [6]. There is an obvious need for further research to determine whether a reliable pattern of deficit actually exists. Honea in her review of morphometric approaches in schizophrenia has criticised the fact that MRI technology, target populations and diagnostic classifications have varied extensively between studies [12]. Steen et al. [13], in a recent review of volume of interest (VOI) studies in first episode schizophrenia, also noted that few robust conclusions could be drawn and was critical of the evidence available as few brain structures were evaluated in multiple studies and most studies carried

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out were small in scale. Similar concerns have been voiced with regard to available data from patients with bipolar disorder [14].

With the existing arguments suggesting related neuropathological mechanisms and processes are present in bipolar disorder and schizophrenia, recent models of the neuropathological processes in schizophrenia which propose two distinct stages; a neurodevelopmental deficit and in its wake, a post onset neuropathological deterioration [14,15] may also be relevant to bipolar disorder. Such a model implies there may be key brain areas of deficit at illness onset in both conditions with further neuropathology spreading as illness chronicity develops. For example some research suggests similar structural changes in both illnesses at illness onset, which diverge with progression [1]. However evidence of consistent patterns of brain changes in the early stages of illness remains limited. For example there are few imaging studies in the early stages of bipolar disorder, making it difficult to map brain changes associated with disease evolution.

The study of a population suffering a first episode of psychotic illness offers a unique opportunity to test such proposals and explore key disease processes underpinning decline into psychosis, as confounders such as disease chronicity [2] and the effects of long-term medication are largely absent [11,15].

The aim of the present investigation was to use voxel-based morphometry techniques to examine GM and WM volume changes at illness onset, compared to well matched healthy participants, in psychotic patients diagnosed with schizophrenia or bipolar disorder. This should aid efforts to determine differences and similarities in the structural brain alterations present in these illnesses at their onset.

2. Methods and materials

2.1. Participants

Participants were patients recruited to the Northern Ireland First Episode Psychosis Study (NIFEPS), a longitudinal, population-based, first contact study of all incident cases of psychosis collected over a two year period (January 2003 to December 2004). Of the 374 cases identified (3.82/10,000 population at risk), 278 (73.4%) agreed to a full clinical assessment.

2.2. Diagnostic criteria

Diagnostic classification was attained by clinical consensus reviews of patient histories and structured interviews using the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) [16]. Based on first assessment of the 90 psychosis patients 25 (28%) satisfied ICD-10 criteria for schizophrenia (SCZ) and 24 (27%) for bipolar disorder with psychosis (BP). Patients could have a previous presentation to mental health services with a non-psychotic diagnosis but the purpose here was to collect a population who presented for the first time with psychosis or bipolar disorder. Thus, we only excluded patients who on initial assessment turned out to have a previous diagnosis of psychosis. A diagnosis of mania/hypomania was regarded as equivalent of psychosis. A small number of bipolar patients had a previous episode of non-psychotic depression or a presentation with an anxiety disorder but had not previously presented with either psychotic or manic symptoms. After matching no significant differences were found between each patient group and their respective controls in terms of key variables (Table 1). Examination of the PANSS data from the clinical population collected showed there was no significant difference between those patients scanned and the rest of the patient group suggesting that those scanned were representative of those who entered the study.

Medication data was available on 48 (25 SCZ/22 BD) of the psychosis group (Table 1). Treatment dosage levels were comparable in both groups in the initial stages of the illness. However, most of the schizophrenia patients were still being maintained on antipsychotic medication to control symptoms at time of scan whilst the majority of the bipolar disorder group was medication-free by this stage.

2.3. Control selection

Healthy comparison subjects ($n = 88$) were recruited from patients' GP practices and from staff of a local hospital. Controls were selected to be similar to patients on distributions of gender and age. These comparison subjects were screened for psychotic disorder using the Psychosis Screening Questionnaire [17]. None of the participants reported a chronic neurological illness, current substance use disorder or a history of substance dependence. Socio-demographic data was also collected in order to account for possible socio-demographic confounds in the volumetric analyses. For the purposes of this study, patients were individually matched on a case–control basis on gender, age, premorbid IQ and socio-economic status with their respective controls.

2.4. Ethical approval

Ethical approval was obtained from the office of Research Ethics Committees Northern Ireland.

2.5. MRI data acquisition and processing

MRI scans were obtained using a GE Sigma 1.5 T scanner (General Electric, Milwaukee, WI). A coronal high-resolution T1 volume acquisition protocol was used. A 3D Inversion-Recovery-prepared Fast Spoiled Gradient echo (IR-Prepped FSPGR) sequence was used, with the following parameters: TR/TE = 9.6/2.4, TI = 450, FOV = 220 mm × 165 mm, 0.87 mm pixel size, flip angle 20°, slice thickness 1.5 mm, acquisition time 6 min 51 s. 2D DICOM T1 MR images were subsequently combined into 3D volume (NifTI file format) and interpolated to create 1 mm × 1mm × 1 mm isotropic voxels using SPM5 (Wellcome Institute, London, UK) for morphometric analysis.

Voxel based morphometry (VBM) offers a rapid and extensive way to explore structural brain changes in psychosis and compliments VOI methods [12]. VBM permits a voxel-wise comparison of the local tissue properties (GM or WM volume) between two groups of participants. This technique is based on the normalization of all subject images to the same stereotactic space, segmentation of the normalized images into tissue compartments, smoothing the resultant images using a convolution with a Gaussian kernel, and finally statistical analysis to establish regions where structural properties are significantly different e.g., GM volume or concentration. The computational methods used also take advantage of recent advances and innovations in brain segmentation and normalization that overcome weaknesses in previous methods.

The present study applied VBM5 (http://dbm.neuro.uni-jena.de), which uses a new unified segmentation approach. VBM5 increases the quality of segmentation by applying a Hidden Markov Field (HMRF) model on the segmented tissue maps [18]. Following the example of Meisenzahl [19] we chose to estimate tissue probability maps without making use of tissue class priors as this option is believed to improve the delineation of subcortical structures and sulci. In order to compare tissue class volumes between our control and patient groups the final tissue maps of GM, WM and cerebrospinal fluid (CSF) produced were modulated by normalization to the MNI standard space (Montreal Neurological Institute). The normalization was performed by first estimating the optimum 12-variable affine transformation for matching images and then optimizing the normalization using 16 nonlinear

Table 1
Demographic data for patient and control groups. All control patient comparisons were non-significant except current IQ status in the schizophrenia patients which was significantly lower than matched control subjects ($p < 0.001$).

Characteristic	Schizophrenia analysis		Bipolar analysis	
Mean (sd)	Schizophrenia ($N = 25$)	Matched controls ($N = 25$)	Bipolar ($N = 24$)	Matched controls ($N = 24$)
Male/female	19/6	19/6	8/16	8/16
Age	28.8 (9.0)	28.2 (8.5)	36.0 (10.0)	35.6 (9.7)
WAIS IQ	88 (16)	104 (15)	106 (9)	106 (16)
NART	105 (10)	106 (13)	104 (16)	109 (12)
Parental socio-economic status	3.00 (1.54)	2.68 (1.53)	2.95 (1.32)	3.00 (1.41)
PANSS	69 (14)		52 (10)	
Medication Typ/ATyp/Lith	1/24/0		0/19/2	
Atypical used	R (9)/O (14)/Q (2)		R (6)/O (10)/Q (3)	
Medication duration (months)	14.4 (9.2)		5.5 (8.4)	

R, risperidone; O, olanzapine; Q, quetiapine.