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


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 that may also be involved in the neurobiology of full-blown schizophrenia. 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.

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, structural alterations were identified in the temporal lobe, the anterior cingulate cortex and cerebellum. 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, and subsequent disease transition may be associated with additional longitudinal volume reductions in limbic, temporal and cerebellar regions compared with non-transition. Furthermore, ultra-high-risk individuals with a subsequent disease manifestation may have alterations in cingulate, limbic, perisylvian and intrasylvian structures already at baseline.

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 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. 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.

This prodromal concept has been challenged by a considerable overlap between prodromal symptoms and psychopathological phenomena found in the general population, 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 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 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.

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 with the Personal Assessment and Crisis Evaluation (PACE) criteria, described significant associations between an increased symptomatological proximity to overt psychosis and: reduced hippocampal volumes; a sensorimotor gating deficit; and decreased amplitudes of auditory evoked P300 potentials.

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, 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 vs. 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). 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); attenuated psychotic symptoms; and BLIPS as defined by the PACE criteria (Appendix).

The following recruitment criteria were identically implemented in all participating sites of the multicentre GRNS project and were employed by previous studies.

- **Exclusion criteria:**
  - At-risk mental state participants with a history of psychotic disorders in the first-degree relatives, or a 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, 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 vs. ARMS-NT participants.

- **Method:**
  - The ARMS-E group consisted of participants without attenuated psychotic symptoms and BLIPS, who had had >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, the ARMS-L sample comprised individuals with >1 attenuated psychotic symptom within the past 3 months, appearing several times per week and/or with >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.;
  - (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 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. Psychopathology was additionally rated with the Positive and Negative Syndrome Scale (PANSS) and Montgomery-Åsberg Depression Scales (MADRS).

- **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.** In participants meeting the transition criteria the diagnosis of schizophrenia-spectrum disorders was determined using the ICD-10 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
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 volumes into 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 was finished: by proportionally scaling each participant's modulated, normalised grey matter tissue map compared between samples by calculating the squared distance to voxel value in grey matter 104. 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 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.

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>ARMS–E</th>
<th>ARMS–L</th>
<th>P</th>
<th>ARMS–NT</th>
<th>ARMS–T</th>
<th>P</th>
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<tbody>
<tr>
<td>Sociodemographic variables</td>
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<td>n</td>
<td>75</td>
<td>20</td>
<td>26</td>
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<td></td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Age at scan, years; mean (s.d.)</td>
<td>25.1 (3.8)</td>
<td>25.6 (5.7)</td>
<td>24.8 (6.0)</td>
<td>NS5</td>
<td>25.9 (6.7)</td>
<td>22.4 (2.8)</td>
<td>&lt; 0.05</td>
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<tr>
<td>Gender (male/female), %</td>
<td>61.3/38.7</td>
<td>50.0/50.0</td>
<td>73.1/26.9</td>
<td>NS5</td>
<td>61.1/38.9</td>
<td>73.3/26.7</td>
<td>NS5</td>
</tr>
<tr>
<td>Handedness (right/left/ambidextrous), %</td>
<td>88.0/8.0/4.0</td>
<td>85.0/10.0/5.0</td>
<td>88.5/3.8/7.7</td>
<td>NS5</td>
<td>83.3/11.5/5.6</td>
<td>100.0/0.0/0.0</td>
<td>NS5</td>
</tr>
<tr>
<td>Educational years, mean (s.d.)</td>
<td>12.4 (1.8)</td>
<td>12.3 (0.9)</td>
<td>11.8 (1.4)</td>
<td>NS5</td>
<td>12.3 (1.0)</td>
<td>12.0 (1.2)</td>
<td>NS5</td>
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<td>Premorbid IQ, Global functioning and trait factors</td>
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<td>MWT-B, mean (s.d.)</td>
<td>–</td>
<td>110.1 (14.0)</td>
<td>104.7 (16.0)</td>
<td>NS5</td>
<td>113.4 (13.6)</td>
<td>109.2 (18.0)</td>
<td>NS5</td>
</tr>
<tr>
<td>GAF reduction &gt; 30</td>
<td>–</td>
<td>65.0</td>
<td>76.9</td>
<td>NS5</td>
<td>55.6</td>
<td>100.0</td>
<td>&lt; 0.05</td>
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<tr>
<td>Participants with first-degree relatives with psychiatric symptoms, %</td>
<td>–</td>
<td>1.0</td>
<td>19.2</td>
<td>NS5</td>
<td>17.6</td>
<td>26.7</td>
<td>NS5</td>
</tr>
<tr>
<td>Participants with first-degree relatives with affective psychoses, %</td>
<td>–</td>
<td>15.0</td>
<td>7.7</td>
<td>NS3</td>
<td>17.6</td>
<td>13.3</td>
<td></td>
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<tr>
<td>Participants with pre-/perinatal complications, %</td>
<td>–</td>
<td>31.3</td>
<td>36.0</td>
<td>NS5</td>
<td>31.3</td>
<td>40.0</td>
<td>NS5</td>
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<tr>
<td>Psychopathology, mean (s.d.)</td>
<td></td>
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<tr>
<td>Basic symptoms item count</td>
<td>–</td>
<td>2.5 (1.6)</td>
<td>3.5 (2.4)</td>
<td>NS4</td>
<td>2.4 (1.9)</td>
<td>3.3 (2.2)</td>
<td>NS5</td>
</tr>
<tr>
<td>Attenuated psychotic symptoms item count</td>
<td>–</td>
<td>0.0 (0.0)</td>
<td>1.6 (1.2)</td>
<td>–</td>
<td>0.4 (0.7)</td>
<td>1.5 (1.0)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>PANSS sum score</td>
<td>–</td>
<td>54.7 (11.3)</td>
<td>55.0 (20.5)</td>
<td>NS5</td>
<td>51.3 (11.2)</td>
<td>58.2 (22.1)</td>
<td>NS5</td>
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<tr>
<td>PANSS positive score</td>
<td>–</td>
<td>9.2 (3.1)</td>
<td>11.8 (3.9)</td>
<td>NS5</td>
<td>10.0 (2.4)</td>
<td>12.9 (4.5)</td>
<td>&lt; 0.05</td>
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<tr>
<td>PANSS negative score</td>
<td>–</td>
<td>14.7 (6.2)</td>
<td>14.6 (7.2)</td>
<td>NS5</td>
<td>12.9 (5.6)</td>
<td>16.3 (9.0)</td>
<td>NS5</td>
</tr>
<tr>
<td>MADRS sum score</td>
<td>–</td>
<td>18.6 (8.3)</td>
<td>14.9 (9.3)</td>
<td>NS5</td>
<td>17.1 (7.2)</td>
<td>11.1 (8.1)</td>
<td>NS5</td>
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<tr>
<td>Global anatomical parameters</td>
<td></td>
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<tr>
<td>Grey matter volume (mm3), mean (s.d.)</td>
<td>653.1 (73.6)</td>
<td>660.1 (62.7)</td>
<td>682.5 (76.8)</td>
<td>NS4</td>
<td>653.7 (60.6)</td>
<td>698.0 (52.6)</td>
<td>NS5</td>
</tr>
<tr>
<td>White matter volume (mm3), mean (s.d.)</td>
<td>523.2 (66.5)</td>
<td>527.7 (66.0)</td>
<td>530.0 (53.0)</td>
<td>NS4</td>
<td>526.8 (63.0)</td>
<td>530.2 (47.8)</td>
<td>NS5</td>
</tr>
<tr>
<td>Cerebrospinal fluid (mm3), mean (s.d.)</td>
<td>458.9 (98.6)</td>
<td>446.5 (97.6)</td>
<td>483.7 (90.8)</td>
<td>NS4</td>
<td>451.0 (97.6)</td>
<td>485.0 (97.8)</td>
<td>NS5</td>
</tr>
<tr>
<td>Total intracranial volume (mm3), mean (s.d.)</td>
<td>1635.2 (204.5)</td>
<td>1634.3 (182.8)</td>
<td>1692.6 (158.6)</td>
<td>NS4</td>
<td>1631.5 (177.8)</td>
<td>1713.1 (135.4)</td>
<td>NS5</td>
</tr>
<tr>
<td>Distance2 to voxel value in grey matter 105, mean (s.d.)</td>
<td>146.0 (9.1)</td>
<td>144.6 (8.8)</td>
<td>147.2 (13.1)</td>
<td>NS4</td>
<td>146.7 (8.6)</td>
<td>142.5 (7.9)</td>
<td>NS5</td>
</tr>
</tbody>
</table>

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.
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. and applied in Meisenzahl et al. 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. Then, a family-wise error (FWE) corrected cluster-size threshold of P < 0.05 was applied, producing a spatial extent threshold of 5.4 cm³ in design 1 and 5.2 cm³ 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.22 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 (χ² = 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 = 8404 voxels, P_{FWE} = 0.005; left: k = 9418, P_{FWE} = 0.003) that involved fusiform, superior, middle and inferior temporal gyr, 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 gyr.). 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 = 126 520, P_{FWE} < 0.0001) 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 gyrri (left cluster: \(k = 10,925, P_{\text{FWE}} < 0.001\), right cluster: \(k = 20,174, P_{\text{FWE}} < 0.001\)) 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 gyrri (largest effect size \(k = 22,017, P_{\text{FWE}} < 0.001\)). 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). 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 (largest effect size \(k = 121,860, P_{\text{FWE}} < 0.001\));
(b) the right medial temporal lobe covering the hippocampus, parahippocampus, amygdala and extending into the fusiform gyrus (largest effect size \(k = 9,400, P_{\text{FWE}} = 0.002\));
(c) the left perisylvian region, including the Rolandic operculum, postcentral, supramarginal and superior temporal gyrus (largest effect size \(k = 7,133, P_{\text{FWE}} = 0.013\));
(d) the right medial parietal cortex and precuneus (largest effect size \(k = 6,882, P_{\text{FWE}} = 0.016\));
(e) parts of the superior, middle and inferior temporal gyri (largest effect size \(k = 6,693, P_{\text{FWE}} = 0.018\)); and
(f) the right cerebellar hemisphere (largest effect size \(k = 5,598, P_{\text{FWE}} = 0.044\)).
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,9 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.7 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 processes may result in progressive structural brain changes that, 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.5–6,14 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 abnormalities in established schizophrenia,30,51 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,30,51 with more severe impairments being associated with the late at-risk mental state 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 participants with subsequent disease manifestation.5 Data from this 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. D5). 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. D5). 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 cortex2 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,30,51 with more severe impairments being associated with the late at-risk mental state 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.
groups, our main VBM analysis revealed patterns of neuro-anatomical 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 orbital frontal 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 abnormal-
ities, 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 abnormalities within these regions.

Alterations of the medial temporal lobe regions were previously reported in individuals with manifest schizophrenia8,10,54,55 and people with an at-risk mental state.2,3,5,6 In this context, Seidman et al2 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 al6 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,44 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,6,57 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 al2 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 process14,47 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.52 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 different 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 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 studies61 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.
without global functioning and trait markers: At-risk mental state participants with/without basic symptoms, with/without 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:

- thought interferences
- thought perseveration
- thought pressure
- thought blockages
- disturbances of receptive language, either heard or read
- decreased ability to discriminate between ideas and perception, fantasy and true memories
- unstable ideas of reference (subject-centrism)
- derealisation
- visual perception disturbances
- acoustic perception disturbances.

and/or

- showing a reduction in the Global Assessment of Functioning Score and/or
- 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:
  - hallucinations
  - delusions
  - formal thought disorder
  - gross disorganised or catatonic behaviour.

References
