Psychiatry Research: Neuroimaging 191 (2011) 166–173

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Longitudinal changes in brain structure following the first episode of psychosis

Pilar de Castro-Manglano [a,*], Andrea Mechelli [b], Cesar Soutullo [a], Josemanuel Gimenez-Amaya [c], Felipe Ortuño [a], Philip McGuire [b]

[a] Department of Psychiatry and Medical Psychology, University Hospital of Navarra, University of Navarra, Avda. Pío XII, no. 36. 31008, Pamplona, Navarra, Spain
[b] Department of Psychosis Studies, Institute of Psychiatry, King's College London, The Crespigny Park, London SE5 8AF, UK
[c] Department of Anatomy, Histology and Neuroscience, Autonoma University of Madrid, c/Arzobispo Morcillo, s/n. 28029, Madrid, SPAIN

ARTICLE INFO

Article history:
Received 4 May 2010
Received in revised form 6 October 2010
Accepted 29 October 2010

Keywords:
First psychotic episode
Schizophrenia
Affective psychosis
Voxel-based morphometry (VBM)
Structural MRI
Longitudinal study

ABSTRACT

Both schizophrenia and bipolar disorder have been associated with progressive changes in grey matter (GM) volume. However, the temporal trajectories of these changes are poorly understood. The aim of this study was to assess longitudinal changes in grey matter volume subsequent to the first episode of schizophrenia and of affective psychoses. Adolescent patients with a first episode psychosis ($n=26$) were scanned twice using magnetic resonance imaging, at first presentation and after a 3-year follow-up period. An age-matched group of healthy volunteers ($n=17$) was scanned at the same time points. Within-group and between-group changes in regional grey matter volume were examined using voxel-based morphometry. There were significant group by time interactions ($p_{FDRcorr}<0.05$) in the frontal, temporal, parietal, cerebellar cortex, and in the thalamus, mainly reflecting longitudinal reductions in the controls but not in the patients. Subdivision of the patient group revealed that there were similar longitudinal reductions in patients with affective psychoses as in the controls but no volumetric changes in patients with schizophrenia. Psychosis with onset in adolescence or early adulthood may be associated with a delay or a loss of longitudinal reductions in regional grey matter volume that normally occur at this stage of development. These changes may be specific to schizophrenia.

1. Introduction

Normal brain development is characterised by a preadolescent increase in grey matter (GM) volume, with GM volume in frontal and parietal regions maximal at 12 years and temporal GM volume peaking at 16 years of age (Giedd et al., 1999). This is followed by a loss of GM in the frontal and parietal cortices that continues through adolescence and into adulthood (Giedd et al., 1999). Data from volumetric neuroimaging studies suggest that brain development may be disrupted in both schizophrenia and affective psychoses (Hirayasu et al., 1998; Pantelis et al., 2005; Moorhead et al., 2007; Koo et al., 2008). In adolescents with childhood-onset schizophrenia, an accelerated rate of GM loss over a 2-year period has been reported in the frontal, cingulate, parietal and temporal cortex (Rapoport et al., 1999; Farrow et al., 2005; Thompson et al., 2001). In adolescents with a first episode of affective psychosis, longitudinal reductions in the inferior temporal and anterior cingulate gyri over the first 2 years of illness have been reported (Farrow et al., 2005). On the other hand, longitudinal increases in global cortical GM volume in first episode affective psychosis have been reported in association with mood stabilizer treatment (Nakamura et al., 2007).

While these findings suggest that there may be longitudinal volumetric changes in psychotic disorders, the extent to which the results depend on the type of disorder (schizophreniform or affective), the stage of the illness, and the effects of treatment is still unclear. We sought to address these issues in the present study. Our first aim was to examine, using voxel-based morphometry (VBM), longitudinal changes in GM volume in the first 3 years after the onset of psychosis in adolescent and young adult patients. The second objective was to compare these data in patients with schizophrenia and affective psychoses. The first hypothesis was that the onset of psychosis in adolescence or early adulthood would be associated with an alteration in the normal pattern of longitudinal changes in regional GM volume. Our second hypothesis was that this alteration would be more evident in patients with schizophrenia than in those with an affective psychosis (Kasai et al., 2003; Farrow et al., 2005).

2. Methods

2.1. Subjects

From 2003 to 2008, patients were recruited at the clinical Child and Adolescent Psychiatry Department of the University Hospital of Navarra.

* Corresponding author. Tel.: +34 948 255 400 (work), +34 696 710 671 (Mobile); fax: +34 948 296 500.
E-mail addresses: pcastro@unav.es (P. de Castro-Manglano), Andrea.Mechelli@kcl.ac.uk (A. Mechelli), csoutullo@unav.es (C. Soutullo), josemanuel.gimenezamaya@uam.es (J. Gimenez-Amaya), fortunos@unav.es (F. Ortuño), philip.mcguire@kcl.ac.uk (P. McGuire).

0925-4927/$ – see front matter.
doi:10.1016/j.pscychresns.2010.10.010

A quarter came from the local region of Navarra, and the rest came from other parts of Spain. Healthy volunteers were recruited from the Navarra area through local advertisement. All participants provided informed consent. Ethical approval was granted by the University Clinic of the University of Navarra, by the Local Government (no. 8/2000, R680/2000) and by the Spanish Human Experimentation Ethical Committee in accordance with the Helsinki Declaration of 1975.

Inclusion criteria were as follows: first presentation of symptoms meeting criteria for a functional psychosis (International classification of diseases (ICD-10): F20 schizophrenia and F30–39 affective disorders-psychotic coding; World Health Organization and Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TR) classification); and age at first evaluation between 11 and 29 years old. Psychotic symptoms were defined as hallucination, delusions, formal thought disorder or prominent negative symptoms, which persisted for a minimum of 1 week. Exclusion criteria were as follows: the presence of a concomitant axis I disorder; alcohol or illicit substance abuse; a significant neurological or medical illness, or a history of head trauma resulting in loss of consciousness for over 1 h; previous episode of psychosis; previous psychotic symptoms (ICD-10: F10) (World Health Organization, 1992) following consumption of illicit substances; and being unable to complete or to perform some of the different evaluations included in the protocol.

Healthy volunteers were recruited from the same geographical area through local advertisement. They had no current or previous history of psychiatric disorder or substance use, no history of head trauma, neurological illness, serious medical or surgical illness, and no family history of any psychiatric disorder, as assessed by an experienced psychiatrist in a detailed clinical interview. All patients and controls were white Europeans.

At baseline there were 26 patients (mean age 18.5 years [S.D. ± 4.0]), comprising 15 males and 11 females. Twenty-two patients were re-assessed at follow-up (mean age of 21.6 years [S.D. ± 4.2]). Two patients committed suicide during the follow-up period, and two declined to participate in follow-up assessments. There were 17 healthy volunteers (mean age at baseline 18.3 years [S.D. ± 5.8]), comprising 9 males and 8 females.

At the time of the first scan, most of the patients (22 out of 26) were receiving treatment with antipsychotic medication (olanzapine $n=10$, risperidone $n=7$, ziprasidone $n=4$, aripiprazole $n=1$, haloperidol plus clozapine and olanzapine $n=2$). On average, there was a 10-week period between the onset of psychosis and the start of treatment (duration of untreated psychosis (DUP)), while the mean duration of antipsychotic treatment in patients under treatment until the scan was performed (duration of antipsychotic exposure (DAE)) was 28.46 weeks (S.D. ± 57.7; Table 1). Some patients had also been treated with mood stabilizers ($n=9$) or antidepressants ($n=15$) at that time. At the time of the second scan, four patients with affective psychosis were not under treatment. Eighteen patients were taking antipsychotic medication (clozapine ($n=3$), risperidone ($n=3$), aripiprazole ($n=2$), quetiapine ($n=2$), olanzapine ($n=6$), ziprasidone ($n=2$), haloperidol + olanzapine or ziprasidone ($n=2$)), and 12 patients were taking mood stabilizers (valproic acid ($n=4$), lithium + valproic acid ($n=1$), lamotrigine ($n=5$), lamotrigine + valproic acid ($n=2$)) during all the follow-up period, with prescribing being done by their clinical teams. The mean of dosage of treatment was not collected.

At follow-up, eight patients met the diagnostic criteria for schizophrenia and fourteen patients were diagnosed with an affective disorder: four with major depression with psychotic symptoms, and ten with bipolar I disorder.

2.2. Study design

All participants were scanned twice, at baseline (time 1); within the first month of their first episode of psychosis, and 3 years later (time 2). Clinical assessment was made at each time and it comprised a Clinical Interview using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997), and the administration of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Hamilton Depression Rating Scale (HDRS) (Bagby et al., 2004), the Clinical Global Impression Scale (CGI) (Kadouri et al., 2007), and the Global Assessment of Functioning scale (GAF) (Hilsenroth et al., 2000). Details of family history of psychiatric illness and medical personal illness were collected at baseline, and adherence to treatment and number of admissions over the 3 years of illness were recorded at follow-up.

2.3. MRI data acquisition

Magnetic resonance images were acquired using a 1.5 Tesla Siemens Symphony Maestro Class Imaging System (Erlangen Germany), at the University Clinic of Navarra, Spain. Axial images were collected using a 3D gradient echo acquisition for T1 weighted images, and spin-echo sequences for T2 weighted images. The voxel dimensions were $1.0\times1.0\times1.5$ mm^3; matrix size 256×256; field of

Table 1
Sociodemographic and clinical features, and total GM volume in patients and controls.

Parameters	Patients (26)		Healthy controls (17)	T/χ^2	P
	Mean (S.D.)		Mean (S.D.)		
	Baseline (T1)	Time 2 (T2)			
Age, years	18.5 (4.0)	21.6 (4.2)	18.3 (5.8)/21.3 (6.8)	0.165[a]	0.87
Gender (male/female) (no.)	15 males/11 females		9 males/8 females	0.157[b]	0.62
Diagnosis	8 FES/14 FEAP		–	–	–
Years of education	10.6 (3)		11.4 (4)	0.094[a]	0.75
Hamilton Depression	16.5 (7.4)	9.0 (5.1)	–	5.00[c]	0.000
PANSS:					
Positive symptoms	17.2 (6.1)	12 (6.6)	–	1.94[c]	0.066
Negative symptoms	19.1 (7.3)	14.6 (7.9)	–	2.25[c]	0.036
Total score	42.3 (13.7)	57.2 (22.9)	–	7.27[c]	0.000
GAF	75.3 (23.6)	64.5 (18.0)	90.6 (5.1)	−7.53[c]	0.000
CGI	5.17 (0.72)	3.15 (1.22)	–	5.96[c]	0.000
DAE (S.D.)	28.5 (57.8)		–	–	–
DUP (S.D.)	9.9 (18.2)		–	–	–
Time between scans (weeks)	142.4 (55.3)		155.5 (74.8)	−0.627[a]	0.128

PANSS: Positive and Negative Syndrome Scale; GAF: Global Assessment of Functioning scale; CGI: Clinical Global Impression; DAE: lifetime duration of antipsychotic exposure (in weeks); DUP: duration of untreated psychosis (in weeks).
Significance threshold defined at $P<0.05$.
[a] The t value.
[b] The Pearson's χ^2 value.
[c] The Paired t-test value between clinical scale variables over time.