PAPER

Radiological findings in individuals at high risk of psychosis

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Objective: To assess the prevalence of radiological magnetic resonance imaging (MRI) findings in individuals at high risk of schizophrenia.

Methods: MRI scans from individuals at high risk of schizophrenia (HR; n = 37) were assessed by a radiologist blind to group status and compared with scans from patients with first episode psychosis (FE; n = 30), depressive controls (DC; n = 17), and healthy controls (HC; n = 26).

Results: There was a significantly higher proportion of radiological findings in individuals at high risk of schizophrenia (35%) and patients with first-episode psychosis (40%) than in patients with depression (18%) or healthy controls (12%). These differences were specific to findings regarded as potentially clinically significant as opposed to normal variants; however, there was no indication for medical treatment.

Conclusions: The results suggest that a large proportion of those at high risk of psychosis have radiological findings on MRI scanning, and that the prevalence of radiological findings in this group is similar to that in patients with first episode psychosis.

While there is an extensive literature on magnetic resonance imaging (MRI) abnormalities in psychotic disorders, most of the findings are of relatively small reductions in global and regional grey matter volume that are evident at a group level but are not detectable in an individual patient in a radiological examination.¹ Nevertheless there are some abnormalities that can be detected by visual inspection, such as enlarged fluid spaces, ventricular enlargement, and cerebral atrophy.^{2–8} Radiological findings in first episode patients have focused mainly on cavum septi pellucidi, which is more common in this group than in controls.^{9–12}

It is not clear as yet at what stage of the disorder these brain abnormalities occur. Neurodevelopmental models of schizophrenia propose that brain abnormalities are present before the onset of psychosis, but there is also evidence that at least some of MRI abnormalities progress over the course of the disorder.¹³

MRI studies of non-psychotic subjects who are at high risk of psychosis indicate that regional volumetric abnormalities comparable to those seen in schizophrenia are evident in those who are vulnerable to psychosis. Thus Lawrie *et al*¹⁴ found that the relatives of patients with schizophrenia had reduced left medial temporal volume, while decreased global white and grey matter volumes were found in the non-psychotic co-twins of patients with schizophrenia,¹⁵ and decreased left amygdala and hippocampal volume has been described in the offspring of schizophrenic patients.¹⁶ More recently, Pantelis *et al*¹⁷ showed that individuals at high risk of psychosis who had “prodromal” symptoms had reduced grey matter in the right medial temporal, inferior frontal cortex, and cingulate cortex.

The only radiological study in individuals at high risk of psychosis concentrated on cavum septi pellucidi and found no differences between first episode patients, relatives at high risk, and healthy volunteers.¹¹ To date there has been no study on radiological abnormalities in individuals at high risk of psychosis more generally.

Our aim in the present study was to assess the prevalence of radiological MRI findings (normal variants and pathological brain abnormalities) in individuals at high risk of schizophrenia. These individuals show subthreshold

psychotic symptoms or other risk factors of developing a full blown psychosis.¹⁷ We compared this with that in patients with first episode psychosis, patients with depression, and healthy controls. We tested the hypothesis that the perturbation of neurodevelopment that is thought to predispose individuals to psychosis would result in a higher frequency of radiological abnormalities in people at high risk of schizophrenia than in controls, comparable to that in first episode patients.

METHODS

The MRI data were collected within the framework of the research project “Prediction and early detection of schizophrenia—a prospective multilevel approach” at the psychiatric outpatient department and the neuroradiological department of the University Hospital Basel, Switzerland. This study has been described in detail elsewhere.^{18, 19}

A specialised clinic for early detection of psychosis was established at our outpatient department in Basel, Switzerland. Referrals of patients thought to be at high risk of psychosis or in the early phase of psychosis were received from local general practitioners, psychiatrists in private practice, and the general psychiatric outpatient department.

Exclusion criteria were: schizophrenia previously diagnosed and treated with major tranquillisers for more than three weeks, substance induced psychosis, psychotic symptomatology secondary to an “organic” disorder, psychotic symptomatology within a diagnosed affective psychosis or borderline personality disorder, age under 18 years, inadequate knowledge of the German language, and IQ less than 70 (assessed using the achievement measure system, Leistungsprüfsystem,²⁰ and MWT²¹).

After exclusion criteria were applied, all individuals were screened using two instruments: the Basel Screening Instrument for Psychosis (BSIP) and the Brief Psychiatric

Abbreviations: BLIPS, brief limited intermittent psychotic symptoms; BPRS, Brief Psychiatric Rating Scale; BSIP, Basel Screening Instrument for Psychosis; DC, depressive controls; DSM-III-R, *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised; FE, first episode psychosis; HC, healthy controls; HR, high risk of schizophrenia; ICD-10, *International Classification of Diseases*, 10th revision

Table 1 Demographic data of the patient and control groups

	Individuals at high risk of schizophrenia (HR; n = 37)	Patients with first episode psychosis (FE; n = 30)	Depressive controls (DC; n = 17)	Healthy controls (HC; n = 26)	Significance of pairwise comparisons
Sex (male:female)	18:19 (49%:51%)	22:8 (73%:27%)	6:11 (35%:65%)	17:9 (65%:35%)	χ^2 test: HR v FE, $p < 0.05$; HR v DC, NS; HR v HC, NS; FE v DC, $p < 0.05$; FE v HC, NS
Age (y) (mean (SD))	27.9 (9.9)	30.3 (6.9)	26.1 (4.9)	22.5 (4.4)	ANOVA: $p < 0.01$; post-hoc test (Bonferroni): HR v FE, NS; HR v DC, NS; HR v HC, $p < 0.05$; FE v DC, NS; FE v HC, $p < 0.01$
Educational level					χ^2 test: HR v FE, NS; HR v DC, NS; HR v HC, $p < 0.05$; FE v DC, NS; FE v HC, $p < 0.01$
I (less than 9 y)	13	15	5	3	
II (9–11 y)	14	8	6	8	
III (12–13 y)	4	3	3	11	
IV (>13 y)	6	4	3	4	
BPRS global score (mean (SD))	39.6 (9.7)	50.9 (13.2)	33.4 (12.3)	–	ANOVA (HR, FE, DC): $p < 0.001$; post-hoc test (Bonferroni): HR v FE, $p < 0.001$; HR v DC, NS; FE v DC, $p < 0.001$
Currently received antipsychotic drugs	5	14	0	0	

ANOVA, analysis of variance; BPRS, Brief Psychiatric Rating Scale; DC, depressive controls; FE, first episode psychosis; HC, healthy controls; HR, high risk of schizophrenia; y, years.

Rating Scale (BPRS). The former, a 46 item checklist, was specifically constructed for this study and focuses on different groups of risk indicators established in previous studies: prodromal symptoms according to DSM-III-R, which developed within the previous five years; further unspecific prodromal symptoms which developed within the previous two years^{22, 23}; previous or current psychotic symptoms, which were neither diagnosed nor treated; a notable “kink” in the lifetime (decrease in psychosocial functioning) within the previous five years; regular drug abuse within the previous two years; and psychotic disorders of first or second degree relatives. For establishing psychiatric diagnoses we used the ICD-10 research criteria.

If there were certain combinations of risk indicators, the individuals were regarded as being “at risk”.^{18, 19} This at risk group consists of a group of “high risk” subjects and a group of patients with a lower risk. We used selection criteria of the high risk group similar to those described by Yung *et al.*¹⁷ To be considered as high risk, subjects had to show “attenuated” psychotic symptoms or brief limited intermittent psychotic symptoms (BLIPS) or to have a genetic risk of psychosis and at least two other risk factors or indicators of disease onset, such as prodromal symptoms or marked social decline. The low risk group consists of patients without a genetic risk who show a combination of certain other specific risk factors and indicators.

The BPRS was used to identify patients who were already beyond the prodromal phase and were frankly psychotic, using the criteria of Yung *et al.*¹⁷ These patients fulfil the criteria for first episode psychosis (according to Yung

et al.); however, only in a few cases will schizophrenia eventually be diagnosed. After diagnosing first episode psychosis we begin treatment, which should reduce the likelihood that these patients will progress toward the diagnostic criteria of schizophrenia.

We screened 206 individuals in the first three years of the study; 32 were categorised as not being at risk of schizophrenia, while 98 were assigned to the risk group, though 40 of those at risk refused to participate in research or were not compliant after an initial agreement. Of the remaining 58 individuals at risk, 37 high risk patients consented to have MRI.

Seventy six of the 206 subjects screened met criteria for a first episode psychosis; 36 of these were invited to have MRI, and 30 consented.

A control group of 17 patients with depression was recruited from the local psychiatric outpatient department. These subjects met ICD-10 criteria for a depressive episode (F32.0, F32.1, F32.2) or a recurrent depressive disorder (F33.0, F33.1, F33.2).

A group of 26 healthy volunteers was recruited by approaching students of a trade school, from hospital staff, and through advertisements. These subjects had no current psychiatric disorder, as assessed by a clinical interview, and no history of psychiatric illness, head trauma, neurological illness, serious medical or surgical illness, substance abuse, or family history of psychiatric disorders.

All subjects gave written informed consent to participate in the study, which was approved by the local research and ethic

Table 2 Proportion of magnetic resonance images with abnormal findings in individuals at high risk and in control groups

	High risk of schizophrenia (HR; n = 37)	First-episode psychosis (FE; n = 30)	Depressive controls (DC; n = 17)	Healthy controls (HC; n = 26)	Significance of pairwise comparisons
Any radiological findings	13 (35%)	12 (40%)	3 (18%)	3 (12%)	HR v FE, NS; HR v DC, NS; HR v HC, $p < 0.05$; FE v DC, NS; FE v HC, $p < 0.05$
Normal variations	7 (19%)	5 (17%)	2 (12%)	3 (12%)	All comparisons, NS
Pathological findings	6 (16%)	7 (23%)	1 (6%)	0	HR v FE, NS; HR v DC, NS; HR v HC, $p < 0.05$; FE v DC, NS; FE v HC, $p < 0.01$

DC, depressive controls; FE, first episode psychosis; HC, healthy controls; HR, high risk of schizophrenia.

Table 3 Summary of the radiological findings in each group

Individuals with brain abnormalities	Brain abnormalities (number of patients)	
	Normal variants	Pathological abnormalities
Individuals at high risk of schizophrenia (n = 13)	Cavum septi pellucidi (2) Neuroepithelial cyst (1) Asymmetrical ventricular system (2) Prominent Virchow-Robin spaces (1) Possible frontal atrophy (2) Single T2w hyperintensity (1)	Cavernoma, parasagittal left (1) Lacuna, temporal (1) Fronto-parietal atrophy (1) Hypointense lesions, temporal (1) Hyperintensities, cortical (1) Generalised atrophy (4)
First episode psychosis (n = 12)	Single hyperintense lesion (2) Neuroepithelial cyst (3) Arachnoid cyst (1) Cavum septi pellucidi (1)	Generalised atrophy (3) Subdural effusion (1) Hamartoma, right temporal (1) Frontal atrophy (2)
Depressive controls (n = 3)	Neuroepithelial cysts (1) Possible frontal atrophy (1)	Periventricular hyperintensities (1) Pronounced ventricular asymmetry (1)
Healthy controls (n = 3)	Prominent temporal horns (1)	

Figures represent number of subjects with each finding; subjects may have more than one abnormality.

committee (University of Basel, Switzerland). The study complies with the Declaration of Helsinki.

Structural MRI acquisition

All subjects were scanned on a 1.5 T clinical scanner system (VISION, Siemens, Erlangen, Germany) at the University Hospital Basel. Dual echo images were acquired parallel to the anterior and posterior commissure (AC-PC) line (first echo time 20 ms, second echo time 85 ms; repetition time 4300 ms, 50 slices of 3 mm slice thickness covering the entire brain; matrix size 256×192, field of view 23×17.25 cm, respectively).

MRI scans were evaluated by two neuroradiologists (EWR, SH) for the presence of normal variants and pathological findings. These assessors were blind to group status; their reports were classified as being with or without any findings. Findings were further categorised as *normal variants*—that is, findings within the realm of normal variation (for example, neuroepithelial cyst, fewer than six Virchow-Robin spaces, asymmetrical ventricular system, single T2w hyperintensity, cavum septi pellucidi, arachnoid cyst); and *pathological findings*—that is, findings requiring medical review (for example, cavernoma, subdural haematoma, tumours) or that were regarded as potentially relevant to psychiatric disorders (atrophy >6 mm; more than three T2w hyperintense lesions or T2w hyperintense subcortical areas). Findings were categorised using criteria suggested by Bryan *et al.*,²⁴ Katzman *et al.*,²⁵ and Galderisi *et al.*³

Inter-rater reliability was evaluated in a subset of 30 scans. Only 4% of findings were rated differently and κ was 0.932 (SE = 0.067 (95% confidence interval (CI), 0.800 to 1.063)).

Statistical analyses

Clinical and sociodemographic differences between groups were examined using one way analysis of variance (ANOVA) or χ^2 (tables 1 and 2). Statistical analyses were carried out with the Statistical Package for the Social Sciences (SPSS 12.0).

RESULTS

Sociodemographic and clinical data

All participants were white. Both the high risk group and the first episode group were older and had a lower mean educational level than the healthy volunteers (table 1). The first episode group also had a higher proportion of male subjects than the high risk and depressive control group. As expected, the patients with first episode psychosis had a

higher BPRS global score than the high risk and the depressive control groups (table 1).

Only five of the high risk individuals were currently receiving antipsychotic agents. Fourteen of the first episode patients were on antipsychotic drugs, 10 of them for no longer than one month and the other four for between one and three months (table 1).

MRI data

The frequency of radiological findings was highest in individuals at high risk and patients with a first episode of psychosis: 40% of the first episode patients (n = 12) and 35% of the individuals at high risk (n = 13), compared with 18% (n = 3) of the depressive and 12% of healthy controls (n = 3), had findings such as hyperintense or hypointense lesions, atrophy, subdural effusions, hyperintense cortical zones, cavernoma, or small lacunas (table 2). The frequency of any finding was significantly higher in both the first episode ($p < 0.05$) and the high risk groups ($p < 0.05$) than in the healthy controls (table 2). There was no significant difference between the individuals at high risk and the first episode patients.

There were no significant between group differences in the frequency of normal variants, but both those at high risk and the first episode patients showed significantly more pathological findings than the healthy controls (table 2). The different radiological findings are summarised in table 3. In some subjects there was more than one finding.

In order to control for the effects of sex, age, and education, different correlation analyses were undertaken. These analyses revealed no significant correlation between the proportion of MRI findings and potential confounding variables (sex, $r = 0.09$, NS; age, $r = 0.16$, NS; education, $r = -0.08$, NS) over all groups. In correlation analyses between the separate groups and the variables, there were no significant effects of sex (FE group: $r = 0.31$, NS; HR group: $r = 0.19$, NS; DC group: $r = 0.30$, NS; HC group: $r = -0.24$, NS), age (FE group: $r = 0.00$, NS; HR group: $r = 0.18$, NS; DC group: $r = 0.25$, NS; HC group: $r = -0.30$, NS), or educational level (FE group: $r = 0.04$, NS; HR group: $r = -0.11$, NS; DC group: $r = 0.33$, NS; HC group: $r = -0.25$, NS).

DISCUSSION

Although there is an extensive body of literature describing structural brain abnormalities in psychotic disorders,¹ these have largely been identified using quantitative image analysis

techniques, as opposed to visual inspection by a radiologist. Most of the findings in these studies involve relatively subtle differences that can be detected at a group level but are not large enough to be detected in an individual subject, and may not be evident in a clinical MRI examination. There have been relatively few studies of radiological findings in psychotic disorders.²⁶ Two studies detected abnormal morphology in between 22% and 31% of patients with first episode schizophrenia.^{5, 6} These findings ranged between abnormal but clinically insignificant to gross pathology. These findings are entirely consistent with our study.

There have been even fewer radiological studies of people at high risk of psychosis. Keshavan *et al*¹¹ compared the children of patients with schizophrenia with controls and with patients with first episode psychosis, but restricted the analysis to the cavum septi pellucidi. Their study showed an absence of significant differences in the occurrence of cavum septi pellucidi between high risk individuals, first episode patients, and healthy controls.

The proportion of normal variants was similar in all four groups. Normal variants—for example, cavum septi pellucidi—may reflect neurodevelopmental abnormalities.¹² Most previous studies have focused on cavum septi pellucidi, which has been found to be equally prevalent in schizophrenic and normal subjects as well as in patients with first episode schizophrenia and young relatives at high risk of schizophrenia.^{11, 27} However, an increased prevalence of large cavum septi pellucidi (approximately 6 mm or longer) has been reported in chronic and first episode schizophrenia.^{9, 10} Our findings suggest that the similarity in the frequency of normal variants in high risk and first episode groups and controls extends to a range of findings in addition to cavum septi pellucidi, including neuroepithelial cysts, Virchow-Robin spaces, asymmetrical ventricular system, single T2w hyperintensity, and arachnoid cysts.

In contrast, pathological findings were more common in patients with first episode psychosis and in the individuals at high risk of psychosis than in either depressed patients or controls. The differences between the high risk and control groups are unlikely to have been related to treatment with antipsychotic drugs, as only five of the high risk group were currently receiving antipsychotic treatment. Although 14 of the 30 first episode patients were currently on antipsychotic drugs, the duration of treatment was relatively short (less than one month for 10 patients and between one and three months for four, so even in this group it is unlikely that drug treatment accounted for the findings). While some of these findings, such as cortical atrophy or ventricular enlargement, are well established features of psychotic disorders, the similar frequency of pathological findings in the high risk group suggests that they may be correlates of an increased vulnerability to psychosis. This would be consistent with quantitative MRI studies which have found that subjects at increased risk because of a family history, schizotypy, or the presence of prodromal features show similar volumetric abnormalities to patients with psychosis.^{13, 28, 29}

All 31 individuals showing brain abnormalities were referred for further neurological evaluation. These investigations did not result in a neurological diagnosis or require medical intervention. One reason for carrying out MRI in patients with first episode psychosis is to identify rare cases in which the psychosis has an organic origin other than being caused by schizophrenia or bipolar disorder.²⁶ There were no such cases in the present study, as would be expected, because patients whose symptoms were attributable to organic brain diseases were excluded. Nevertheless, even after exclusion of such subjects, a large proportion of first episode and high risk subjects with “pathological” radiological findings has been found.

As expected, the majority of our healthy controls had a normal MRI. Only 12% of the healthy control subjects had radiological abnormalities, which is comparable to 18% described by Katzman *et al*²⁵ in an investigation of 1000 asymptomatic volunteers. The frequency in our patients with depression did not differ significantly from that in our healthy controls. However, given the small number of subjects in this group, we cannot exclude the possibility that we were unable to detect differences because of limited statistical power. The proportion of abnormal findings in depression (18%) is consistent with the only study that has examined the frequency of qualitative brain morphology findings in both schizophrenia and major depression (22%).³⁰

Both the first episode and the high risk groups were older than the healthy controls, which may have influenced the frequency of abnormalities that are commoner in later life such as cortical atrophy. However the mean age in these groups was 30 and 28, and the between group differences did not show a significant correlation for age. Similarly, the first-episode and high risk groups had lower levels of education than the healthy controls, but the between group differences did not show a significant correlation with educational level.

The different types of radiological abnormalities (table 3) in first episode patients and individuals at high risk of psychosis suggest that the underlying cerebral disruption in prodrome and psychosis may result in a propensity toward brain abnormalities.^{6, 7} The high prevalence of radiological abnormalities in both the first episode and the high risk group may reflect an underlying subtle brain pathology, possibly in connection with neurodevelopmental disturbances.

Conclusions

Radiological abnormalities were more common in patients during the first episode of psychosis and in individuals at high risk of psychosis than in healthy controls or patients with depression. This may reflect a disturbance of neurodevelopment which predisposes the individual to psychosis.

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