Regional Gray Matter Volume Abnormalities in the At Risk Mental State

Stefan J. Borgwardt, Anita Riecher-Rössler, Paola Dazzan, Xavier Chitnis, Jacqueline Aston, Margret Drewe, Ute Gschwandtner, Sven Haller, Marlon Pflüger, Evelyne Rechsteiner, Marcus D'Souza, Rolf-Dieter Stieglitz, Ernst-Wilhelm Radü, and Philip K. McGuire

Background: Individuals with an At Risk Mental State (ARMS) have a very high risk of developing a psychotic disorder but the basis of this risk is unclear. We addressed this issue by studying gray matter volume in this group with magnetic resonance imaging (MRI).

Methods: Thirty-five individuals with an ARMS, 25 patients with first episode schizophrenia, and 22 healthy volunteers were studied using a 1.5T MRI scanner. Twelve (34%) of the ARMS group developed schizophrenia in the 2 years subsequent to scanning.

Results: There were significant volumetric differences between the three groups in the left insula, superior temporal gyrus, cingulate gyrus and precuneus. In these regions, the volume in the ARMS group was smaller than in volunteers but not significantly different from that in the first episode (FE) group. Direct comparison of the ARMS and control groups revealed additional areas of reduced volume in the left medial temporal cortex. Within the ARMS group, those subjects who later developed psychosis had less gray matter than subjects who did not in the right insula, inferior frontal and superior temporal gyrus.

Conclusions: The ARMS was associated with reductions in gray matter volume in areas that are also reduced in schizophrenia, suggesting that these are a correlate of an increased vulnerability to psychosis. Volumetric differences within the ARMS group may be related to the subsequent onset of schizophrenia in a subset of those at high risk.

Key Words: At risk mental state, early detection, gray matter, MRI, schizophrenia, voxel-based morphometry

Neuroimaging studies clearly indicate that schizophrenia is associated with neuroanatomical abnormalities, with robust evidence of reduced gray matter volume in a number of regions (Shenton *et al.* 2001; Wright *et al.* 2000). However, the extent to which these findings are related to a vulnerability to schizophrenia, as opposed to the disorder per se, is less certain. Thus qualitatively similar abnormalities are also evident in the siblings, offspring, and co-twins of patients with schizophrenia, even though they are not psychotic (Baare *et al.* 2001; Hulshoff Pol *et al.* 2004; Keshavan *et al.* 1997; Lawrie *et al.* 1999; Seidman *et al.* 1999; Staal *et al.* 2000; Sharma *et al.* 1999).

Individuals with an 'At Risk Mental State' (ARMS) have an increased vulnerability to psychosis, with the risk associated with presence of 'prodromal' symptoms. Around 35% of such subjects develop psychosis within 12 months, although the proportion has varied between studies (Mason *et al.* 2004; Miller *et al.* 2003; Yung *et al.* 2003). Relatively little is known about the nature of neuroanatomical abnormalities in this group (Table 1). Using magnetic resonance imaging (MRI) and a region of interest analysis, Phillips *et al.* (2002) reported that hippocampal volume in subjects with an ARMS was smaller than that in controls but not smaller than in patients with first episode (FE) psychosis. In addition, within the at risk group, the subset who developed a psychotic disorder when followed up subsequent to scanning had a larger left hippocampal volume than the healthy subgroup. More recently, in a voxel-based analysis of MRI data (which examined the entire brain) from the same center, Pantelis *et al.* (2003) found that within a group of subjects with the ARMS, those who later became psychotic had smaller inferior frontal, cingulate, superior temporal, and hippocampal volumes than those who did not.

The aim of the present study was to use MRI to clarify the nature of neuroanatomical abnormalities in subjects with an ARMS by comparing them with both controls and patients with FE psychosis. The ARMS subjects were then followed up (without active treatment), and subcategorized according to whether or not they subsequently developed psychosis so that the baseline MRI data from these two subgroups could be compared. We had previously examined the MRI data from the same subjects for macroscopic radiological abnormalities and found that these were more common among the ARMS subjects than controls, but equally prevalent in ARMS and FE subjects (Borgwardt *et al.* 2006). In the present study, we examined regional gray matter volume using a voxel-based morphometric (VBM) approach. By surveying the whole brain, VBM provides a nonbiased measure of regional differences in volumes of gray matter (Ashburner and Friston 2000). On the basis of previous MRI studies of the ARMS and of other groups at high risk of schizophrenia, we predicted that subjects with an ARMS would show volumetric deficits relative to controls that were qualitatively similar to those in patients with FE schizophrenia. Our second hypothesis, based on the study by Pantelis *et al.* (2003), was that ARMS subjects who later developed psychosis would show reduced gray matter volume relative to ARMS subjects who did not in the inferior frontal, cingulate, superior temporal cortex, and the hippocampus.

Methods and Materials

Participants

The MRI data were collected as part of a research program (Prediction and early detection of schizophrenia - a prospective

From the Psychiatric Outpatient Department (SJB, AR-R, JA, MD, UG, MP, ER, MD'S, R-DS) and the Neuroradiological Department (SH, E-WR), University Hospital Basel, Switzerland; Section of Neuroimaging (SJB, PD, PKM), and the Department of Biostatistics and Computer (XC), Institute of Psychiatry, King's College London, United Kingdom.

Address reprint requests to Stefan J. Borgwardt, M.D., Psychiatric Outpatient Department, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland; E-mail: sborgwardt@uhbs.ch.

Received June 2, 2006; revised July 11, 2006; accepted August 4, 2006.

0006-3223/07/$32.00
doi:10.1016/j.biopsych.2006.08.009

Table 1. MRI Findings in the At Risk Mental State (ARMS)

			Baseline MRI Findings	
	n	MRI Method	ARMS Versus Healthy Controls	Converters Versus Non-converters
Phillips *et al.* 2002	60 ARMS (20 ARMS-T vs. 40 ARMS-NT); 139 healthy controls	Region of interest (ROI) analysis of hippocampal and whole brain volume	Smaller left and right hippocampi in ARMS compared to healthy controls	Larger left hippocampus in converters compared to non converters
Pantelis *et al.* 2003	75 ARMS (23 ARMS-T vs. 52 ARMS-NT)	Voxel-based morphometry (VBM) analysis	-[No control group]	Converters had smaller gray matter volume in the right medial temporal, lateral temporal, inferior frontal cortex, and in the cingulate bilaterally
Garner *et al.* 2005	31 ARMS-T vs. 63 ARMS-NT	ROI analysis of pituitary volume	-[No control group]	Converters had a significantly larger (12%) pituitary volume
Velakoulis *et al.* 2006	135 ARMS (39 ARMS-T vs. 96 ARMS-NT); 87 healthy controls	ROI analysis of hippocampal, amygdala, whole brain and intracranial volumes	No differences	No differences

ARMS-T, subjects with an ARMS who made transition to psychosis; ARMS-NT, subjects with an ARMS who did not made transition to psychosis; ROI, region of interest; VBM, voxel-based morphometry; MRI, magnetic resonance imaging.

multilevel approach), supported by the Swiss National Science Foundation (No. 3200-057216-99; 3200-057216/3) that has been described in detail elsewhere (Riecher-Rössler et al, in press).

Subjects with an ARMS and patients experiencing their FE of psychosis were recruited through a specialized clinic for the early detection of psychosis at the Psychiatric Outpatient Department, University Hospital in Basel, Switzerland. The following exclusion criteria applied to both these groups: history of previous psychotic disorder (treated with major tranquilizers for $>$ 3 weeks); psychotic symptomatology clearly due to 'organic' disorder or substance abuse according to ICD-10 research criteria; psychotic symptomatology clearly associated with an affective psychosis or a borderline personality disorder; age under 18 years; inadequate knowledge of the German language; and IQ less than 70. After these exclusion criteria were applied, subjects were assessed using the 'Basel Screening Instrument for Psychosis' (BSIP) (Riecher-Rössler et al, in press), the Brief Psychiatric Rating Scale (BPRS) (Lukoff *et al.* 1986; Ventura *et al.* 1993), and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1989). The BSIP was used to evaluate 'prodromal' symptoms (defined according to DSM-III-R) occurring in the last 5 years; nonspecific 'prodromal' signs (Riecher *et al.* 1991; Hafner *et al.* 1991) in the last 2 years; previous or current psychotic symptoms, psychosocial functioning over the last 5 years, substance dependency; and psychotic disorders among first and second degree relatives (Riecher-Rössler *et al.* 2006).

The family history of psychosis was obtained using a semi-structured interview from the subject and, whenever possible, a first-degree relative. The frequency of current and previous alcohol use was estimated using a semi-structured interview. To assess the premorbid IQ we used the MWT, an established measure in German-speaking subjects (Lehrl 1991).

The ARMS group (n = 35) was defined using criteria corresponding to the Personal Assessment and Crisis Evaluation (PACE) criteria (Yung *et al.* 1998) employed in the two previous MRI studies of the ARMS (Pantelis *et al.* 2003; Phillips *et al.* 2002). Inclusion thus required one or more of the following: a) "attenuated" psychotic symptoms, b) brief limited intermittent psychotic symptoms (BLIPS), or c) a first degree relative with a psychotic disorder plus at least two indicators of a clinical change, such as a marked decline in social or occupational functioning. Inclusion because of "attenuated" psychotic symptoms required scores of 2 or 3 on the hallucination item, 3 or 4 on the unusual thought content or suspiciousness items of the BPRS for at least several times a week and persisting for more than 1 week. Inclusion because of BLIPS required scores of 4 or above on the hallucination item, or 5 or above on the unusual thought content, suspiciousness or conceptual disorganization items of the BPRS, with each symptom lasting less than 1 week before resolving spontaneously.

The FE group (n = 25) was defined as subjects who met the operational criteria for first episode psychosis described by Yung *et al.* (1998), again as used to define first episode psychosis in the previous MRI studies of the ARMS (Pantelis *et al.* 2003; Phillips *et al.* 2002). Inclusion required scores of 4 or above on the hallucination item, or 5 or above on the unusual thought content, suspiciousness or conceptual disorganization items of the BPRS. The symptoms must have occurred at least several times a week and persisted for more than 1 week.

Healthy volunteers (n = 22) were recruited from the same geographical area as the other groups, through local advertisements. These individuals had no current psychiatric disorder, no history of psychiatric illness, head trauma, neurological illness, serious medical or surgical illness, substance abuse, and no family history of any psychiatric disorder as assessed by an experienced psychiatrist in a detailed clinical interview.

After complete description of the study to the subjects, written informed consent was obtained.

All the participants were Caucasian. Most (32/35; 91%) of the ARMS group had never taken antipsychotics or mood stabilizers, and were receiving nonspecific psychological support or antidepressive/sedative medication on an outpatient basis. Three ARMS subjects were receiving low doses of an atypical antipsychotic.

A large proportion of FE patients were scanned within 1-3 days of first contact, therefore most of the FE patients (15/25; 60%) were also antipsychotic-naive. Six had been taking antipsychotics for $<$ 1 month and 4 had been taking them for 1-3 months. None of the controls (C) had previously received antipsychotic medication. The ARMS, FE and C groups did not differ significantly in ethnicity, gender, handedness, current and previous alcohol intake, or total intracranial brain volume. The groups were matched for premorbid IQ: ARMS: 109 (14), FE: 103