BJPsych | The British Journal of Psychiatry (2009) 195, 218–226. doi: 10.1192/bjp.bp.108.052068

Neuroanatomical correlates of different vulnerability states for psychosis and their clinical outcomes

Nikolaos Koutsouleris, Gisela J. E. Schmitt, Christian Gaser, Ronald Bottlender, Johanna Scheuerecker, Philip McGuire, Bernhard Burgermeister, Christine Born, Maximilian Reiser, Hans-Jürgen Möller and Eva M. Meisenzahl

Background
Structural brain abnormalities have been described in individuals with an at-risk mental state for psychosis. However, the neuroanatomical underpinnings of the early and late at-risk mental state relative to clinical outcome remain unclear.

Aims
To investigate grey matter volume abnormalities in participants in a putatively early or late at-risk mental state relative to their prospective clinical outcome.

Method
Voxel-based morphometry of magnetic resonance imaging data from 20 people with a putatively early at-risk mental state (ARMS–E group) and 26 people with a late at-risk mental state (ARMS–L group) as well as from 15 participants with at-risk mental states with subsequent disease transition (ARMS–T group) and 18 participants without subsequent disease transition (ARMS–NT group) were compared with 75 healthy volunteers.

Results
Compared with healthy controls, ARMS–L participants had grey matter volume losses in frontotemporolimbic structures. Participants in the ARMS–E group showed bilateral temporolimbic alterations and subtle prefrontal abnormalities. Participants in the ARMS–T group had prefrontal alterations relative to those in the ARMS–NT group and in the healthy controls that overlapped with the findings in the ARMS–L group.

Conclusions
Brain alterations associated with the early at-risk mental state may relate to an elevated susceptibility to psychosis, whereas alterations underlying the late at-risk mental state may indicate a subsequent transition to psychosis.

Declaration of interest
None.

Neuroimaging studies of people at risk of developing psychosis have provided evidence that the schizophrenia prodrome is associated with subtle structural brain alterations in frontal, limbic and perisylvian brain regions[1–8] that may also be involved in the neurobiology of full-blown schizophrenia.[9–11] Genetic high-risk studies revealed neuroanatomical anomalies in the medial temporal lobe structures, the anterior cingulate cortex as well as the prefrontal cortex of asymptomatic individuals with a positive familial history of psychotic illness. These alterations may represent genetically mediated trait markers of the neurobiological vulnerability to the disease.[6,8,12]

Prodromal research has increasingly focused on ultra-high-risk populations defined by sets of risk factors combining prodromal symptoms, declining functioning and traditional genetic high-risk criteria. Following this 'close-in' strategy,[13] structural alterations were identified in the temporal lobe, the anterior cingulate cortex and cerebellum.[2,3,5] Moreover, these patterns and the time course of their development could be further differentiated according to the ultra-high-risk individuals' prodromal state and outcome: ultra-high-risk individuals with psychotic symptoms without subsequent disease manifestation may have exclusive temporal and limbic grey matter volume reductions over time compared with non-psychotic ultra-high-risk individuals,[4] and subsequent disease transition may be associated with additional longitudinal volume reductions in limbic, temporal and cerebellar regions compared with non-transition.[4,5] Furthermore, ultra-high-risk individuals with a subsequent disease manifestation may have alterations in cingulate, limbic, perisylvian and intrasylvian structures already at baseline.[2,3,5]

These findings suggest that pre-existing brain anomalies promote a pathophysiological process leading to accumulating brain alterations in parallel with the emergence of prodromal symptoms (see Pantelis *et al*[14] for review): initially, these symptoms may appear as subtle cognitive–perceptive 'basic symptoms' distinguishing the early prodromal stage of psychosis from mild depressive syndromes and indicating an elevated risk of a later disease manifestation.[15–18] Subsequently, attenuated psychotic symptoms and brief limited psychotic symptoms (BLIPS) may hallmark the late prodromal stage, which is characterised by a much higher, imminent risk of disease transition.[19–21]

This prodromal concept has been challenged by a considerable overlap between prodromal symptoms and psychopathological phenomena found in the general population,[22,23] as well as by the absence of an ultimate disease transition in a significant proportion of ultra-high-risk individuals. Similarly, it is unclear which neurobiological abnormalities may be accurate predictors or just vulnerability markers of psychosis: Phillips *et al*[24] found hippocampal volume reductions in non-psychotic ultra-high-risk individuals compared with healthy controls, but no such alterations in ultra-high-risk individuals with psychotic symptoms and subsequent disease transition. Borgwardt *et al*[2,3] detected volume increments in the left parahippocampal, fusiform and perisylvian regions of ultra-high-risk individuals who later developed schizophrenia compared with those who did not. These findings raise the question of possible neuroplastic brain changes around the time of disease onset.[24,25]

Recent prospective research into the neurobiological differences of high-risk participants suspected to be in an early

or late at-risk mental state for psychosis based on established at-risk mental state criteria, which combined the basic symptom concept[26] with the Personal Assessment and Crisis Evaluation (PACE) criteria,[20] described significant associations between an increased symptomatological proximity to overt psychosis and: reduced hippocampal volumes;[27] a sensorimotor gating deficit;[28] and decreased amplitudes of auditory evoked P300 potentials.[29] Within this context, we used the identical at-risk mental state criteria together with voxel-based morphometry (VBM) in order to: investigate structural brain differences between participants in a putative early at-risk mental state (ARMS–E group) or late at-risk mental state (ARMS–L group) for psychosis; and to delineate which of these differences were associated with a later disease manifestation by comparing those at-risk mental state participants with subsequent transition to psychosis (ARMS–T group) with those without transition (ARMS–NT group). The at-risk mental state samples were compared directly and relative to matched healthy individuals. Based on the previous literature of structural brain abnormalities in the at-risk mental state and in established psychosis,[1–6,9,10,27,30,31] we hypothesised: that the ARMS–E and ARMS–L samples could be differentiated according to the spatial extent and magnitude of alterations within the prefrontal cortex, the language-related perisylvian structures, the limbic system and the cerebellum; and that distinct alterations would be present in the prefrontal, perisylvian and limbic structures of ARMS–T *v.* ARMS–NT participants.

Method

Participants

Forty-six at-risk mental state participants, including 20 ARMS–E and 26 ARMS–L individuals (Table 1), were recruited at the Early Detection and Intervention Centre for Mental Crises (FETZ) of the Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University, Germany. The FETZ participated in a prospective high-risk multicentre study within the German Research Network on Schizophrenia (GRNS).[32] Potential at-risk mental state participants were referred to the FETZ by primary healthcare services and were examined using a standardised inclusion criteria checklist (ICC) with operationalised definitions of different types of prodromal symptoms: basic symptoms (Appendix) taken from the Bonn Scale for Assessment of Prodromal Symptoms (BSABS);[26,33] attenuated psychotic symptoms; and BLIPS as defined by the PACE criteria (Appendix).[20,21] The following recruitment criteria were identically implemented in all participating sites of the multicentre GRNS project and were employed by previous studies.[27–29,34]

Potential participants with an at-risk mental state meeting defined sets of state and/or trait markers were included in the study. Inclusion based on global functioning and trait factors required a >30 point reduction in the DSM–IV Global Assessment of Functioning (GAF)[35] scale score and either a familial history of psychotic disorders in the first-degree relatives, or a personal history of pre-/perinatal complications. Inclusion based on psychopathological state markers required $\geqslant 1$ positive item in the basic symptoms, attenuated psychotic symptoms or BLIPS categories of the ICC. The at-risk mental state participants were divided into two samples according to their symptomatological proximity to psychosis based on the presence and absence of specific psychopathological state criteria. This two-stage conceptualisation of the at-risk mental state distinguished between a putatively early, or non-psychotic, at-risk mental state, with increased but not imminent risk of psychosis and a putatively late, or psychotic, at-risk mental state, with a higher or imminent risk of psychosis.[16,27–29,36]

The ARMS–E group consisted of participants without attenuated psychotic symptoms and BLIPS, who had had $\geqslant 1$ basic symptom (Appendix) on several occasions within the past 3 months and appearing first at least 12 months prior to study inclusion and/or who met a global functioning and trait criterion (see above). In line with the PACE criteria,[19] the ARMS–L sample comprised individuals with $\geqslant 1$ attenuated psychotic symptom within the past 3 months, appearing several times per week and/or with $\geqslant 1$ BLIPS, spontaneously resolving within 1 week. Basic symptoms and/or global functioning and trait criteria markers were not exclusion criteria for this sample.

Exclusion criteria were:

(a) transition to psychosis as defined by Yung *et al*;[19]

(b) a past or present diagnosis of schizophrenia-spectrum or bipolar disorders, as well as delirium, dementia, amnestic or other cognitive disorders, mental retardation and psychiatric disorders due to a somatic factor or related to psychotropic substances, following the DSM–IV[35] criteria;

(c) alcohol or drug abuse according to DSM–IV within 3 months prior to examination; and

(d) past or present inflammatory, traumatic or epileptic diseases of the central nervous system.

At study inclusion, the personal and familial history was obtained using a semi-structured clinical interview, which covered pre- and perinatal complications, developmental abnormalities during childhood and adolescence, past or present somatic diseases and psychiatric conditions, previous or current medications, nicotine, alcohol and drug use, as well as socioeconomic status. The premorbid IQ of the at-risk mental state participants was assessed using the Mehrfachwahl-Wortschatz-Intelligenztest (MWT–B), an established instrument in German-speaking populations.[37] Psychopathology was additionally rated with the Positive and Negative Syndrome Scale (PANSS)[38] and Montgomery–Åsberg Depression Scales (MADRS).[39]

A regular clinical follow-up was performed at monthly intervals during the first year and quarterly in the following 3 years. At each assessment, participants were re-evaluated using the ICC in order to detect shifts in the prodromal symptomatology towards a different at-risk mental state or a possible transition to psychosis.[19] In participants meeting the transition criteria the diagnosis of schizophrenia-spectrum disorders was determined using the ICD–10[40] diagnostic research criteria at time of transition and after 1 year. Thirty-three people in the ARMS groups (13 ARMS–E, 20 ARMS–L) completed the 4-year follow-up, of whom 15 developed psychosis (ARMS–T: 1 ARMS–E, 14 ARMS–L). The mean time to transition was 188 days (range 35–777) for the entire ARMS–T group and 142 days (range 35–642) for the 14 ARMS–L participants. One individual in the ARMS–E group developed psychosis after 777 days. The ICD–10 diagnoses were schizophrenia ($n=9$), schizoaffective psychosis ($n=5$) and schizotypal disorder ($n=1$). Six participants did not finish follow-up and seven dropped out from the study as they refused to participate or because they could not be contacted. No participants received antipsychotic agents prior to magnetic resonance imaging (MRI) and clinical examination.

Seventy-five healthy controls matched group-wise for age, gender, handedness and educational years to the entire ARMS group were recruited for MRI examination and assessed at scan time with the same standardised clinical interview as the ARMS participants (Table 1). Only those healthy volunteers were included that had no personal or familial history (first-degree relatives) of neurological and/or psychiatric conditions. All the control group and participants in the ARMS group provided their

Table 1 Statistical analysis of sociodemographic, clinical and global anatomical parameters

Variable	Controls	ARMS–E	ARMS–L	*P*	ARMS–NT	ARMS–T	*P*
Sociodemographic variables							
n	75	20	26	–	18	15	–
Age at scan, years: mean (s.d.)	25.1 (3.8)	25.6 (5.7)	24.8 (6.0)	NS[a]	25.9 (6.7)	22.4 (2.8)	<0.05[a]
Gender (male/female), %	61.3/38.7	50.0/50.0	73.1/26.9	NS[b]	61.1/38.9	73.3/26.7	NS[b]
Handedness (right/left/ambidextruous), %	88.0/8.0/4.0	85.0/10.0/5.0	88.5/3.8/7.7	NS[b]	83.3/11.1/5.6	100.0/0.0/0.0	NS[b]
Educational years, mean (s.d)	12.4 (1.8)	12.3 (0.9)	11.8 (1.4)	NS[c]	12.3 (1.0)	12.0 (1.2)	NS[c]
Premorbid IQ, Global functioning and trait factors							
MWT-B, mean (s.d.)	–	110.1 (14.0)	104.7 (16.0)	NS[c]	113.4 (13.6)	109.2 (18.0)	NS[c]
GAF reduction >30	–	65.0	76.9	NS[b]	55.6	100.0	<0.01[b]
Participants with first-degree relatives with schizophrenic psychoses, %	–	10.0	19.2	NS[b]	17.6	26.7	NS[b]
Participants with first-degree relatives with affective psychoses, %	–	15.0	7.7	NS[b]	17.6	13.3	NS[b]
Participants with pre-/perinatal complications, %	–	31.3	36.0	NS[b]	31.3	40.0	NS[b]
Psychopathology, mean (s.d.)							
Basic symptoms item count	–	2.5 (1.6)	3.5 (2.4)	NS[d]	2.4 (1.9)	3.3 (2.2)	NS[d]
Attenuated psychotic symptoms item count	–	0.0 (0.0)	1.6 (1.2)	–	0.4 (0.7)	1.5 (1.0)	<0.01[d]
BLIPS item count	–	0.0 (0.0)	1.8 (2.1)	–	0.3 (0.8)	1.3 (1.4)	<0.05[d]
PANSS sum score	–	54.7 (11.3)	55.0 (20.5)	NS[c]	51.3 (11.2)	58.4 (22.1)	NS[c]
PANSS positive score	–	9.2 (3.1)	11.8 (3.9)	NS[c]	10.0 (2.4)	12.9 (4.5)	<0.05[c]
PANSS negative score	–	14.7 (6.2)	14.6 (7.2)	NS[c]	12.9 (5.6)	16.3 (9.0)	NS[c]
MADRS sum score	–	18.6 (8.3)	14.9 (9.3)	NS[c]	17.1 (7.2)	11.1 (8.1)	NS[c]
Global anatomical parameters							
Grey matter volume (mm^3), mean (s.d.)	653.1 (73.6)	660.1 (62.7)	682.5 (76.8)	NS[a]	653.7 (60.6)	698.0 (52.6)	NS[a]
White matter volume (mm^3), mean (s.d.)	523.2 (66.5)	527.7 (66.0)	530.0 (53.0)	NS[a]	526.8 (63.0)	530.2 (47.8)	NS[a]
Cerebrospinal fluid (mm^3), mean (s.d.)	458.9 (98.6)	446.5 (97.6)	483.7 (90.8)	NS[a]	451.0 (97.6)	485.0 (97.8)	NS[a]
Total intracranial volume (mm^3), mean (s.d.)	1635.2 (204.5)	1634.3 (182.8)	1696.2 (158.6)	NS[a]	1631.5 (177.8)	1713.1 (135.4)	NS[a]
Distance^2 to voxel value in grey matter 10^3, mean (s.d.)	146.0 (9.1)	144.6 (8.8)	147.2 (13.1)	NS[a]	146.7 (8.6)	142.5 (7.9)	NS[a]

ARMS–E, early at-risk mental state group; ARMS–L, late at-risk mental state group; ARMS–NT, at-risk mental state without subsequent disease transition group; ARMS–T, at-risk mental state with subsequent transition to psychosis group; MWT-B, Mehrfachwahl-Wortschatz-Intelligenztest; GAF, Global Assessment of Functioning; BLIPS, brief limited psychotic symptoms; PANSS, Positive and Negative Symptom Scale; MADRS, Montgomery–Asberg Depression Scales.
a. One-way analysis of variance with three groups (control, ARMS–E, ARMS–L groups or control, ARMS–NT, ARMS–T groups).
b. Fisher's exact test.
c. Student *t*-test.
d. Mann–Whitney *U*-test.

written informed consent prior to study inclusion. The study was approved by the Local Research Ethics Committee of the Ludwig-Maximilians-University.

MRI data acquisition

Magnetic resonance images were obtained on a 1.5 T Magnetom Vision scanner (Siemens, Erlangen, Germany) using a T_1-weighted 3D-MPRAGE sequence (repetition time (TR) 11.6 ms, echo time (TE) 4.9 ms, field of view 230 mm, matrix 512 × 512, 126 contiguous axial slices of 1.5 mm thickness, voxel size 0.45 × 0.45 × 1.5 mm). Scans were checked for image artefacts and gross anatomical abnormalities. Data analysis was performed using the SPM5 software package (Wellcome Department of Cognitive Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm/software/spm5) running under MATLAB 2007a (The MathWorks, Natick, MA, USA; www.mathworks.com) on Linux.

MRI data pre-processing

The VBM5 toolbox (http://dbm.neuro.uni-jena.de), an extension of SPM5, was used to segment the images into grey matter, white matter and cerebrospinal fluid (CSF) tissue maps and to normalise these maps to the standard space defined by the anatomical template of the Montreal Neurological Institute (MNI–152; www.bic.mni.mcgill.ca/cgi/icbm_view). This pre-processing protocol has been described previously.[1] In summary, the VBM5 toolbox provides several enhancements compared with the standard SPM5 algorithms as it combines the unified segmentation approach of SPM5[41] with a hidden Markov field (HMRF) model[42] in order to optimise the quality of tissue segmentation by increasing the signal-to-noise ratio of the data. Furthermore, the present study utilised the toolbox's option of writing the normalised tissue maps without making use of the *a priori* knowledge of the ICBM (International Consortium for Brain Mapping) tissue priors. These tissue priors are derived from the brains of healthy participants and may therefore introduce a segmentation bias in the final tissue maps of patient populations that may deviate anatomically from the healthy controls. In the current study, the use of this option led to a significantly better delineation of fine sulcal and gyral cortical folding compared with the classical statistical parametric mapping (SPM) approach.

Global grey matter, white matter, CSF and total intracranial volumes were computed using the native-space tissue maps of each participant. Moreover, the anatomical heterogeneity was compared between samples by calculating the squared distance of each person's modulated, normalised grey matter tissue map to the sample mean using the VBM5 toolbox (Table 1). Data pre-processing was finished: by proportionally scaling each person's modulated, normalised grey matter tissue map to the respective global grey matter volume in order to remove the effects of global brain size differences on local brain structures; and by applying an isotropic 10 mm full-width-at-half-maximum Gaussian filter to the scaled grey matter tissue maps.

Statistical analysis

Within the framework of the general linear model two analyses of covariance (ANCOVA) were designed in order to investigate focal

grey matter volume differences between the control group, ARMS–E group and ARMS–L group (design 1) and the control group, ARMS–NT group and ARMS–T group (design 2). Age and gender were entered as nuisance regressors in the statistical designs in order to regress out possible effects of these parameters on between-group grey matter volume differences. Statistical inference was performed at the cluster-level by assessing the SPM{*t*} images using the non-stationary random field theory described by Hayasaka *et al*[43] and applied in Meisenzahl *et al*.[1]

Statistical inference started with the definition of a primary threshold in order to identify contiguous voxels for the cluster-level analysis at a relatively lenient voxel level of $P<0.01$, uncorrected.[1] Then, a family-wise error (FWE) corrected cluster-size threshold[44] of $P<0.05$ was applied, producing a spatial extent threshold of 5.4 cm^3 in design 1 and 5.2 cm^3 in design 2. Finally, cluster sizes were adjusted for smoothness non-uniformity by means of the VBM5 toolbox. Anatomical regions covered by significant clusters were identified using automated anatomical labeling.[45] Grey matter volume differences in these regions were quantified by calculating the effect sizes (Cohen's *D*) of the SPM{*t*} maps and by extracting the percentage between-group differences (% difference) from the contrast images (see online Table DS4).

Statistical inference of between-group differences was performed as follows: for design 1, grey matter volume differences (decreases, increases) were assessed using *T* contrasts between the ARMS–E group and the control group ([control group > ARMS–E group], [control group < ARMS–E group]) and between the ARMS–L group and the control group ([control group > ARMS–L group], [control group < ARMS–L group]). Then, grey matter differences (decreases, increases) were directly examined between the ARMS–E group and the ARMS–L group ([ARMS–E group > ARMS–L group], [ARMS–E group < ARMS–L group]). The analysis of grey matter differences in the same way for design 2.

Owing to the relative gender imbalance between the ARMS–E group and the ARMS–L group (Table 1), a supplementary VBM analysis was performed in order to investigate possible gender effects on the between-group differences observed in the [ARMS–E group > ARMS–L group] contrast. Therefore, a two-factorial ANCOVA was constructed with gender and ARMS group entered as factors and age defined as the nuisance covariate. Interactions between grey matter volume reductions in ARMS–L group *v.* ARMS–E group and (1) male ARMS *v.* female ARMS, or (2) female ARMS *v.* male ARMS were evaluated at the cluster-level threshold of $P<0.05$, FWE-corrected using [male ARMS < female ARMS] × [ARMS–E group > ARMS–L group] and [male ARMS > female ARMS] × [ARMS–E group > ARMS–L group] contrasts.

The different spatial extents of the frontal clusters detected by the [control group > ARMS–L group] contrast and the [ARMS–E group > ARMS–L group] contrast (see online Fig. DS1) pointed to subtle frontal grey matter volume abnormalities in the ARMS–E group that did not reach significance in the [control group > ARMS–E group] contrast. Therefore, correlations between grey matter volume and increasing symptomatological proximity to psychosis were assessed in a supplementary general linear model design that modelled the symptomatological proximity as a three-level gradation by assigning values of 3, 2 and 1 to the control group, ARMS–E group and ARMS–L group respectively. Age and gender were entered as nuisance regressors in the statistical design. Two contrasts tested for positive [control group > ARMS–E group > ARMS–L group] and negative [control group < ARMS–E group < ARMS–L group] correlations following the same statistical inference strategy as described above.

Results

Sociodemographic and clinical parameters

No significant differences were found between the control group, ARMS–E and ARMS–L groups with respect to age, handedness and educational years (Table 1). The gender distribution between the ARMS–E and ARMS–L participants was relatively unbalanced (ARMS–E group: 50% females; ARMS–L group: 27% females), but not significantly different between groups ($\chi^2=2.59$, $P=0.274$). No significant sociodemographic differences were found between the control, ARMS–NT and ARMS–T groups, except for age ($F=3.16$, $P=0.048$).

The premorbid IQ was neither significantly different in the ARMS–E group *v.* ARMS–L group, nor in ARMS–NT group *v.* ARMS–T group. Reduced global functioning did not differ between the ARMS–E and ARMS–L groups, but all 15 ARMS–T participants showed a GAF reduction of >30 points at study inclusion compared with 55.6% in the ARMS–NT group. The ARMS groups were not significantly different with respect to the prevalence of schizophrenic or affective psychosis in the first-degree relatives or pre-/perinatal complications. No significant differences were detected between the ARMS–E and ARMS–L groups regarding PANSS and MADRS scores. The ARMS–T group scored significantly higher in the PANSS positive symptoms score and showed a trend towards a lower total MADRS score. The overall prevalence of basic symptoms was higher in the ARMS–L group *v.* ARMS–E group and the ARMS–T group *v.* ARMS–NT group. The ARMS–T participants showed a significantly higher prevalence of attenuated psychotic symptoms and BLIPS compared with the ARMS–NT participants at baseline.

Global anatomical parameters

No significant differences between the control, ARMS–E and ARMS–L groups, as well as the control, ARMS–NT and ARMS–T groups were found regarding global grey matter, white matter, CSF, total intracranial volumes and anatomical heterogeneity (Table 1.)

VBM analysis: control *v.* ARMS–E *v.* ARMS–L groups

In the VBM analysis of the control *v.* ARMS–E *v.* ARMS–L groups (online Fig. DS1 and online Tables DS1 and DS2) no significant grey matter volume increments were observed in the ARMS–E group *v.* the control group, ARMS–L group *v.* control group and ARMS–E group *v.* ARMS–L group.

[Control group > ARMS–E group] contrast

This contrast identified two temporal clusters of grey matter volume losses (right: $k_c=8404$ voxels, $P_{FWE}=0.005$; left: $k_c=9418$, $P_{FWE}=0.003$) that involved fusiform, superior, middle and inferior temporal gyri, as well as amygdala and hippocampus, bilaterally. The maximum effect sizes within these clusters ranged between 0.5 (temporal pole) and 0.7 (inferior temporal and fusiform gyri). The percentage differences lay between 4.1% (temporal pole) and 6.4% (middle temporal gyrus).

[Control group > ARMS–L group] contrast

An extended bilateral cluster ($k_c=126\,520$, $P_{FWE}<0.001$) of grey matter volume reductions occupied primarily frontal regions:

(a) the frontal interhemispheric area spanning the dorsomedial and ventromedial prefrontal cortex as well as the olfactory cortices and extending into the anterior cingulate cortex and the caudate nucleus, bilaterally;

(b) the lateral prefrontal areas, including the dorsolateral and ventrolateral prefrontal cortex, with an extension into the left anterior insula and stretching bilaterally from the frontopolar regions to the supplementary motor areas and precentral gyri; and

(c) the orbitofrontal areas, reaching from the medial to the lateral orbitofrontal cortex.

Four smaller clusters of grey matter volume reductions were identified in:

(a) the left posterior temporal and inferior parietal regions;

(b) the right medial temporal lobe (amygdala, hippocampus and parahippocampus), including the fusiform gyrus;

(c) the frontal interhemispheric region occupying portions of the anterior cingulate cortex, caudate and thalamus; and finally

(d) within the right-hemispheric medial parietal cortex and precuneus.

Effect sizes were medium to high (0.5–0.9) with maximum effects within the left dorsomedial prefrontal cortex and the right dorsolateral prefrontal cortex. The largest percentage volume reductions were observed in the right anterior cingulate cortex (6.7%) and in adjacent parts of the left Broca's area and precentral cortex (7.1%).

[ARMS–E group > ARMS–L group] contrast

This contrast identified similar, but less extended frontal clusters of grey matter volume reductions compared with the [control group > ARMS–L group] contrast. The effect sizes were medium to high with maxima in the left subgenual anterior cingulate cortex as well as in the ventromedial prefrontal cortex and dorsomedial prefrontal cortex, bilaterally. The percentage grey matter volume reductions in ARMS–L participants relative to ARMS–E participants were comparable to the [control group < ARMS–L group] contrast, with maxima in the anterior cingulate cortex, bilaterally.

VBM analysis: control *v.* ARMS–NT *v.* ARMS–T groups

In the VBM analysis of control *v.* ARMS–NT *v.* ARMS–T groups (online Fig. DS2 and online Tables DS3 and DS4) no significant grey matter volume increments were observed in the following groups: ARMS–NT *v.* control, ARMS–T *v.* control and ARMS–T *v.* ARMS–NT.

[Control group > ARMS–NT group] contrast

This contrast detected three clusters of grey matter volume reductions that covered parts of the left and right dorsolateral prefrontal cortex, as well as the precentral, postcentral and supramarginal gyri (left cluster: $k_c = 10\,925$, $P_{FWE} < 0.001$, right cluster: $k_c = 20\,174$, $P_{FWE} < 0.001$) as well as the right medial and lateral temporal lobe structures, including the amygdala, hippocampus, parahippocampus, superior temporal gyrus, middle and inferior temporal, fusiform and lingual gyri ($k_c = 22\,017$, $P_{FWE} < 0.001$). Across these regions the maximum effect sizes ranged from 0.5 (right Broca's area) to 1.0 (right precentral and left postcentral gyri). The maximum percentage differences were detected in the border region between the dorsolateral prefrontal cortex and the precentral gyrus (% difference 10.4) as well as in the superior temporal sulcus (% difference 8.1).

[Control group > ARMS–T group] contrast

A frontal cluster of grey matter volume losses ($k_c = 124078$, $P_{FWE} < 0.001$) was observed in the ARMS–T group compared with the control group. Its spatial localisation was similar to the cluster found in the [control group > ARMS–L group] contrast and involved predominantly the right dorsolateral prefrontal cortex, ventrolateral prefrontal cortex and large portions of the dorsomedial prefrontal cortex, ventromedial prefrontal cortex and orbitofrontal cortex, bilaterally. The largest effect sizes and percentage differences were detected within the right anterior cingulate cortex ($D = 1.0$, % difference 10.2) and dorsomedial prefrontal cortex ($D = 1.0$, % difference 9.0).

[ARMS–NT group > ARMS–T group] contrast

This contrast revealed a prefrontal cluster of grey matter volume reductions ($k_c = 34\,146$, $P_{FWE} < 0.001$) similar to the cluster observed in the [control group > ARMS–T group] contrast. It covered significant portions of the dorsomedial prefrontal cortex (left: 29.3%, right: 34.8%), anterior cingulate cortex (left: 23.1%, right: 29.5%) and orbitofrontal cortex (left: 39.8%, right: 34.4%) with medium to large effect sizes (0.5–0.9) and percentage differences ranging between 5.2% and 10.6%.

Supplementary analyses

Gender × ARMS group interactions

No significant clusters were observed in the interaction [male ARMS participants < female ARMS participants] × (ARMS–E group < ARMS–L group] (online Fig. DS3). In contrast, the interaction [male ARMS participants < female ARMS participants] × [ARMS–E group > ARMS–L group] identified:

(a) two bilateral prefrontal clusters characterised by a larger left- ($k_c = 21\,378$, $P_{FWE} < 0.001$) than right-hemispheric ($k_c = 5419$, $P_{FWE} = 0.049$) extent; and

(b) a predominantly left-hemispheric occipital cluster ($k_c = 5784$, $P_{FWE} = 0.037$).

The overlap between these clusters and the clusters detected by the [ARMS–E group > ARMS–L group] contrast was spatially confined to small border regions between the dorsolateral prefrontal cortex and ventrolateral prefrontal cortex, bilaterally.

Correlations between grey matter volume and symptomatological proximity to psychosis

No significant negative correlations between grey matter volume and symptomatological proximity to psychosis were detected (online Fig. DS4). Positive correlations emerged in a pattern of anatomical regions previously described in the [control group > ARMS–L group] contrast. Six clusters occupied:

(a) large bilateral portions of the prefrontal and orbitofrontal regions with extensions into the cingulate and precentral cortices, the thalamus, left insula and caudate nuclei ($k_c = 121\,860$, $P_{FWE} < 0.001$);

(b) the right medial temporal lobe covering the hippocampus, parahippocampus, amygdala and extending into the fusiform gyrus ($k_c = 9400$, $P_{FWE} = 0.002$);

(c) the left perisylvian region, including the Rolandic operculum, postcentral, supramarginal and superior temporal gyrus ($k_c = 7133$, $P_{FWE} = 0.013$);

(d) the right medial parietal cortex and precuneus ($k_c = 6882$, $P_{FWE} = 0.016$);

(e) parts of the superior, middle and inferior temporal gyri ($k_c = 6693$, $P_{FWE} = 0.018$); and

(f) the right cerebellar hemisphere ($k_c = 5598$, $P_{FWE} = 0.044$).

Discussion

Prefrontal abnormalities and their relation to clinical outcome

Our first hypothesis, that the ARMS–L participants could be distinguished from the ARMS–E group based on the extent and magnitude of brain abnormalities was confirmed. The most pronounced alterations were found in the ARMS–L group, with extended volume losses spanning the prefrontal and orbitofrontal cortices and involving parts of the anterior cingulate cortex, insula as well as medial and lateral temporal brain regions. Furthermore, we detected grey matter volume abnormalities, which gradually increased with the symptomatological proximity to psychosis (control group to ARMS–E group to ARMS–L group) within the same pattern of brain regions found to be altered in the ARMS–L group *v.* control group. These findings are in keeping with previous studies of ultra-high-risk participants and people with first-episode schizophrenia.[1,9,14] Studies involving participants from the PACE clinic in Melbourne reported abnormal anterior cingulate cortex and paracingulate morphology,[46] as well as progressive changes in the anterior cingulate cortex, orbitofrontal cortex and ventrolateral prefrontal cortex of ultra-high-risk participants with subsequent disease manifestation.[5] Data from the genetically defined sample of the Edinburgh High Risk Study (EHRS) revealed grey matter density reductions within the anterior cingulate cortex and orbitofrontal cortex of 146 high-risk participants compared with 36 healthy controls.[6] In this context, a careful interpretation of our results may be that emerging frontal brain alterations parallel the growing risk of psychosis within the framework of a late neurodevelopmental process.[47] This process may represent the sequelae of brain anomalies acquired during the prenatal phase and early childhood. It may be triggered during brain maturation in early adulthood when higher-order cortical association areas are placed 'under functional demand'.[14,47] On the basis of a predisposing neurobiological vulnerability, this process may result in progressive structural brain changes that occur around the time of disease onset and primarily affect prefrontal as well as temporal cortical regions.[2–6,14] Alternatively, these brain abnormalities may be interpreted as a neurobiological trait marker for a subgroup of at-risk mental state participants characterised by a liability to attenuated or transient psychotic symptoms.

To further differentiate between neuroanatomical markers of an elevated susceptibility to psychosis and those linked to an ultimate disease manifestation, we investigated grey matter abnormalities relative to the clinical outcome of our two at-risk mental state samples. During the clinical follow-up period of 4 years, 14 ARMS–L participants converted to psychosis, whereas this happened only in 1 ARMS–E participant. The low conversion rate of our ARMS–E group is inconsistent with the study of Klosterkötter *et al*,[26] who reported that 50% of their 160 at-risk mental state participants, who were selected for having basic symptoms, converted to psychosis during a follow-up period of 10 years. The discrepancy between these different conversion rates may be because of:

(a) our small ARMS–E sample size compared with Klosterkötter *et al*;[26]

(b) our significantly shorter follow-up period of 4 years;

(c) the differences regarding the mean age at study inclusion, which was 29.7 years (s.d. = 11.4) in the study of Klosterkötter *et al*;[26] and

(d) the larger proportion of female participants in the ARMS–E *v.* ARMS–L group, potentially resulting in a later mean age at disease onset in the ARMS–E sample.[48]

Recent findings suggested that different types of prodromal states may exist, with a substantial proportion (33%) of converters having prodromal phases of more than 6 years.[36] Therefore, a longer follow-up period of an enlarged ARMS–E sample will provide a more definite answer with respect to the conversion rate of these participants and regarding the temporal sequence of at-risk mental states during the prodromal phase of psychosis. Our current study suggests that our at-risk mental state samples differ in their predictive power, and therefore represent two levels of risk for an ultimate disease transition. This interpretation is in line with the clinical risk model of Maier *et al*,[49] who proposed a gradual development of the schizophrenia prodrome over several stages that are characterised by an increasing symptomatological proximity to full-blown schizophrenia and an increasing predictive power regarding an ultimate disease transition. Within this concept, the early at-risk mental state may be regarded as a precursor of psychosis marked by an elevated level of vulnerability for the disease, whereas the late at-risk mental state may be interpreted as a 'real' prodromal phase of psychosis because of its considerable predictive validity.

In keeping with the study of Yung *et al*,[21] we found that the ARMS–T participants experienced more frequently a significant functional decline as well as a higher prevalence of basic symptoms, attenuated psychotic symptoms and BLIPS as compared with the ARMS–NT individuals. Consistent with our second hypothesis, prefrontal structural alterations in the ARMS–T participants were identified on average 6 months prior to disease transition, which largely overlapped with the abnormalities of the ARMS–L sample (online Fig. DS5). An additional analysis of the quantitative differences between the ARMS–L and ARMS–T samples revealed that the ARMS–T participants had more pronounced prefrontal grey matter volume reductions compared with the entire ARMS–L sample, with a maximum difference of 4.5% in the right anterior cingulate cortex (online Fig. DS5). Moreover, we observed divergent patterns of structural abnormalities in the ARMS–NT and ARMS–T participants compared with the healthy controls: the prefrontal abnormalities detected in the ARMS–NT group *v.* the control group were confined to the dorsolateral prefrontal cortex, bilaterally, whereas only right medial and lateral temporal lobe alterations were found only in the control group *v.* ARMS–NT group. These findings are consistent with previous studies reporting grey matter volume reductions in the anterior cingulate cortex[2,3] and progressive prefrontal grey matter losses in ARMS–T relative to ARMS–NT participants.[47] Previous neuroimaging studies reported significant correlations between poor neurocognitive measures and prefrontal cortex abnormalities in established schizophrenia.[50,51] In this context, neuropsychological data have shown that cognitive and executive functioning are already impaired in at-risk mental state participants prior to disease onset,[52] with more severe impairments being associated with the late at-risk mental state[36] and a further deterioration being linked to subsequent disease manifestation.[53] Based on these results and our own findings, we may cautiously interpret prefrontal brain alterations pre-dating psychosis as a marker of clinical outcome and not only as a marker of liability to attenuated or transient psychotic symptoms.

Temporal lobe abnormalities in different at-risk mental states

In addition to the grey matter volume reductions commonly found in the medial temporal lobe of both at-risk mental state

groups, our main VBM analysis revealed patterns of neuroanatomical abnormalities that seemed to differ qualitatively between the two at-risk samples. Structural abnormalities in the ARMS–E group did not involve the prefrontal or orbitofrontal areas, but were restricted to the temporolimbic structures, bilaterally. Conversely, the ARMS–L group showed structural anomalies in the left superior temporal gyrus and in the prefrontal and orbitofrontal cortices undetected by the ARMS–E *v.* control group comparison. Besides these divergent patterns, our supplementary VBM analysis identified grey matter volume abnormalities that gradually increased from the control group to the ARMS–E group to the ARMS–L group within a frontotemporolimbic pattern that was highly similar to the pattern detected by the ARMS–L *v.* control groups contrast (online Fig DS4). Taken together, these findings suggest that:

(a) basic symptoms define a risk level of psychosis that is not only associated with medial and lateral temporal lobe abnormalities, but also with subtle perisylvian, prefrontal, parietal, thalamic and cerebellar anomalies; and

(b) attenuated psychotic symptoms and/or BLIPS mark a higher level of risk characterised by more pronounced structural anomalies within these regions.

Alterations of the medial temporal lobe regions were previously reported in individuals with manifest schizophrenia[9,10,54,55] and people with an at-risk mental state.[2,3,5,6] In this context, Seidman *et al*[7] discussed limbic abnormalities as a crucial vulnerability indicator of psychosis that may be associated with impaired verbal declarative memory functions in individuals with an at-risk mental state. In line with these data, Job *et al*[4] reported exclusive longitudinal grey matter density losses in the medial, but also lateral temporal lobe regions (superior temporal gyrus, inferior temporal gyrus) of people with an asymptomatic at-risk mental state who later developed transient or isolated psychotic symptoms. Moreover, they found further exclusive temporolimbic grey matter density losses in those participants who subsequently developed schizophrenia.

The non-reduction of left hippocampal volume found in the ARMS–L group *v.* control group is consistent with the results of Phillips *et al*,[24] who reported a similar finding in 20 ultra-high-risk individuals with psychotic symptoms *v.* 40 non-psychotic ultra-high-risk individuals. The authors also detected associations between a larger hippocampus at baseline and subsequent disease transition. Moreover, recent EHRS studies revealed positive correlations between the grey matter density of the superior temporal gyrus and productive symptoms in at-risk mental state participants,[56,57] which is in contrast to the negative correlations between temporal brain volumes and positive symptoms of individuals with manifest schizophrenia.[58,59] Finally, Borgwardt *et al*[2] identified grey matter volume increments in 12 ARMS–T *v.* 23 ARMS–NT participants, which were bilaterally localised in the parahippocampus, thalamus as well as the occipital, temporal and parietal brain regions.

These findings may point to a complex pattern of brain abnormalities underlying different vulnerability levels of psychosis that involve not only volume reductions, but also volume increments within interconnected cortical and subcortical structures.[57] In the context of these findings, our cross-sectional and correlational VBM findings may be cautiously interpreted within the framework of a late neurodevelopmental process[14,47] that results in progressive volumetric declines within frontotemporolimbic brain structures, but that also leads to the transient normalisation of distinct cortical regions (left hippocampus) around the time of disease onset. Alternatively, these grey matter alterations may be interpreted as long-standing neuroanatomical patterns that pre-date the onset of prodromal symptoms and represent trait markers of different levels of vulnerability to psychosis.

Limitations and implications

The definition of the at-risk mental state groups followed a two-stage conceptualisation of the prodrome that distinguishes between putatively early and late prodromal stages.[32] As discussed above, the low predictive validity of our ARMS–E group regarding a subsequent transition to psychosis questions the hypothetical prodromal syndromic sequence following a single trajectory of 'unspecific symptoms to predictive basic symptoms to attenuated psychotic symptoms to transient psychotic symptoms'.[60] Thus, we could not decide whether our observations in the putatively 'early' and 'late' at-risk mental state groups represent two neurobiological cut-outs from a longitudinal course of brain changes, leading ultimately to the manifestation of overt psychosis, or whether they represent two differential risk levels for psychosis with distinct, possibly long-standing neuroanatomical underpinnings. Nevertheless, our finding of accumulating brain abnormalities being associated with an increasing symptomatological proximity to psychosis is in keeping with previous studies, which reported a deterioration of neurocognitive, neurophysiological and neuroanatomical markers in similarly defined individuals with an 'early' and a 'late' at-risk mental state.[27–29] Future prospective studies combining repeated MRI and clinical examinations may further disentangle how brain abnormalities pertaining to different vulnerability states interact with different possible trajectories of emerging psychosis.

Although we controlled for gender effects, we cannot completely rule out an effect of the unbalanced gender distribution between the ARMS–E and ARMS–L groups. However, the results of our group × gender analysis overlapped with the ARMS–E group *v.* ARMS–L group findings only in relatively small prefrontal areas, bilaterally. It is noteworthy that the result of an abnormal sexual dimorphism modulating the structural abnormalities in the ARMS–L group is partly consistent with previous MRI studies[61] investigating gender-mediated structural brain alterations in people with established schizophrenia. Furthermore, this finding may be in keeping with a stronger cognitive impairment observed in male *v.* female participants.[62–64] Larger at-risk mental state gender subgroups are needed to further elucidate the impact of gender-mediated pathophysiological processes on the development of cortical abnormalities during the at-risk mental state.

To our knowledge, this is the first study that characterised structural brain abnormalities in an at-risk mental state sample selected for basic symptoms. Furthermore, we employed the new unified segmentation algorithms of SPM5 with the enhancements of the VBM toolbox to meet the criticism of previous SPM versions.[65] Consistent with recent MRI studies,[2,3,5,66] we employed cluster-level inference to detect spatially contiguous, but subtle abnormalities.

In summary, our findings support the hypothesis that structural changes within the temporolimbic system may be present in a putatively 'early' at-risk mental state. A higher level of susceptibility to attenuated and/or transient psychotic symptoms may be associated with prefrontal and orbitofrontal alterations. From the retrospective view of clinical outcome, our findings suggest that prefrontal and orbitofrontal brain abnormalities pre-date a subsequent disease manifestation. Finally, our data may point to a complex, possibly dynamic pattern of frontotemporolimbic brain alterations underlying an increasing vulnerability to psychosis.

Nikolaos Koutsouleris, MD, **Gisela J.E. Schmitt**, MD, Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University, Munich, Germany; **Christian Gaser**, PhD, Department of Psychiatry, Friedrich-Schiller-University, Jena, Germany; **Ronald Bottlender**, MD, **Johanna Scheuerecker**, PhD, Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University, Munich, Germany; **Philip McGuire**, FRCPsych, MD, PhD, Department of Psychological Medicine, Institute of Psychiatry, King's College London, UK; **Bernhard Burgermeister**, PhD, Department of Psychiatry and Psychotherapy, **Christine Born**, MD, **Maximilian Reiser**, MD, Department of Radiology; **Hans-Jürgen Möller**, MD, **Eva M. Meisenzahl**, MD, Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University, Munich, Germany.

Correspondence: Eva M. Meisenzahl, Clinic of Psychiatry and Psychotherapy, Luwdig-Maxmilians-University, Nussbaumstr. 7, 80336 Munich, Germany. Email: Eva.Meisenzahl@med.uni-muenchen.de

First received 4 Mar 2008, final revision 9 Jan 2009, accepted 10 Feb 2009

Acknowledgements

We would like to thank Dr. Reinhold Bader, Linux Cluster Systems for the Munich and Bavarian Universities, for his support in integrating the VBM5 and SPM5 algorithms into the batch system of the Linux cluster.

Appendix

Inclusion criteria for the early at-risk mental state group (ARMS–E) and late at-risk mental state group (ARMS–L) participants. Adopted from Häfner *et al*[82]

Early at-risk mental state (ARMS–E)

At-risk mental state participants without attenuated psychotic symptoms and/or brief limited psychotic symptoms (BLIPS):

(a) having one or more of the following basic symptoms appeared first at least 12 months prior to study inclusion and several times per week during the last 3 months:

- (i) thought interferences
- (ii) thought perseveration
- (iii) thought pressure
- (iv) thought blockages
- (v) disturbances of receptive language, either heard or read
- (vi) decreased ability to discriminate between ideas and perception, fantasy and true memories
- (vii) unstable ideas of reference (subject-centrism)
- (viii) derealisation
- (ix) visual perception disturbances
- (x) acoustic perception disturbances.

and/or

(b) showing a reduction in the Global Assessment of Functioning Score (DSM–IV) of at least 30 points (within the past year) combined with at least one of the following trait markers:

- (i) first-degree relative with a lifetime-diagnosis of schizophrenia or a schizophrenia-spectrum disorder
- (ii) pre- or perinatal complications.

Late at-risk mental state (ARMS–L)

At-risk mental state participants with/without basic symptoms, with/without global functioning and trait markers:

(a) having at least one of the following attenuated positive symptoms within the last 3 months, appearing several times per week for a period of at least 1 week:

- (i) ideas of reference
- (ii) odd beliefs or magical thinking
- (iii) unusual perceptual experiences
- (iv) odd thinking and speech
- (v) suspiciousness or paranoid ideation

and/or

(b) having at least one of the following BLIPS, defined as the appearance of one of the following psychotic symptoms for less than 1 week (interval between episodes at least 1 week), resolving spontaneously:

- (i) hallucinations
- (ii) delusions
- (iii) formal thought disorder
- (iv) gross disorganised or catatonic behaviour.

References

1 Meisenzahl EM, Koutsouleris N, Gaser C, Bottlender R, Schmitt GJE, McGuire P, et al. Structural brain alterations in subjects at high-risk of psychosis: a voxel-based morphometric study. *Schizophr Res* 2008; **102**: 150–62.

2 Borgwardt SJ, Riecher-Rössler A, Dazzan P, Chitnis X, Aston J, Drewe M, et al. Regional gray matter volume abnormalities in the at risk mental state. *Biol Psychiatry* 2007; **61**: 1148–56.

3 Borgwardt SJ, McGuire PK, Aston J, Berger G, Dazzan P, Gschwandtner U, et al. Structural brain abnormalities in individuals with an at-risk mental state who later develop psychosis. *Br J Psychiatry* 2007; **191** (suppl 51): s69–75.

4 Job DE, Whalley HC, Johnstone EC, Lawrie SM. Grey matter changes over time in high risk subjects developing schizophrenia. *Neuroimage* 2005; **25**: 1023–30.

5 Pantelis C, Velakoulis D, McGorry PD, Wood SJ, Suckling J, Phillips LJ, et al. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet* 2003; **361**: 281–8.

6 Job DE, Whalley HC, McConnell S, Glabus M, Johnstone EC, Lawrie SM. Voxel-based morphometry of grey matter densities in subjects at high risk of schizophrenia. *Schizophr Res* 2003; **64**: 1–13.

7 Seidman LJ, Pantelis C, Keshavan MS, Faraone SV, Goldstein JM, Horton NJ, et al. A review and new report of medial temporal lobe dysfunction as a vulnerability indicator for schizophrenia: a magnetic resonance imaging morphometric family study of the parahippocampal gyrus. *Schizophr Bull* 2003; **29**: 803–30.

8 Lawrie SM, Whalley H, Kestelman JN, Abukmeil SS, Byrne M, Hodges A, et al. Magnetic resonance imaging of brain in people at high risk of developing schizophrenia. *Lancet* 1999; **353**: 30–3.

9 Meisenzahl EM, Koutsouleris N, Bottlender R, Scheuerecker J, Jäger M, Teipel SJ, et al. Structural brain alterations at different stages of schizophrenia: a voxel-based morphometric study. *Schizophr Res* 2008; **104**: 44–60.

10 Koutsouleris N, Gaser C, Jäger M, Bottlender R, Frodl T, Holzinger S, et al. Structural correlates of psychopathological symptom dimensions in schizophrenia: a voxel-based morphometric study. *Neuroimage* 2008; **39**: 1600–12.

11 Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *Am J Psychiatry* 2005; **162**: 2233–45.

12 Harris JM, Moorhead TWJ, Miller P, McIntosh AM, Bonnici HM, Owens DGC, et al. Increased prefrontal gyrification in a large high-risk cohort characterizes those who develop schizophrenia and reflects abnormal prefrontal development. *Biol Psychiatry* 2007; **62**: 722–9.

13 Phillips LJ, McGorry PD, Yung AR, McGlashan TH, Cornblatt B, Klosterkötter J. Prepsychotic phase of schizophrenia and related disorders: recent progress and future opportunities. *Br J Psychiatry* 2005; **187** (suppl 48): s33–44.

14 Pantelis C, Yücel M, Wood SJ, Velakoulis D, Sun D, Berger G, et al. Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. *Schizophr Bull* 2005; **31**: 672–96.

15 Häfner H, Maurer K. Early detection of schizophrenia: current evidence and future perspectives. *World Psychiatry* 2006; **5**: 130–8.

16 Ruhrmann S, Schultze-Lutter F, Klosterkötter J. Early detection and intervention in the initial prodromal phase of schizophrenia. *Pharmacopsychiatry* 2003; **36** (Suppl 3): s162–7.

17 Hambrecht M, Lammertink M, Klosterkötter J, Matuschek E, Pukrop R. Subjective and objective neuropsychological abnormalities in a psychosis prodrome clinic. *Br J Psychiatry* 2002; **181** (suppl 43): s30–7.

18 Klosterkötter J, Schultze-Lutter F, Gross G. Early self-experienced neuropsychological deficits and subsequent schizophrenic diseases:

an 8-year average follow-up prospective study. *Acta Psychiatrica Scandinavica* 1997; **95**: 396–404.

19 Yung AR, Phillips LJ, McGorry PD, McFarlane CA, Francey S, Harrigan S, et al. Prediction of psychosis. A step towards indicated prevention of schizophrenia. *Br J Psychiatry* 1998; **172** (suppl 33): 14–20.

20 Yung AR, Phillips LJ, Yuen HP, Francey SM, McFarlane CA, Hallgren M, et al. Psychosis prediction: 12-month follow up of a high-risk (''prodromal'') group. *Schizophr Res* 2003; **60**: 21–32.

21 Yung AR, Phillips LJ, Yuen HP, McGorry PD. Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. *Schizophr Res* 2004; **67**: 131–42.

22 Johns LC, Cannon M, Singleton N, Murray RM, Farrell M, Brugha T, et al. Prevalence and correlates of self-reported psychotic symptoms in the British population. *Br J Psychiatry* 2004; **185**: 298–305.

23 Johns LC, Nazroo JY, Bebbington P, Kuipers E. Occurrence of hallucinatory experiences in a community sample and ethnic variations. *Br J Psychiatry* 2002; **180**: 174–8.

24 Phillips LJ, Velakoulis D, Pantelis C, Wood S, Yuen HP, Yung AR, et al. Non-reduction in hippocampal volume is associated with higher risk of psychosis. *Schizophr Res* 2002; **58**: 145–58.

25 Frost DO, Tamminga CA, Medoff DR, Caviness V, Innocenti G, Carpenter WT. Neuroplasticity and schizophrenia. *Biol Psychiatry* 2004; **56**: 540–3.

26 Klosterkötter J, Hellmich M, Steinmeyer EM, Schultze-Lutter F. Diagnosing schizophrenia in the initial prodromal phase. *Arch Gen Psychiatry* 2001; **58**: 158–64.

27 Hurlemann R, Jessen F, Wagner M, Frommann I, Ruhrmann S, Brockhaus A, et al. Interrelated neuropsychological and anatomical evidence of hippocampal pathology in the at-risk mental state. *Psychol Med* 2008; **38**: 843–51.

28 Quednow BB, Frommann I, Berning J, Kühn KU, Maier W, Wagner M. Impaired sensorimotor gating of the acoustic startle response in the prodrome of schizophrenia. *Biol Psychiatry* 2008; **64**: 766–73.

29 Frommann I, Brinkmeyer J, Ruhrmann S, Hack E, Brockhaus-Dumke A, Bechdolf A, et al. Auditory P300 in individuals clinically at risk for psychosis. *Int J Psychophysiol* 2008; **70**: 192–205.

30 Job DE, Whalley HC, McConnell S, Glabus M, Johnstone EC, Lawrie SM. Structural gray matter differences between first-episode schizophrenics and normal controls using voxel-based morphometry. *Neuroimage* 2002; **17**: 880–9.

31 Lawrie SM, Whalley HC, Abukmeil SS, Kestelman JN, Donnelly L, Miller P, et al. Brain structure, genetic liability, and psychotic symptoms in subjects at high risk of developing schizophrenia. *Biol Psychiatry* 2001; **49**: 811–823.

33 Häfner H, Maurer K, Ruhrmann S, Bechdolf A, Klosterkötter J, Wagner M, et al. Early detection and secondary prevention of psychosis: facts and visions. *Eur Arch Psychiatry Clin Neurosci* 2004; **254**: 117–28.

33 Kojoh K, Hirasawa S. The Bonn Scale for the Assessment of Basic Symptoms (BSABS). *Arch Psychiatr Diagn Clin Eval* 1990; **4**: 587–97.

34 Schultze-Lutter F, Ruhrmann S, Picker H, von Reventlow HG, Daumann B, Brockhaus-Dumke A, et al. Relationship between subjective and objective cognitive function in the early and late prodrome. *Br J Psychiatry* 2007; **191** (suppl 51): s43–51.

35 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorder (4th edn) (DSM–IV)*. APA, 1994.

36 Schultze-Lutter F, Ruhrmann S, Picker H, von Reventlow HG, Brockhaus-Dumke A, Klosterkötter J. Basic symptoms in early psychotic and depressive disorders. *Br J Psychiatry* 2007; **191** (suppl 51): s31–7.

37 Lehrl S. *Mehrfachwahl-Wortschatz-Intelligenztest MWT-B* (5th edn). Spitta Verlag, 2005.

38 Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987; **13**: 261–76.

39 Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979; **134**: 382–9.

40 World Health Organization. *The ICD–10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. WHO, 1992.

41 Ashburner J, Friston KJ. Unified segmentation. *Neuroimage* 2005; **26**: 839–51.

42 Bach Cuadra M, Cammoun L, Butz T, Cuisenaire O, Thiran JP. Comparison and validation of tissue modelization and statistical classification methods in T1-weighted MR brain images. *IEEE Trans Med Imaging* 2005; **24**: 1548–65.

43 Hayasaka S, Phan KL, Liberzon I, Worsley KJ, Nichols TE. Nonstationary cluster-size inference with random field and permutation methods. *Neuroimage* 2004; **22**: 676–87.

44 Worsley K, Marrett S, Neelin P, Vandal A, Evans KFA. A unified statistical approach for determining significant signals in images of cerebral activation. *Hum Brain Mapping* 1996; **4**: 58–73.

45 Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 2002; **15**: 273–89.

46 Yücel M, Wood SJ, Phillips LJ, Stuart GW, Smith DJ, Yung A, et al. Morphology of the anterior cingulate cortex in young men at ultra-high risk of developing a psychotic illness. *Br J Psychiatry* 2003; **182**: 518–24.

47 Pantelis C, Yücel M, Wood SJ, McGorry PD, Velakoulis D. Early and late neurodevelopmental disturbances in schizophrenia and their functional consequences. *Aust N Z J Psychiatry* 2003; **37**: 399–406.

48 Loranger AW. Sex difference in age at onset of schizophrenia. *Arch Gen Psychiatry* 1984; **41**: 157–61.

49 Maier W, Cornblatt BA, Merikangas KR. Transition to schizophrenia and related disorders: toward a taxonomy of risk. *Schizophr Bull* 2003; **29**: 693–701.

50 Wolf DH, Gur RC, Valdez JN, Loughead J, Elliott MA, Gur RE, et al. Alterations of frontotemporal connectivity during word encoding in schizophrenia. *Psychiatry Res* 2007; **154**: 221–32.

51 Weiss AP, Heckers S. Neuroimaging of declarative memory in schizophrenia. *Scand J Psychol* 2001; **42**: 239–50.

52 Brewer WJ, Francey SM, Wood SJ, Jackson HJ, Pantelis C, Phillips LJ, et al. Memory impairments identified in people at ultra-high risk for psychosis who later develop first-episode psychosis. *Am J Psychiatry* 2005; **162**: 71–8.

53 Wood SJ, Brewer WJ, Koutsouradis P, Phillips LJ, Francey SM, Proffitt TM, et al. Cognitive decline following psychosis onset: data from the PACE clinic. *Br J Psychiatry* 2007; **191** (suppl 51): s52–7.

54 Kuroki N, Shenton ME, Salisbury DF, Hirayasu Y, Onitsuka T, Ersner-Hershfield H, et al. Middle and inferior temporal gyrus gray matter volume abnormalities in first-episode schizophrenia: an MRI study. *Am J Psychiatry* 2006; **163**: 2103–10.

55 Onitsuka T, Shenton ME, Salisbury DF, Dickey CC, Kasai K, Toner SK, et al. Middle and inferior temporal gyrus gray matter volume abnormalities in chronic schizophrenia: an MRI study. *Am J Psychiatry* 2004; **161**: 1603–11.

56 Spencer MD, Moorhead TWJ, McIntosh AM, Stanfield AC, Muir WJ, Hoare P, et al. Grey matter correlates of early psychotic symptoms in adolescents at enhanced risk of psychosis: a voxel-based study. *Neuroimage* 2007; **35**: 1181–91.

57 Lymer GKS, Job DE, William T, Moorhead J, McIntosh AM, Owens DGC, et al. Brain–behaviour relationships in people at high genetic risk of schizophrenia. *Neuroimage* 2006; **33**: 275–85.

58 Rajarethinam R, DeQuardo JR, Miedler J, Arndt S, Kirbat R, Brunberg JA, et al. Hippocampus and amygdala in schizophrenia: assessment of the relationship of neuroanatomy to psychopathology. *Psychiatry Res* 2001; **108**: 79–87.

59 Shenton ME, Kikinis R, Jolesz FA, Pollak SD, LeMay M, Wible CG, et al. Abnormalities of the left temporal lobe and thought disorder in schizophrenia. A quantitative magnetic resonance imaging study. *N Engl J Med* 1992; **327**: 604–12.

60 Schultze-Lutter F, Ruhrmann S, Berning J, Maier W, Klosterkötter J. Basic symptoms and ultrahigh risk criteria: symptom development in the initial prodromal state. *Schizophr Bull* 2008; June 25 (epub ahead of print).

61 Goldstein JM, Seidman LJ, O'Brien LM, Horton NJ, Kennedy DN, Makris N, et al. Impact of normal sexual dimorphisms on sex differences in structural brain abnormalities in schizophrenia assessed by magnetic resonance imaging. *Arch Gen Psychiatry* 2002; **59**: 154–64.

62 Walder DJ, Seidman LJ, Makris N, Tsuang MT, Kennedy DN, Goldstein JM. Neuroanatomic substrates of sex differences in language dysfunction in schizophrenia: a pilot study. *Schizophr Res* 2007; **90**: 295–301.

63 Goldstein JM, Seidman LJ, Goodman JM, Koren D, Lee H, Weintraub S, et al. Are there sex differences in neuropsychological functions among patients with schizophrenia? *Am J Psychiatry* 1998; **155**: 1358–64.

64 Goldstein JM, Seidman LJ, Santangelo S, Knapp PH, Tsuang MT. Are schizophrenic men at higher risk for developmental deficits than schizophrenic women? Implications for adult neuropsychological functions. *J Psychiatr Res* 1994; **28**: 483–98.

65 Davatzikos C. Why voxel-based morphometric analysis should be used with great caution when characterizing group differences. *Neuroimage* 2004; **23**: 17–20.

66 Moorhead TWJ, Job DE, Spencer MD, Whalley HC, Johnstone EC, Lawrie SM. Empirical comparison of maximal voxel and non-isotropic adjusted cluster extent results in a voxel-based morphometry study of comorbid learning disability with schizophrenia. *Neuroimage* 2005; **28**: 544–52.

EXTRA CONTENT ONLINE