



## No evidence for structural brain changes in young adolescents at ultra high risk for psychosis

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### ARTICLE INFO

#### Article history:

Received 14 August 2008

Received in revised form 7 April 2009

Accepted 12 April 2009

Available online 5 May 2009

#### Keywords:

Psychosis

Ultra high risk

Adolescence

Structural MRI

Voxelbased morphometry

Neurodevelopment

### ABSTRACT

**Objective:** The onset of psychosis is thought to be preceded by neurodevelopmental changes in the brain. However, the timing of these changes has not been established. We investigated structural brain changes in a sample of young adolescents (12–18 years) at ultra high-risk for psychosis (UHR).

**Methods:** Structural MRI data from young UHR subjects ( $n = 54$ ) and typically developing, matched controls ( $n = 54$ ) were acquired with a 1.5 Tesla scanner and compared.

**Results:** None of the measures differed between UHR subjects and controls.

**Conclusions:** Our results do not support the presence of gross neuroanatomical changes in young UHR subjects. This suggests that early changes are too subtle to detect with conventional imaging techniques. Therefore, changes observed in older cohorts may only onset later developmentally or occur secondary to prodromal symptoms.

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### 1. Introduction

A growing body of evidence suggests early neurodevelopmental brain changes preceding psychosis that are thought to progress into adolescence and adulthood (Rapoport et al., 2005). Recently, neuroimaging studies have focused on genetic and clinical high-risk cohorts to define the nature of these changes and to identify which of these may mark vulnerability for psychosis (Cannon, 2005). Subjects of clinical high-risk cohorts are commonly referred to as being at “ultra high-risk” (UHR), at “prodromal high-risk” or having an “at risk mental state” (ARMS) for psychosis. Several research groups have reported premorbid structural and functional brain changes in these cohorts. However, the timing of these changes is not established (for reviews see Pantelis et al., 2005; Wood et al., 2008): It is unclear whether they are truly premorbid or rather associated with prodromal symptoms.

A large volumetric MRI study in a UHR population aged 20 years reported smaller whole brain volume for subjects at UHR for psychosis compared to controls (Velakoulis et al., 2006), while several voxelbased morphometry (VBM) studies have shown changes in both gray (GM; Borgwardt et al., 2007, 2008; Meisenzahl et al., 2008; Pantelis et al., 2003) and white matter (WM; Walterfang et al., 2008; Witthaus et al., 2008) clusters in young adults (20–25 years) at UHR, predominantly in (pre-)frontal and temporal lobe areas. Interestingly, longitudinal reports suggest a differential development of changes in brain structure for individuals who convert to psychosis compared to those who do not (Pantelis et al., 2003; Walterfang et al., 2008). Reports to date of brain changes in subjects at UHR have focused on the age range of 20–25 years, when psychosis typically first occurs (Kessler et al., 2007). However, on average the earliest prodromal signs occur 4.8 years before onset (Hafner and Maurer, 2006). If neurobiological changes precede psychotic breakdown, these should be present in the at-risk period irrespective of the age at which psychotic breakdown occurs. To test whether this is indeed the case, we investigated brain structure volumes in a well-defined sample of young adolescents at UHR for psychosis (aged 12–18 years). We

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hypothesized that the UHR group would have smaller total brain volume and less GM and WM density in (pre-) frontal and medial temporal lobe areas.

## 2. Methods

### 2.1. Subjects

Fifty-four adolescents (52 Caucasian, 2 Asian) meeting at least 1 of 4 criteria for UHR were referred by general practitioners or other psychiatric clinics and included in this study. A further 54 matched typically developing adolescents (52 Caucasian, 1 Asian, 1 Hispanic) were included. There was also a subgroup of nineteen (35%) UHR patients that met criteria for pervasive developmental disorder – not otherwise specified (PDD-NOS; [American Psychiatric Association, 1994](#)). While these subjects in general showed behavioral problems at an earlier age ([Sprong et al., 2008](#)), they also met at least one of the UHR criteria in the last year.

A complete overview of UHR inclusion criteria is displayed in [Table 1](#). Briefly, the following criteria were applied: 1) attenuated positive symptoms, 2) brief, limited, or intermittent psychotic symptoms, 3) a 30% reduction in overall level of social, occupational/school-, and psychological functioning (i.e. GAF-score) in the past year, combined with a genetic risk of psychosis, and 4) two or more of a selection of nine basic symptoms, i.e. subjective deficits in cognitive, perceptual, and motor functioning. The first three inclusion criteria were assessed with the Structured Interview for Prodromal Syndromes (SIPS; [McGlashan et al., 2001](#)). The fourth inclusion criterion was assessed with the Bonn Scale for the Assessment of Basic Symptoms-Prediction List (BSABS-P; [Schultze-Lutter and Klosterkötter, 2002](#)). The numbers of individuals per UHR criterion are listed in [Table 2](#). The study design allowed for repeated measures to be performed at 9, 18 and 24 months after inclusion. At these assessments, subjects were re-evaluated to determine possible transition to psychosis according to SIPS criteria ([McGlashan et al., 2001](#)). Additionally, transition was retrospectively confirmed by clinical expert consensus (HvE, PS).

The subgroup of patients with PDD-NOS had received a prepubertal DSM-IV diagnosis of PDD-NOS ([American Psychiatric Association, 1994](#)), while also meeting criteria for MCDD (i.e. early childhood-onset impairments in affect regulation, social behavior/sensitivity, and cognition ([Cohen et al., 1994](#))). Children with PDD-NOS, MCDD subtype are at risk for developing psychotic disorders later in life ([Van Engeland and Van der Gaag, 1994](#)). The diagnosis was confirmed in a psychiatric examination including the Autism Diagnostic Interview-Revised ([Lord et al., 1994](#)), as well as a parent interview based on the diagnostic criteria for MCDD, which was developed for internal use at the UMC. Diagnoses were confirmed by expert clinical opinion (HvE, PS). A more detailed description of this UHR-subgroup is available elsewhere ([Sprong et al., 2008](#)).

Typically developing controls were recruited from secondary schools in the region of Utrecht. They were excluded if they met one of the UHR-criteria, if they or any first degree relative had a history of any psychiatric illness, or if there was a second-degree relative with a psychotic disorder. Exclusion criteria were assessed with SIPS & BSABS-P interviews and (parent) questionnaires.

**Table 1**  
Inclusion criteria.

<b>Attenuated positive symptoms (APS)</b>
Presence of at least one of the following SIPS symptoms with a score between 3 and 5 and an appearance of several times per week for a period of at least one week:
<ul style="list-style-type: none"> <li>• Unusual thought content/delusional ideas (P1)</li> <li>• Suspiciousness/persecutory ideas (P2)</li> <li>• Grandiosity (P3)</li> <li>• Perceptual abnormalities/hallucinations (P4)</li> <li>• Disorganized communication (P5)</li> <li>• Odd behaviour or appearance (D1)</li> </ul>
<b>Brief limited intermittent psychotic symptoms (BLIPS)</b>
Presence of at least one of the following PANSS symptoms that resolve spontaneously in 7 days and an interval between episodes with these symptoms of at least one week (two episodes of BLIPS separated by less than one week are considered as being one episode; if the total duration then becomes more than one week, the transition criterion is fulfilled):
<ul style="list-style-type: none"> <li>• Hallucinations (PANSS P3 score <math>\geq 4</math>)</li> <li>• Delusions (PANSS P1, P5, P6 score <math>\geq 4</math>)</li> <li>• Formal thought disorder (PANSS P2 score <math>\geq 4</math>)</li> </ul>
<b>Familial risk plus reduced functioning</b>
A change in mental state or functioning leading to a reduction of 30% or more on the Global Assessment of Functioning scale for at least one month within the last year compared to the highest level of previous functioning, plus at least one of the following risk indicators:
<ul style="list-style-type: none"> <li>• One first- or second-degree relative with a history of any DSM-IV psychotic disorder (not due to a medical factor or substance induced)</li> <li>• A schizotypal personality disorder of the index person according to DSM-IV</li> </ul>
<b>Basic symptoms</b>
Presence of at least two of the following symptoms from the cluster "cognitive disturbances" for more than one year, with a BSABS-P score $\geq 3$ during the last three months:
<ul style="list-style-type: none"> <li>• Inability to divide attention (A.8.4)</li> <li>• Thought interferences (C.1.1)</li> <li>• Thought pressure (C.1.3)</li> <li>• Thought blockages (C.1.4)</li> <li>• Disturbances of receptive speech (C.1.6)</li> <li>• Disturbances of expressive speech (C.1.7)</li> <li>• Disturbances of abstract thinking ("concretism"; C.1.16)</li> <li>• Unstable ideas of reference ("subject-centrism"; C.1.17)</li> <li>• Captivation of attention by details of the visual field (C.2.9)</li> </ul>

SIPS – Structured Interview for Prodromal Syndromes; PANSS – Positive and Negative Syndrome Scale; BSABS-P – Bonn Scale for the Assessment of Basic Symptoms – Prediction List.

In addition to the screening instruments a modified version of the revised self-report Schizotypal Personality Questionnaire (SPQ-R) was used to assess schizotypal personality traits ([Raine, 1991; Vollema and Hoijtink, 2000](#)).

All participants were aged between 12 and 18 years and none of them were psychotic at the time of inclusion in the study. Subjects were excluded if there was evidence for any past or present neurological disorder (e.g., epilepsy). Drug- and alcohol abuse were additional exclusion criteria, although patients were allowed to have a history of drug use if symptoms had also been present in the absence of drugs. Eleven patients reported having used drugs at least five times within the last year (all Marijuana and two patients with additional use of psychostimulants). Three of these patients were considered to be frequent users (at least once a week within the last month) at the time of assessment. Also, all individuals

had a level of verbal intellectual functioning (VIQ)  $\geq 75$ , as assessed with the Wechsler Intelligence Scales (Wechsler, 1997, 2002). All subjects signed an informed consent, and for those younger than 16, parents co-signed. Sample characteristics are summarized in Table 2.

## 2.2. MRI acquisition

Magnetic resonance images were acquired on a Philips Gyroscan (Philips Medical Systems, Best, the Netherlands) operating at 1.5 T. For volumetric measurements T1-weighted 3D fast-field echo scans with 1.5-mm contiguous coronal slices of the whole head (TE 4.6 ms; TR 30 ms; flip angle 30°; FOV 256 mm; in plane voxel size, 1 mm<sup>2</sup>) and T2-weighted dual-echo turbo spin-echo scans with 3.0-mm contiguous coronal

slices (TE1 14 ms; TE2 80 ms; TR 6350 ms; flip angle 90°; FOV, 256 mm; in plane voxel size 1 mm<sup>2</sup>) were acquired. In addition, T2-weighted dual echo turbo spin echo scans with 17 axial 5 mm slices and a 1.2 mm gap (TE1 9 ms, TE2 100 ms, flip angle 90°, FOV 250 mm, in plane voxel size 0.98 mm  $\times$  0.98 mm) were acquired for clinical neurodiagnostic evaluation.

## 2.3. MRI-processing

### 2.3.1. Volumetric measurements

MRI scans were coded to ensure rater blindness to subject identity and diagnosis and half of the scans were randomly flipped over the *y*-axis to ensure blindness to laterality. The processing pipeline has been described previously and included semi-automated assessment of intracranial volume, total brain volume, lateral ventricles, third ventricle and cerebellum, as well as fully automated assessment of gray (GM) and white matter (WM) volumes and the cortical lobes (Durstson et al., 2004; Palmen et al., 2005).

### 2.3.2. Voxelbased morphometry

GM and WM segments were created for individual MRI-scans in the automated pipeline described above (Schnack et al., 2001). For the voxelbased analyses, these segments were blurred using a 3D Gaussian kernel (FWHM = 8 mm), in order to gain statistical power. The voxel values of these blurred GM and WM segments reflect the local presence, or concentration, of GM and WM, respectively, and these images are referred to as 'density maps.'

In order to compare brain tissue at the same anatomical location in all subjects, the GM and WM segments were transformed into a standardized coordinate system. These transformations were calculated in two steps. First, the T1-weighted images were linearly transformed to the model brain, the previously determined 'most average' brain (Hulshoff Pol et al., 2001). In this linear step a joint entropy mutual information metric was optimized (Maes et al., 1997). In the second step nonlinear (elastic) transformations were calculated to register the linearly transformed images to the model brain up to a scale of 4 mm (FWHM), thus removing global shape differences between the brains, but retaining local differences. For this step the program ANIMAL (Collins et al., 1995) was used. The GM and WM density maps were now transformed to the model space by applying the concatenated linear and nonlinear transformations. Finally, the maps were resampled to voxels of size 2  $\times$  2  $\times$  2.4 mm<sup>3</sup>.

## 2.4. Statistical analysis

All statistical analyses were conducted using the SPSS statistical package, version 15.0 (SPSS Inc., Chicago, IL, USA). Chi-square and independent sample *t*-tests were used to assess differences in clinical and socio-demographic variables and brain volumes. Any significant differences were then further investigated *post hoc* with either non-parametric tests for 2 samples or independent-sample *t* tests (two-tailed). Cohen *d* standardized effect sizes were calculated from the pairwise comparisons. An effect size of 0.20 is typically regarded as small, 0.50 as moderate, and 0.80 as large. Separate analyses were also performed for UHR subjects that were included on the basis of criteria 4 and subjects with PDD-

**Table 2**  
Demographic data and characteristics.

	Ultra high risk subjects (n = 54)		Healthy comparison subjects (n = 54)		Statistic	p
	Mean $\pm$ SD		Mean $\pm$ SD			
Age at scan (years)	15.76 $\pm$ 2.05		15.75 $\pm$ 1.49		<i>t</i> = .04	<i>p</i> = .970
Total IQ	100.30 $\pm$ 13.38		107.11 $\pm$ 14.29		<i>t</i> = -2.56	<i>p</i> = .012
Height (cm)	173.60 $\pm$ 10.44		172.50 $\pm$ 9.07		<i>t</i> = .56	<i>p</i> = .576
Parental education (years)	13.46 $\pm$ 2.01		14.18 $\pm$ 2.42		<i>t</i> = -1.69	<i>p</i> = .095
SIPS total	25.3 $\pm$ 12.3		1.8 $\pm$ 2.8		<i>U</i> = 13.5	<i>p</i> < .001
- Positive symptoms	8.4 $\pm$ 3.7		0.6 $\pm$ 1.0		<i>U</i> = 43.0	<i>p</i> < .001
- Negative symptoms	6.0 $\pm$ 4.8		0.4 $\pm$ 1.1		<i>U</i> = 183.5	<i>p</i> < .001
- Disorganized symptoms	4.6 $\pm$ 3.9		0.3 $\pm$ 0.6		<i>U</i> = 237.0	<i>p</i> < .001
- General symptoms	6.2 $\pm$ 4.1		0.5 $\pm$ 1.2		<i>U</i> = 216.5	<i>p</i> < .001
BSABS-P total	21.6 $\pm$ 14.5		0.9 $\pm$ 1.3		<i>U</i> = 361.5	<i>p</i> < .001
- Cognitive disturbances	12.9 $\pm$ 8.3		0.7 $\pm$ 1.0		<i>U</i> = 120.5	<i>p</i> < .001
- Perceptual disturbances	7.6 $\pm$ 7.3		0.2 $\pm$ 0.5		<i>U</i> = 153.0	<i>p</i> < .001
- Motor disturbances	1.4 $\pm$ 2.2		0.0 $\pm$ 0.0		<i>U</i> = 729.0	<i>p</i> < .001
SPQ total	39.7 $\pm$ 19.7		13.2 $\pm$ 10.8		<i>U</i> = 486.0	<i>p</i> < .001
- Positive schizotypy	14.6 $\pm$ 8.3		4.4 $\pm$ 4.7		<i>U</i> = 418.0	<i>p</i> < .001
- Negative schizotypy	16.0 $\pm$ 9.4		7.0 $\pm$ 6.2		<i>U</i> = 612.0	<i>p</i> < .001
- Disorganization	9.1 $\pm$ 5.4		1.9 $\pm$ 2.1		<i>U</i> = 365.5	<i>p</i> < .001
GAF score	57.5 $\pm$ 14.8		93.2 $\pm$ 8.0		<i>U</i> = 76.5	<i>p</i> < .001
	N	%	N	%		
Male	33	61.1	27	50.0	$\chi^2 = 1.35$	<i>p</i> = .245
Right-handed	49	90.7	48	88.9	$\chi^2 = .88$	<i>p</i> = .645
Any medication	24	44.4				
Antipsychotic	12	22.2				
Antidepressant	11	20.4				
Others	10	18.5				
Prodromal state criteria						
Attenuated positive symptoms			48			80.0
Brief or intermittent psychotic symptoms			2			3.3
Genetic risk + reduced functioning			1			1.7
Basic symptoms			28			46.7

SIPS = Structured Interview for Prodromal Symptoms; BSABS-P = Bonn Scale for the Assessment of Basic Symptoms-Prediction list; SPQ = Schizotypal Personality Questionnaire, GAF = Global Assessment of Functioning.

NOS because subjects in these groups may potentially represent separate subgroups. For VBM, the same statistical analyses were carried out on regional GM and WM densities throughout the brain, but with covariates for age, gender and hand preference (right vs. non-right). A correction for multiple comparisons was carried out according to the false discovery rate ( $\alpha < 0.05$ , two-tailed), allowing for an overall 5% chance of false positives (Genovese et al., 2002). Finally, relationships between brain volumes and clinical symptom scores were examined with Spearman's rho. Here the  $p$  level was adjusted to  $p < .01$  to correct for multiple comparisons.

### 3. Results

#### 3.1. Sociodemographic and clinical parameters

Subjects were matched for age, gender, handedness, height and parental education (Table 2). Controls had significantly higher Total IQ (TIQ) scores than the UHR group ( $t = -2.56$ ,  $df = 106$ ,  $p < .012$ ). Clinical parameters differed between both groups ( $p < .001$ ), with the UHR-group reporting more symptoms and lower GAF-scores (Table 2). Fifty-one of 54 UHR subjects completed the eighteen months follow-up period at which transition to psychosis was determined. Two subjects had dropped out, as they felt assessments were too time-consuming and one subject had only been included less than a year previously. In total, seven out of 51 (14%) UHR subjects had converted to psychosis, of whom four had transitioned within the first year after inclusion (8%). For clinical parameters, converters scored higher than non-converters on SIPS total score ( $n = 54$ ,  $U = 78$ ,  $p < .026$ ) and disorganized symptoms ( $n = 54$ ,  $U = 86$ ,  $p < .042$ ).

#### 3.2. Brain volumes

There were no differences in brain volumes between the UHR and control group (Table 3). These results were unchanged when TIQ was included as a covariate in a General Linear Model analysis. Effect sizes were small to intermediate (range  $[d] = -.27-.31$ ). Subgroup analysis for patients with PDD-NOS (19) and patients fulfilling more than one UHR criterion yielded similar results. Given the current effect size for total brain ( $d = -.14$ ), a post-hoc power analysis showed that it would require a sample size of  $n > 1300$  to provide sufficient statistical power to detect a group difference of this magnitude.

#### 3.3. Voxelbased morphometry

There were no differences in gray or white matter density between the UHR and control groups. Exploratory analyses at more liberal statistical thresholds also showed no differences.

#### 3.4. Correlational analyses

There were no correlations between clinical parameters and brain volumes.

### 4. Discussion

The aim of the current study was to investigate whether structural brain changes are present in young adolescents at

**Table 3**

Brain volumes (cc) for individuals at ultra high risk and healthy comparison subjects.

	Ultra high risk subjects	Healthy comparison subjects	$t$ ( $df = 112$ )	$p$	Effect size ( $d$ )
Intracranium	1482.75 ± 117.27	1500.11 ± 140.12	-.70	.49	-.13
Total brain	1356.13 ± 110.96	1372.17 ± 120.43	-.72	.47	-.14
Cerebral gray matter	744.87 ± 64.95	758.51 ± 70.78	-.84	.40	-.20
Cerebral white matter	446.51 ± 54.30	450.26 ± 56.11	-.35	.73	-.07
Frontal lobe	298.06 ± 27.24	298.61 ± 29.00	-.10	.92	-.02
Frontal gray matter	189.89 ± 16.81	191.06 ± 17.95	-.35	.73	-.07
Frontal white matter	108.17 ± 12.69	107.55 ± 13.78	.24	.81	.05
Parietal lobe	214.29 ± 18.25	219.00 ± 20.64	-1.26	.21	-.24
Parietal gray matter	135.18 ± 10.89	138.15 ± 12.49	-1.32	.19	-.25
Parietal white matter	79.11 ± 10.70	80.85 ± 11.00	-.61	.54	-.16
Temporal lobe	217.87 ± 19.60	221.74 ± 19.03	-1.04	.30	-.20
Temporal gray matter	157.50 ± 14.20	160.34 ± 13.64	-1.06	.29	-.20
Temporal white matter	60.37 ± 9.10	61.40 ± 8.50	-.61	.54	-.12
Occipital lobe	112.44 ± 11.64	115.53 ± 15.13	-1.19	.24	-.23
Occipital gray matter	68.29 ± 7.71	70.57 ± 9.17	-1.40	.17	-.27
Occipital white matter	44.14 ± 6.44	44.96 ± 7.45	-.61	.54	-.12
Cerebellum	153.09 ± 13.38	152.37 ± 13.25	.28	.78	.05
Lateral ventricles	12.77 ± 6.65	11.61 ± 9.73	.72	.47	.14
Third ventricle	0.66 ± 0.34	0.57 ± 0.24	1.48	.14	.31

clinical high risk for psychosis. In our young UHR sample of adolescents aged 12–18 years, we find no evidence for gross or regional brain changes. Furthermore, we find no correlations between brain volumes and clinical symptoms.

These results suggest that the brain changes reported in older UHR populations (Borgwardt et al., 2007, 2008; Meisenzahl et al., 2008; Pantelis et al., 2003; Velakoulis et al., 2006; Walterfang et al., 2008; Witthaus et al., 2008) may only onset later developmentally or be secondary to prodromal symptoms that precede the onset of psychosis. Such symptoms are already present in our sample, but are not accompanied by structural brain changes. This interpretation of our data is supported by evidence from two other large studies showing no regional brain changes in relatively young UHR samples (Velakoulis et al., 2006; Berger et al., 2007). As such, any brain changes present in early adolescence may be too subtle to detect with conventional scanning procedures at this age (Wood et al., 2008). Other imaging techniques such as diffusion weighted MRI (DeLisi et al., 2006; Hoptman et al., 2008), or cortical pattern matching (Sun et al., 2009) may provide more sensitive measures to detect early changes.

Intriguingly, a few MRI-studies have examined young cohorts with established psychosis and have already shown brain changes in early adolescence (for a review see Arango et al., 2008). This suggests that at onset of psychosis an exacerbation of existing neuropathological changes may take place or that additional mechanisms may be affected, causing a more pronounced change of brain tissue than in the prodromal phase.

In this light it would be relevant to compare individuals where transition to psychosis takes place to those where it does not. However, the number of transitions ( $n=7$ ; 14%) was too low in this study, to allow for such comparisons. A possible explanation for our low conversion rate may be that our subjects are relatively unexposed to environmental risk factors associated with psychosis, such as unemployment, social isolation and cannabis (Reininghaus et al., 2008; Van Os et al., 2005). All subjects were still receiving some type of formal education at the time of assessment and/or were living with at least one parent/caretaker.

Although this study includes a relatively large cohort of young adolescents at risk for psychosis, there are several limitations that should be considered in interpreting the results. First, our cohort includes a different type of high-risk subject than those typically included in other studies: Our group consisted of young adolescents of whom most had already sought help (Sprong et al., 2008), while most UHR cohorts do not have a history of contact with the mental health services. Accordingly, a relatively high percentage of our subjects was already using some form of psychotropic medication (44.4%), half of whom were using antipsychotic drugs. Antipsychotic medication was primarily prescribed for impulse-regulation problems. It is important to note that our medicated subjects still met UHR inclusion criteria. However, it is possible that some of their symptoms were ameliorated as a result of their medication. Other studies have reported on largely unmedicated samples. Nonetheless, our inclusion criteria conform to those used by others (Simon et al., 2006) and therefore the phenotype is more or less comparable to other UHR studies in the literature. If medication has a protective effect in (pre-) psychosis, this may be reflected in our findings, although analyses including medication as a covariate did not confirm this: they yielded similar results to the overall analyses.

Second, our UHR sample included a subgroup of subjects with a diagnosis of PDD-NOS, MCDD subtype (35% of our UHR sample). The inclusion of these subjects could theoretically have introduced a sample bias. However, these individuals met full criteria for UHR and separate analysis of their data yielded results similar to the overall findings. As such, it seems unlikely that the inclusion of this group explains our results.

Finally, our groups were not matched for IQ, although both groups scored well within the normal range (85–115). Interestingly, IQ has been found to decline premorbidly in schizophrenia (Caspi et al., 2003). On average, converters in our study did show lower IQ scores at baseline (8 points), but this did not reach significance due to limited power.

In sum, our results do not support the presence of structural brain changes in young adolescents at clinical high risk for psychosis. They suggest that brain changes preceding psychosis may only onset later developmentally or be secondary to prodromal symptoms. Alternatively, changes may be too subtle to detect in adolescents, due to limitations of morphometric imaging techniques. Longitudinal imaging studies are needed to provide further insight into the developmental aspects of prepsychotic symptoms and their relationship to structural brain changes. Furthermore, they will permit the investigation of possible differential neurodevelopmental trajectories (Shaw et al., 2008) in high risk adolescents.

#### Role of funding source

This work was funded by a grant from ZonMw – the Netherlands organisation for health research and development. ZonMW had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

#### Contributors

Drs. Durston, van Engeland, Schothorst, and Mr. Ziermans conceived the idea and methodology of this study. Drs. Durston, Lahuis, Schothorst, Sprong and Mr. Ziermans were involved in subject recruitment. Drs. Lahuis, Schothorst, Sprong, van Engeland and Mr. Ziermans were involved in clinical and diagnostic assessments. Mr. Ziermans processed MRI images and wrote the manuscript. Dr. Durston and Mr. Ziermans conducted the statistical analyses. Drs. van Haren and Schnack and Ms. Nederveen provided technical support (processing). Dr. Durston contributed in the writing of the manuscript. All authors contributed to and have approved the final manuscript.

#### Conflict of interest

The authors have no competing financial interests to declare in relation to the current work.

#### Acknowledgements

The authors would like to thank Anneke J. Schouten and Petra W. Klaassen who assisted with collecting the data for our analysis.

#### References

- American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV). American Psychiatric Association, Washington DC.
- Arango, C., Moreno, C., Martinez, S., Parellada, M., Descio, M., Moreno, D., Fraguas, D., Gogtay, N., James, A., Rapoport, J., 2008. Longitudinal brain changes in early-onset psychosis. *Schizophr. Bull.* 34, 341–353.
- Berger, G.E., Wood, S.J., Velakoulis, D., Ang, A., Brewer, W.J., Phillips, L.J., Yung, A.R., Proffitt, T.M., Pantelis, C., McGorry, P.D., 2007. Ventricle volumes in emerging psychosis. A cross-sectional and longitudinal MRI study. *Eur. Psychiatr.* 22, S30–S31.
- Borgwardt, S.J., McGuire, P.K., Aston, J., Berger, G., Dazzan, P., Gschwandtner, U., Pfluger, M., D'Souza, M., Radue, E.W., Riecher-Rossler, A., 2007. Structural brain abnormalities in individuals with an at-risk mental state who later develop psychosis. *Br. J. Psychiatr., Suppl.* 51, s69–75.
- Borgwardt, S.J., McGuire, P., Fusar-Poli, P., Radue, E.W., Riecher-Rossler, A., 2008. Anterior cingulate pathology in the prodromal stage of schizophrenia. *Neuroimage* 39, 553–554.
- Cannon, T.D., 2005. Clinical and genetic high-risk strategies in understanding vulnerability to psychosis. *Schizophr. Res.* 79, 35–44.
- Caspi, A., Reichenberg, A., Weiser, M., Rabinowitz, J., Kaplan, Z., Knobler, H., Davidson-Sagi, N., Davidson, M., 2003. Cognitive performance in schizophrenia patients assessed before and following the first psychotic episode. *Schizophr. Res.* 65, 87–94.
- Cohen, D.J., Towbin, K.E., Mayes, L., Volkmar, F., 1994. Developmental psychopathology of Multiplex Developmental Disorder. In: Friedman, S.L., Haywood, H.C. (Eds.), *Developmental Follow-up: Concepts, Genes, Domains, and Methods*. Academic Press Inc., New York, pp. 155–179.
- Collins, D.L., Holmes, C.J., Peters, T.M., Evans, A.C., 1995. Automatic 3-D model-based neuroanatomical segmentation. *Hum. Brain Mapp.* 3, 190–208.
- DeLisi, L.E., Szulc, K.U., Bertisch, H.C., Majcher, M., Brown, K., Bappal, A., Branch, C.A., Ardekani, B.A., 2006. Early detection of schizophrenia by diffusion weighted imaging. *Psychiatry Res.* 148, 61–66.
- Durston, S., Hulshoff Pol, H.E., Schnack, H.G., Buitelaar, J.K., Steenhuis, M.P., Minderaa, R.B., Kahn, R.S., van Engeland, H., 2004. Magnetic resonance imaging of boys with attention-deficit/hyperactivity disorder and their unaffected siblings. *J. Am. Acad. Child Adolesc. Psych.* 43, 332–340.
- Genovese, C.R., Lazar, N.A., Nichols, T., 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage* 15, 870–878.
- Hafner, H., Maurer, K., 2006. Early detection of schizophrenia: current evidence and future perspectives. *World Psychiatry* 5, 130–138.
- Hoptman, M.J., Nierenberg, J., Bertisch, H.C., Catalano, D., Ardekani, B.A., Branch, C.A., DeLisi, L.E., 2008. A DTI study of white matter microstructure in individuals at high genetic risk for schizophrenia. *Schizophr. Res.* 106, 115–124.
- Hulshoff Pol, H.E., Schnack, H.G., Mandl, R.C., van Haren, N.E., Koning, H., Collins, D.L., Evans, A.C., Kahn, R.S., 2001. Focal gray matter density changes in schizophrenia. *Arch. Gen. Psychiatry* 58, 1118–1125.

- Kessler, R.C., Amminger, G.P., Aguilar-Gaxiola, S., Alonso, J., Lee, S., Ustun, T.B., 2007. Age of onset of mental disorders: a review of recent literature. *Curr. Opin. Psychiatry* 20, 359–364.
- Lord, C., Rutter, M., Le Couteur, A., 1994. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J. Autism Dev. Disord.* 24, 659–685.
- Maes, F., Collignon, A., Vandermeulen, D., Marchal, G., Suetens, P., 1997. Multimodality image registration by maximization of mutual information. *IEEE Trans. Med. Imag.* 16, 187–198.
- McGlashan, T.H., Miller, T.J., Woods, S.W., 2001. Structured Interview for Prodromal Syndromes (version 3.0). PRIME Research Clinic, Yale School of Medicine, New Haven.
- Meisenzahl, E.M., Koutsouleris, N., Gaser, C., Bottlender, R., Schmitt, G.J., McGuire, P., Decker, P., Burgermeister, B., Born, C., Reiser, M., Moller, H.J., 2008. Structural brain alterations in subjects at high-risk of psychosis: a voxel-based morphometric study. *Schizophr. Res.* 102, 150–162.
- Palmen, S.J., Hulshoff Pol, H.E., Kemner, C., Schnack, H.G., Durston, S., Lohuis, B.E., Kahn, R.S., Van Engeland, H., 2005. Increased gray-matter volume in medication-naïve high-functioning children with autism spectrum disorder. *Psychol. Med.* 35, 561–570.
- Pantelis, C., Velakoulis, D., McGorry, P.D., Wood, S.J., Suckling, J., Phillips, L.J., Yung, A.R., Bullmore, E.T., Brewer, W., Soulsby, B., Desmond, P., McGuire, P.K., 2003. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet* 361, 281–288.
- Pantelis, C., Yucel, M., Wood, S.J., Velakoulis, D., Sun, D., Berger, G., Stuart, G. W., Yung, A., Phillips, L., McGorry, P.D., 2005. Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. *Schizophr. Bull.* 31, 672–696.
- Raine, A., 1991. The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophr. Bull.* 17, 555–564.
- Rapoport, J.L., Addington, A.M., Frangou, S., Psych, M.R., 2005. The neurodevelopmental model of schizophrenia: update 2005. *Mol. Psychiatry* 10, 434–449.
- Reininghaus, U.A., Morgan, C., Simpson, J., Dazzan, P., Morgan, K., Doody, G.A., Bhugra, D., Leff, J., Jones, P., Murray, R., Fearon, P., Craig, T.K., 2008. Unemployment, social isolation, achievement–expectation mismatch and psychosis: findings from the AESOP Study. *Soc. Psychiatry Psychiatr. Epidemiol.* 43, 743–754.
- Schnack, H.G., Hulshoff Pol, H.E., Baare, W.F., Staal, W.G., Viergever, M.A., Kahn, R.S., 2001. Automated separation of gray and white matter from MR images of the human brain. *Neuroimage* 13, 230–237.
- Schultze-Lutter, F., Klosterkötter, J., 2002. Bonn Scale for the Assessment of Basic Symptoms-Prediction list (BSABS-P). University of Cologne, Cologne.
- Shaw, P., Kabani, N.J., Lerch, J.P., Eckstrand, K., Lenroot, R., Gogtay, N., Greenstein, D., Clasen, L., Evans, A., Rapoport, J.L., Giedd, J.N., Wise, S.P., 2008. Neurodevelopmental trajectories of the human cerebral cortex. *J. Neurosci.* 28, 3586–3594.
- Simon, A.E., Dvorsky, D.N., Boesch, J., Roth, B., Isler, E., Schueler, P., Petralli, C., Umbricht, D., 2006. Defining subjects at risk for psychosis: a comparison of two approaches. *Schizophr. Res.* 81, 83–90.
- Sprong, M., Becker, H.E., Schothorst, P.F., Swaab, H., Ziermans, T.B., Dingemans, P.M., Linszen, D., van Engeland, H., 2008. Pathways to psychosis: a comparison of the pervasive developmental disorder subtype Multiple Complex Developmental Disorder and the “At Risk Mental State”. *Schizophr. Res.* 99, 38–47.
- Sun, D., Philips, L., Velakoulis, D., Yung, A., McGorry, P.D., Wood, S.J., van Erp, T.G., Thompson, P.M., Toga, A.W., Cannon, T.D., Pantelis, C., 2009. Progressive brain structural changes mapped as psychoses develops in ‘at risk’ individuals. *Schizophr. Res.* 108, 85–92.
- Van Engeland, H., Van der Gaag, R.J., 1994. MCDD in childhood: a precursor of schizophrenic spectrum disorders. *Schizophr. Res.* 11, 197.
- Van Os, J., Krabbendam, L., Myin-Germeys, I., Delespaul, P., 2005. The schizophrenia environment. *Curr. Opin. Psychiatry* 18, 141–145.
- Velakoulis, D., Wood, S.J., Wong, M.T., McGorry, P.D., Yung, A., Phillips, L., Smith, D., Brewer, W., Proffitt, T., Desmond, P., Pantelis, C., 2006. Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. *Arch. Gen. Psychiatry* 63, 139–149.
- Vollema, M.G., Hoijtink, H., 2000. The multidimensionality of self-report schizotypy in a psychiatric population: an analysis using multidimensional Rasch models. *Schizophr. Bull.* 26, 565–575.
- Walterfang, M., McGuire, P.K., Yung, A.R., Phillips, L.J., Velakoulis, D., Wood, S.J., Suckling, J., Bullmore, E.T., Brewer, W., Soulsby, B., Desmond, P., McGorry, P.D., Pantelis, C., 2008. White matter volume changes in people who develop psychosis. *Br. J. Psychiatry* 193, 210–215.
- Wechsler, D., 1997. Wechsler Adult Intelligence Scale-III NL: Afnam e scoringshandleiding [Manual]. The Psychological Corporation Ltd. Harcourt Publishers.
- Wechsler, D., 2002. Wechsler Intelligence Scale for Children-III NL: Handleiding en verantwoording [Manual]. The Psychological Corporation Ltd. Harcourt Assessment.
- Witthaus, H., Brune, M., Kaufmann, C., Bohner, G., Ozgurda, S., Gudlowski, Y., Heinz, A., Klingebiel, R., Juckel, G., 2008. White matter abnormalities in subjects at ultra high-risk for schizophrenia and first-episode schizophrenic patients. *Schizophr. Res.* 102, 141–149.
- Wood, S.J., Pantelis, C., Velakoulis, D., Yucel, M., Fornito, A., McGorry, P.D., 2008. Progressive changes in the development toward schizophrenia: studies in subjects at increased symptomatic risk. *Schizophr. Bull.* 34, 322–329.