Progressive Structural Brain Changes During Development of Psychosis

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Background: Ultra-high risk (UHR) for psychosis has been associated with widespread structural brain changes in young adults. The onset of these changes and their subsequent progression over time are not well understood. *Methods:* Rate of brain change over time was investigated in 43 adolescents at UHR for psychosis compared with 30 healthy controls. Brain volumes (total brain, gray matter, white matter [WM], cerebellum, and ventricles), cortical thickness, and voxel-based morphometry were measured at baseline and at follow-up (2 y after baseline) and compared between UHR individuals and controls. Post hoc analyses were done for UHR individuals who became psychotic ($N = 8$) and those who did not ($N = 35$). *Results:* UHR individuals showed a smaller increase in cerebral WM over time than controls and more cortical thinning in the left middle temporal gyrus. Post hoc, a more pronounced decrease over time in total brain and WM volume was found for UHR individuals who became psychotic relative to controls and a greater decrease in total brain volume than individuals who were not psychotic. Furthermore, UHR individuals with subsequent psychosis displayed more thinning than controls in widespread areas in the left anterior cingulate, precuneus, and temporo-parieto-occipital area. Volume loss in the individuals who developed psychosis could not be attributed to medication use. *Conclusion:* The development of psychosis during adolescence is associated with progressive structural brain changes around the time of onset. These changes cannot be attributed to (antipsychotic) medication use and are therefore likely to reflect a pathophysiological process related to clinical manifestation of psychosis.

Key words: ultra-high risk/structural MRI/longitudinal/adolescence

Introduction

Although it is now widely accepted that psychosis is accompanied by structural brain abnormalities, the debate about the timing and progressive nature of these abnormalities is ongoing.[1] Recent findings suggest that early brain changes are likely to develop simultaneously with behavioral alterations around the time of disease onset.[2–4] However, to understand the pathophysiological nature of these changes, it is important to monitor individuals at elevated risk for psychosis over time and compare them with typically developing controls.

Individuals at risk for developing psychosis are commonly referred to as being at "ultra-high risk" (UHR) for psychosis or having an "at-risk mental state." Participants are typically included using a "close-in" strategy[5] based on a predefined set of subthreshold, clinical symptoms and are subsequently followed up over time to monitor possible transition to psychosis. In general, transition rates are high using this type of design (30%–40% within 2 y)[6], permitting the observation of brain changes in close proximity to onset of the disease.

Over the past decade, an increasing number of neuroimaging studies have investigated potential differences between UHR individuals and typically developing controls in brain structure, predominantly using cross-sectional neuroimaging designs. Generally, these studies have reported structural brain changes in UHR individuals, in particular for individuals who subsequently develop psychosis.[7–25] However, several studies failed to find such differences in brain structure, including results from the largest study to date (135 UHR individuals), investigating total brain and hippocampal volume.[26–30] In addition to the cross sectional studies, 6 longitudinal magnetic resonance imaging (MRI) studies have been published (see table 1), reporting progressive, accelerated loss of gray matter (GM), and reduced white matter (WM) growth in frontal and temporal cortices around

Table 1. Longitudinal Structural MRI Studies on Subjects with Ultra-High Risk (UHR) for Psychosis

Authors	N	Gender	Age (SD)	Measures of Interest	Results
Melbourne, Australia Pantelis et al[32]	10 UHR-P	m = 30%	T1: 18.9 (4.5)	VBM:	UHR-P < baseline in cerebellum (L) cingulate gyrus (L + R), parahippocampal/ fusiform gyri (L), orbital frontal cortex (L)
			T2: 20.0 (4.5)	GM	UHR-P > baseline in cuneus (R)
	11 UHR-NP	m = 36%	T1: 20.5 (3.7)		UHR-NP < baseline in cerebellum (L)
			T2: 22.3 (4.0)		
Walterfang et al[36]	10 UHR-P	m = 30%	T1: 18.9 (4.5)	VBM:	UHR-P < baseline in fronto-occipital fasciculus (L)
			T2: 20.0 (4.5)	WM	
	11 UHR-NP	m = 36%	T1: 20.5 (3.7)		UHR-P > baseline in posterior cerebellum (L + R)
			T2: 22.3 (4.0)		UHR-NP > baseline in posterior cerebellum (L)
Sun et al[33]	12 UHR-P	m = 58%	T1: 19.5 (5.1)	Cortical pattern matching:	UHR-P > UHR-NP in prefrontal region (R)
			T2: 20.7 (5.2)		
	23 UHR-NP	m = 52%	T1: 20.2 (4.0)	Brain surface contraction	
			T2: 21.6 (4.0)		
Takahashi et al[34]	12 UHR-P	m = 58%	T1: 19.5 (5.1)	Volumetric ROI: STG	FEP and UHR-P < UHR-NP and controls in % GM reduction of planum polare, planum temporale, and caudal STG
			T2: 20.7 (5.2)		
	23 UHR-NP	m = 52%	T1: 20.2 (4.0)		
			T2: 21.6 (4.0)		
	23 FEP	m = 70%	T1: 21.6 (3.5)		FEP < all groups in % GM reduction of Heschl gyrus (L)
			T2: 23.6 (4.0)		
	22 controls	m = 55%	T1: 22.0 (4.7)		
			T2: 24.1 (4.9)		
Takahashi et al[35]	11 UHR-P	m = 55%	T1: 19.5 (5.3)	Volumetric ROI: GM insular cortex	UHR-P > UHR-NP and controls in % GM reduction
			T2: 20.7 (5.4)		
	20 UHR-NP	m = 55%	T1: 20.3 (4.3)		
			T2: 27.7 (4.3)		
	20 controls	m = 60%	T1: 21.6 (4.7)		
			T2: 23.7 (5.0)		
Basel, Switzerland Borgwardt et al[31]	10 UHR-P	m = 70%	T1: 25.2 (6.7)	VBM:	UHR-P < baseline in orbitofrontal, superior frontal, inferior temporal, medial, and superior parietal cortex
			T2: 28.1 (6.5)	GM	
	10 UHR-NP	m = 58%	T1: 24.2 (6.1)		
			T2: 28.3 (6.4)		

Note: N, number of participants; UHR, Ultra-High Risk; UHR-P, UHR patients who developed psychosis; UHR-NP, UHR patients who did not develop psychosis; m, male; T1, baseline assessment; T2, repeated assessment; VBM, voxel-based morphometry; GM, gray matter; (L), left; (R), right; (L+R), left and right; WM, white matter; FEP, patients with first episode psychosis; ROI, region of interest; STG, superior temporal gyrus.

the onset of psychosis.[31–36] However, only 2 of these studies, focusing on regional volumes of the insula and superior temporal gyrus (STG), included typically developing controls. Furthermore, the contribution of (antipsychotic) medication to the observed brain changes over time remains elusive.[34] UHR individuals are typically unmedicated at baseline and those who become psychotic are usually put on an antipsychotic regimen postonset but preceding the repeat scan. This treatment policy makes it difficult to distinguish between medication- vs disorder-related effects on the developing brain.

Interestingly, the age range of UHR individuals across study sites varies considerably (mean age range: 15.8–27.9 y) with a majority of studies including both adolescent and adult individuals. However, differential maturational trajectories for various brain regions have previously been identified[37,38] and should be taken into account when interpreting disorder-related brain changes during adolescence. For example, individuals with early-onset schizophrenia (defined as onset prior to age 18) show less pronounced changes in brain areas that are affected in childhood onset (defined as onset prior to age 13 y) and adult schizophrenia populations, suggesting that a process unique to adolescent development may be involved.[39] Additionally, in an earlier MRI study[30], we found no evidence for structural changes in adolescents at risk for psychosis between the ages of 12 and 18 years, contrary to earlier findings in older populations.

In the current study, we tracked brain development longitudinally in a sample of adolescents at UHR for

psychosis. The primary objective was to investigate the rate of brain change between these individuals and typically developing adolescents. Individuals were assessed with anatomical MRI scanning twice with a 2-year interval, and 3 complementary methods were used to analyze the data: region of interest, voxel-based morphometry (VBM), and cortical thickness. Post hoc analyses were performed for individuals who had developed psychosis (UHR-P) and those who had not (UHR-NP) over the 2-year follow-up period. We hypothesized that clinical high risk for psychosis would be associated with increased GM loss and reduced WM growth over the 2-year interval compared with controls, in particular in frontal and temporal areas.

Methods

Design

This study is part of the Dutch Prediction of Psychosis Study, a longitudinal project that was approved by the Dutch Central Committee on Research Involving Human Subjects. At baseline (T1), all individuals were between 12 and 18 years of age and were included after informed consent was given. Individuals younger than 18 years of age signed for assent, while their parents signed for informed consent. Individuals aged 18 years or older signed for informed consent themselves. MRI scans were acquired at T1 and follow-up (T2), after 2 years. Clinical status was evaluated at 3 follow-up assessments (9, 18, and 24 mo after inclusion) to determine possible transition to psychosis according to criteria of the Structured Interview for Prodromal Symptoms (SIPS).[40] All assessments were performed at University Medical Center Utrecht in Utrecht, the Netherlands.

Participants

At T1, all UHR individuals were referred to the study by general practitioners or other regional psychiatric clinics. Typically developing controls were recruited from secondary schools in the region of Utrecht, the Netherlands. Of the 108 participants recruited in our original MRI study[30] (54 UHR and 54 typically developing adolescents), 73 (43 UHR individuals and 30 typically developing adolescents) were included at T2. Reasons for discontinuation were as follows: (1) assessments were considered too time consuming by the individual (8 UHR individuals and 19 controls), (2) the individual could no longer be contacted (3 UHR individuals and 1 control), (3) the individual met exclusion criteria at T2 (2 controls), and (4) the individual had metal braces that prevented the use of a second scan (2 controls). Individuals included at both time points did not differ from those who discontinued in terms of their clinical or demographic characteristics.

UHR status was defined by meeting at least 1 of 4 criteria for UHR at T1, which have previously been published[30] and are similar to frequently used criteria for UHR.[6] Briefly, the first 3 inclusion criteria were assessed using the SIPS: (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 (ie global assessment of functioning [GAF]) in the past year, combined with a genetic risk of psychosis. The fourth inclusion criterion was assessed using the Bonn Scale for the Assessment of Basic Symptoms—Prediction List[41] (BSABS-P): (4) 2 or more of a selection of 9 basic symptoms, such as subjective deficits in cognitive, perceptual, and motor functioning. A table with the number of participants per UHR criterion is provided in the supplementary materials.

Presence of a psychotic transition during follow-up was determined by use of the SIPS. Definition of a psychotic syndrome according to SIPS standards refers to psychotic symptoms of particular intensity (eg delusional conviction) and frequency or duration ($\geq$1 h/d for $\geq$4 d/wk during the past month) or of particular impact (seriously disorganizing or dangerous) designed to operationalize the threshold for a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV)[42] Axis I psychotic disorder diagnosis.[43] Chart reviews were used to retrospectively confirm psychotic transition by clinical expert consensus (Herman van Engeland, Patricia Schothorst), and subjects were subsequently diagnosed according to DSM guidelines.

Controls were excluded if they met one of the UHR criteria, if they or a first-degree relative had a history of psychiatric disorder, or if they had a second-degree relative with a psychotic disorder. Exclusion criteria were assessed using SIPS and BSABS-P interviews and (parent) questionnaires. Additionally, both control and UHR individuals were excluded if there was evidence for any past or present neurological disorder (eg epilepsy). Drug and alcohol abuse were additional exclusion criteria, although UHR subjects were permitted a history of drug use, if symptoms had also been present in the absence of drugs. Alcohol and drug use were assessed with sections J and L of the composite international diagnostic interview.[44] At T1, no individuals reported alcohol-related problems in the last month. Four UHR individuals reported frequent use of cannabis in the last month, one of whom had also been using psychostimulants. Finally, individuals were excluded if they had a level of verbal intellectual functioning <75, as assessed at T1 using the Wechsler Intelligence Scales.[45,46]

Group characteristics for UHR individuals and controls are listed in table 2. In total, 7 of 43 (16%) UHR individuals had experienced a psychotic transition at T2. An additional individual was considered borderline psychotic at T2 assessment and showed further clinical deterioration until 10 months after the second scan, as

Table 2. Demographics and Symptom Scores for Controls and UHR Subjects, Separated into Subgroups With and Without Transition to Psychosis

	Controls (n = 30)	UHR (n = 43)	UHR-NP (n = 35)	UHR-P (n = 8)	Controls vs UHR	Controls vs UHR-NP vs UHR-P
Sex, M/F (% M)	15/15 (50)	29/14 (67)	22/13 (63)	7/1 (88)	$\chi^2 = 2.25, P = .13$	$\chi^2 = 3.90, P = .14$
Handedness, R/L/M (% R)	26/2/2 (87)	38/3/2 (88)	31/2/2 (89)	7/1/0 (88)	$\chi^2 = 0.39, P = .97$	$\chi^2 = 1.13, P = .92$
Premorbid IQ	110.0 (13.2)	101.8 (13.4)	103.5 (13.5)	94.4 (11.1)	$F = 6.61, P = .01$	$F = 4.94, P = .01$[a]
Parental education[b]	14.5 (2.3)	13.7 (2.0)	13.9 (2.0)	12.9 (1.8)	$F = 1.74, P = .16$	$F = 1.89, P = .18$
Height T1, cm[c]	173.6 (9.2)	173.5 (11.0)	172.3 (11.2)	177.6 (9.9)	$F = 0.00, P = .96$	$F = 0.85, P = .43$
Height T2, cm[d]	176.3 (9.2)	178.3 (11.2)	177.4 (11.2)	182.4 (10.7)	$F = 0.65, P = .42$	$F = 1.08, P = .35$
Age at T1 scan, y	15.9 (1.4)	15.6 (2.2)	15.3 (2.1)	16.8 (2.2)	$F = 0.55, P = .46$	$F = 2.22, P = .12$
Age at T2 scan, y	18.0 (1.4)	17.6 (2.2)	17.3 (2.1)	18.8 (2.2)	$F = 0.67, P = .38$	$F = 2.51, P = .12$
Days between scans	742 (58)	723 (73)	720 (76)	738 (59)	$F = 1.43, P = .24$	$F = 0.93, P = .40$
Age at onset, y	NA	NA	NA	17.7 (2.6)	NA	NA
Days between onset and T1 scan	NA	NA	NA	358 (283)	NA	NA
Days between onset[e] and T2 scan	NA	NA	NA	478 (168)	NA	NA
SIPS total score at intake	1.4 (1.8)	24.7 (12.9)	23.1 (12.9)	31.6 (10.6)	$U = 0.0, P < .001$	$\chi^2 = 54.52, P < .001$[g,h]
SIPS total score at follow-up	3.3 (3.7)	17.0 (10.9)	14.9 (9.5)	25.9 (12.2)	$U = 124.5, P < .001$	$\chi^2 = 36.86, P < .001$[g,h]
BSABS total score at intake[f]	1.0 (1.4)	20.5 (15.2)	19.6 (13.8)	24.3 (21.6)	$U = 30.0, P < .001$	$\chi^2 = 46.73, P < .001$[g]
BSABS total score at follow-up	0.6 (0.8)	6.4 (9.2)	4.8 (6.8)	13.3 (14.7)	$U = 258.5, P < .001$	$\chi^2 = 25.95, P < .001$[g,h]
GAF score at intake	93.3 (6.7)	59.0 (15.2)	59.0 (15.4)	58.8 (15.3)	$U = 30.5, P < .001$	$\chi^2 = 47.99, P < .001$[g,h]
GAF score at follow-up	89.7 (8.3)	61.2 (11.6)	62.9 (11.3)	53.4 (9.7)	$U = 0.0, P < .001$	$\chi^2 = 47.52, P < .001$[g]
Medication T1, n (%)	NA				NA	
Any		21	19	2		$\chi^2 = 2.24, P < .14$[i]
Atypical antipsychotic		10 (23)	10 (29)	0 (0)		$\chi^2 = 2.98, P < .08$[i]
Mood stabilizer		9 (21)	7 (20)	2 (25)		$\chi^2 = 0.10, P < .75$[i]
Psychostimulant		6 (14)	6 (17)	0 (0)		$\chi^2 = 1.59, P < .21$[i]
Anxiolytic		3 (7)	2 (6)	0 (0)		$\chi^2 = 0.46, P < .50$[i]
Other		3 (7)	3 (9)	0 (0)		$\chi^2 = 0.74, P < .39$[i]
Medication T2, n (%)	NA				NA	
Any		21	18	3		$\chi^2 = 0.51, P < .48$[i]
Atypical antipsychotic		9 (21)	7 (20)	2 (25)		$\chi^2 = 0.10, P < .75$[i]
Mood stabilizer		9 (21)	7 (20)	2 (25)		$\chi^2 = 0.10, P < .75$[i]
Psychostimulant		8 (19)	8 (23)	0 (0)		$\chi^2 = 2.25, P < .13$[i]
Anxiolytic		0 (0)	0 (0)	0 (0)		NA
Other		3 (7)	2 (6)	1 (13)		$\chi^2 = 0.46, P < .50$[i]

Note: Abbreviations are explained in the first footnote to table 1. M/F, male/female; R/L/M, right/left/mixed; NA, not applicable; SIPS, Structured Interview for Prodromal Symptoms; BSABS, Bonn Scale for the Assessment of Basic Symptoms; GAF, global assessment of functioning.
[a]Post hoc comparisons significant for control subjects vs UHR-P subjects: $P < .01$.
[b]Data not available for 1 control subject.
[c]Data not available for 2 control subjects and 5 UHR-NP subjects.
[d]Data not available for 2 UHR-NP.
[e]Data displayed for 7 subjects with transition diagnosed between T1 and T2.
[f]Data not available for 2 UHR-NP subjects and 1 UHR-P.
[g]Post hoc comparisons significant for controls vs UHR-NP and UHR-P: $P < .001$.
[h]Post hoc comparisons significant for UHR-NP and UHR-P: $P < .05$.
[i]Comparisons for UHR-NP vs UHR-P only.

reported by his caregivers and mental health specialists. After careful evaluation, this individual was considered psychotic according to research criteria at that time and was added to the group of converters in the statistical analyses. DSM-IV diagnoses were as follows: 295.10 schizophrenia, disorganized type (n = 1), 295.30 schizophrenia, paranoid subtype (n = 3), 295.70 schizoaffective disorder (n = 1), 296.04 bipolar I disorder (n = 1),

delusional disorder 297.1 (n = 1), 298.9 psychosis—not otherwise specified (n = 1). Details about medication use are given in tables 2 and 3. A number of UHR participants were already using (a low dose of) antipsychotic medication at T1, mostly for impulse regulation deficits. (Dis-)continuation of medication use at T2 was based on treatment decisions made by their individual clinicians. Information on the time between baseline scan and transition for UHR-P individuals is available in the supplementary materials.

MRI Acquisition and Processing

For all subjects, MRI data were acquired on one Philips Gyroscan (Philips Medical Systems, Best, the Netherlands) operating at 1.5 T. Details of the scan protocol are provided as supplementary material. Both the scanner and scan sequences were identical at T1 and T2 assessments.

Volumetric Measurements. MRI scans were coded to ensure rater blindness to subject identity and diagnosis. The processing pipeline has been described previously[47]

Table 3. Psychotropic Medication Use Specified for Ultra–High Risk (UHR) Individuals at Baseline and Follow-Up.

Sex	Age T1	Age T2	Medication T1	Medication T2
UHR-NP				
Female	12.3	14.1	Citalopram 20 mg	Citalopram 80 mg
Female	12.4	14.8	Risperidone 0.5 mg	
Female	14.2	16.2		
Female	14.6	16.7		
Female	15.7	17.8		
Female	15.8	17.8	Atomoxetine 60 mg	
Female	16.0	18.1		
Female	16.1	18.0		
Female	16.7	18.5	Citalopram 20 mg	Citalopram 10 mg
Female	16.8	18.8		
Female	17.7	19.6	Pimpamperone 40 mg, Paroxetine 30 mg	Pimpamperone 40 mg, citalopram 40 mg
Female	17.9	19.9	Fluoxetine 20 mg	Clomipramine 125 mg
Female	18.4	20.3	Fluoxetine 20 mg	
Male	12.3	14.3	Risperidone 1.5 mg	Risperidone 1.5 mg
Male	12.3	14.6	Risperidone 1.5 mg	Risperidone 1 mg
Male	12.4	14.4		
Male	12.5	14.5	Carbamazepine 200 mg	Methylphenidate 40 mg
Male	12.9	14.8	Fluoxetine 7 mg, methylphenidate 28 mg	Fluoxetine 13 mg, methylphenidate 18 mg
Male	13.3	15.3		
Male	13.3	15.4		
Male	13.8	15.9	Risperidone 1 mg, methylphenidate 30 mg	Methylphenidate 25 mg
Male	14.4	16.4	Risperidone 4 mg, methylphenidate 20 mg	Risperidone 2.5 mg, methylphenidate 30 mg
Male	14.5	16.0		
Male	14.5	16.7	Olanzapine 5 mg	Olanzapine 5 mg
Male	14.7	16.5	Methylphenidate 40 mg	
Male	14.7	16.5	Risperidone 1.5 mg	Risperidone 1.5 mg
Male	15.5	17.5		
Male	15.6	17.9	Methylphenidate 54 mg	Methylphenidate 54 mg
Male	15.7	17.6	Risperidone 2 mg	Olanzapine 5 mg, fluoxetine 20 mg
Male	17.2	19.0	Methylphenidate 20 mg	
Male	18.1	19.7		
Male	18.1	19.9		
Male	18.1	20.2	Pimpamperone 40 mg, methylphenidate 54 mg	Pimpamperone 10 mg, methylphenidate 63 mg
Male	18.5	20.4	Venlafaxine 75 mg	Venlafaxine 75 mg
Male	19.6	21.1		
UHR-P				
Female	13.9	16.0		Quetiapine 50 mg, valproic acid 600 mg, domperidone 10 mg
Male	14.2	16.1		
Male	16.9	18.7		
Male	17.1	19.4		Lithium 1600 mg
Male	17.1	19.4		
Male	18.2	20.4	Clomipramine 150 mg	Aripiprazole 3.75 mg
Male	19.3	21.4		
Male	19.4	21.5	Citalopram 30 mg	

Note: Abbreviations are explained in the first footnote to table 1.

and included semiautomated assessment of individual intracranial templates from the T2-weighted scans, which were then used as a mask to extract semiautomated volumes for total brain (TB), lateral ventricles, and cerebellum, as well as fully automated assessment of GM and WM volumes from the nonuniformity corrected T1-weighted images.[48–50] For all measures, volume at T1 was subtracted from volume at T2 and divided by the scan interval to compute change in volume per year.

Cortical Thickness. Cortical thickness was assessed with a customized version of the CLASP algorithm using the GM/WM segments from our pipeline as inputs.[51,52] A 3D surface comprising 81 920 polygons and 40 962 vertices was fitted to the WM/GM intersection, which created the inner surface of the cortex. This was done separately for scans at T1 and T2. To create the outer cortical surface, the inner surface was expanded to fit the GM/cerebrospinal fluid intersection. Cortical thickness was estimated by taking the distance between the 2 surfaces so that each polygon vertex on the outer surface had a counterpart on the inner surface. For each subject, the cortical thickness was calculated for every vertex and smoothed across the surface using a 20-mm surface-based blurring kernel.[53] This improved the chances of detecting population differences, while following the curvature of the surface to preserve any anatomical boundaries within the cortex. Surfaces were registered to an average surface created from 152 subjects (International Consortium of Brain Mapping-152),[54] allowing for local comparisons between subjects. Cortical thickness values for T2 and T1 were subtracted from each other and divided by the scan interval to compute change in thickness per year.

Voxel-Based Morphometry. GM and WM segments were blurred using a 3D Gaussian kernel (full width at half maximum [FWHM] = 8 mm) for T1 and T2 separately. The voxel values of these blurred GM and WM segments reflect the local presence, or concentration, of GM and WM, respectively. 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 2 steps. First, the T1-weighted images were linearly transformed to a model brain, the previously determined "most average" brain.[55] In this linear step, a joint entropy mutual information metric was optimized.[56] 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[57] was used. GM and WM density difference maps were calculated by subtracting each subject's density map at T1 from the density map

at T2. Finally, the density difference maps were resampled to voxels of size $2 \times 2 \times 2.4$ mm^3.

Statistical Analysis

All measures were analyzed in 2-group comparisons (controls vs UHR). Post hoc tests were performed for each pair of groups separately (controls vs UHR-P, controls vs UHR-NP, and UHR-NP vs UHR-P) using dummy variables. All clinical and volumetric variables were checked for normality and homogeneity of variance. If assumptions for normality and homogeneity were not met, nonparametric statistics were applied. Multicollinearity was checked for all regression variables, and there was no indication that this had a confounding effect in the applied regression models.

Sociodemographic and Clinical Variables. Chi-square tests and ANOVA were used to assess differences between groups in sociodemographic variables. Clinical variables were compared using nonparametric tests (Mann-Whitney and Kruskal-Wallis). Results were considered to be statistically significant at $\alpha = 0.05$, 2 tailed.

Volumetric Measures. All volumetric brain measures at T1 were compared between groups using ANCOVA to check whether groups were representative of the sample in our previous study.[30] For all measures, volume at T1 was subtracted from volume at T2 and divided by the scan interval to compute change in volume per year. Change over time was analyzed by means of linear regression. Any outliers, defined as measures with a value of more than 2 SDs from the mean, were removed from the analyses (one control for total brain, GM, and cerebellum, and one UHR-P participant for lateral ventricles). Age at T1, intracranial volume at T1, sex, handedness, and total IQ were entered as covariates and group as an independent predictor. Results were considered to be statistically significant at $\alpha = 0.05$, 2 tailed. A more strict $\alpha = 0.01$ was applied for post hoc analyses to correct for multiple comparisons.

Cortical Thickness and VBM Measures. To evaluate differences in cortical thickness over time, a vertex-by-vertex analysis was carried out. Group differences were calculated using linear regression with age at T1, sex, handedness, and total IQ as covariates and group as an independent predictor. This produced F statistics at each vertex for all variables. Statistical maps were created for the left and right hemisphere separately. Critical F values were determined for each group comparison after a correction for multiple comparisons was carried out according to the false discovery rate (FDR, $\alpha = 0.05$, 2 tailed), allowing for an overall 5% chance of false positives.[58] The statistical procedure for VBM measures was similar to the cortical thickness procedure, only here analysis was carried out per voxel for GM and WM density maps of the whole brain, and statistical

thresholds were determined by critical t values. Only clusters of 5 or more neighboring voxels reaching statistical threshold were considered of interest.

Results

Sociodemographic and Clinical Variables

Groups were matched for sex, handedness, age, height, and time between scans (table 2). IQ scores were higher in the control group compared with the UHR group ($P = .01$). UHR individuals scored higher on SIPS symptom scales and lower on GAF scores than controls at T1 and T2 ($P < .001$). Post hoc comparisons showed that IQ scores were lower only in UHR-P individuals compared with controls ($P = .01$). Additionally, the UHR-P group reported higher SIPS scores at T1 and T2, higher BSABS scores at T2, and lower GAF scores at T2 than the UHR-NP group ($P < .05$). Amount of medication use did not differ statistically between UHR-NP and UHR-P groups, although antipsychotic medication intake at T1 appeared more common in the UHR-NP ($n = 10$, $P = .08$) because none of the UHR-P individuals were using antipsychotics at T1.

Volumetric Measures

Absolute volumes and relative change over time are listed in table 4. At T1, there were no volumetric differences between groups, although the difference in intracranial volume between UHR-P and UHR-NP individuals almost reached significance ($F = 3.70$, $P < .062$). Volumetric change over time of TB, GM, lateral ventricles, and cerebellum did not differ between UHR individuals and controls. For WM, UHR individuals were found to have a reduced increase in cerebral WM compared with controls ($t = -2.04$, $P = .046$). Post hoc analyses showed that there was a greater TB volume loss per year for the UHR-P group compared with the UHR-NP ($t = -4.02$, $P < .001$) and control groups ($t = -2.80$, $P = .009$; figure 1). Additionally, there was a decrease over time in WM volume for UHR-P relative to controls ($t = -2.91$, $P = .007$) but no difference for UHR-NP compared with controls. Group results for TB and WM were the same for both hemispheres (all $P < .01$), except for TB change in the right hemisphere, which did not differ between the control group and the UHR-P group. For GM and cerebellum volumes, change over time did not differ between groups. Lateral ventricles increased more for UHR-P compared with controls ($t = 3.27$, $P = .003$), but this group difference disappeared after removing one extreme outlier (>3 SDs from the mean) in the UHR-P group.

Cortical Thickness

There were no differences in cortical thickness between groups at T1. Over time, cortical thickness decreased more in UHR individuals than in controls in an area located at the caudal part of the left middle temporal gyrus, reaching a statistical threshold of $F = 20.86$. Post hoc, more thinning was found for UHR-P than controls in widespread areas in the left anterior cingulate cortex, precuneus, and parts of the temporo-parieto-occipital area (Brodmann areas 21, 22, 37, and 39), including caudal parts of the receptive speech area in the STG ($F_{min} = 8.96$, $F_{max} = 40.35$; see figure 2). This was not found for UHR-NP vs controls.

Voxel-Based Morphometry

There were differences neither in GM or WM density at T1 nor in change over time between T2 and T1.

Discussion

We report the outcome of a 2-year longitudinal, structural MRI study in a large group of UHR adolescents and typically developing controls. Three complementary methods were used to compare structural brain changes for UHR individuals and controls with additional post hoc comparisons for those who developed psychosis (UHR-P) and those who did not (UHR-NP). UHR was found to be associated with a global reduction of WM growth and an increased cortical thinning in the left middle temporal gyrus over time. UHR-P adolescents showed more prominent changes over time: a greater loss of total brain volume than UHR-NP and controls, a decrease in WM volume and a pattern of progressive cortical thinning compared with controls. No group differences were evident using a more localized, voxel-based approach. Importantly, brain changes in the UHR-P group could not be attributed to antipsychotic medication because only 2 of these subjects received (very low doses) antipsychotics at follow-up.

Only a limited number of longitudinal MRI studies examining global brain changes in UHR individuals have been published and none of these included a typically developing control group. By combining brain analysis methods, we were able to show both global and regional brain changes over time for UHR individuals who subsequently became psychotic, in particular compared with typically developing controls. Our findings suggest that the development of psychosis is related to modest, but detectable, changes in GM and WM over time. Interestingly, these progressive volumetric changes over time occurred in the presence of a relatively large intracranial and total brain volume for UHR-P individuals (see table 4), which is a relatively consistent finding across high-risk studies as reported in a recent meta-analysis[59] and has also been observed in prenatal offspring of mothers with schizophrenia.[60] The loss in cortical thickness found in UHR-P individuals lends support to a pattern of widespread, but regionally specific, thinning of the cortex in association with the onset of psychosis and shows

Table 4. Means and SDs of Absolute Brain Volumes in Cubic Centimeters at Baseline, Follow-Up and the Annual Change in Percentage

|	Controls (n = 30)	UHR (n = 43)	P	UHR-NP (n = 35)	UHR-P (n = 8)	Controls vs UHR-NP	Controls vs UHR-P	UHR-NP vs UHR-P
Intracranium								
T1—baseline	1496.50 (118.93)	1490.51 (120.79)	P = .500	1472.74 (108.70)	1568.25 (147.18)	P = .316	P = .158	P = .062
Whole brain								
T1—baseline	1371.72 (105.01)	1361.54 (116.11)	P = .795	1348.05 (108.97)	1420.56 (135.30)	P = .832	P = .991	P = .704
T2—follow-up	1356.74 (103.29)	1350.00 (117.80)		1341.74 (107.89)	1386.18 (157.75)			
% Change/y	−0.52 (0.91)	−0.45 (0.84)	P = .814	−0.26 (0.66)	−1.28 (1.18)	P = .684	**P = .009**	P < .001
Cerebral gray matter								
T1—baseline	753.73 (63.62)	747.17 (69.61)	P = .478	739.19 (64.81)	782.12 (83.42)	P = .392	P = .427	P = .800
T2—follow-up[a]	725.57 (58.00)	733.43 (72.11)		728.72 (69.19)	754.03 (85.76)			
% Change/y	−1.77 (1.31)	−0.95 (1.89)	P = .149	−0.73 (1.84)	−1.84 (1.68)	P = .061	P = .691	P = .036
Cerebral white matter								
T1—baseline	453.14 (48.35)	449.06 (53.44)	P = .664	444.43 (50.78)	469.29 (63.52)	P = .534	P = .611	P = .506
T2—follow-up[a]	464.48 (45.10)	452.40 (51.00)		449.23 (46.50)	466.29 (69.50)			
% Change/y	1.68 (1.99)	0.35 (2.63)	**P = .046**	0.64 (3.00)	−0.33 (2.01)	P = .076	**P = .007**	P = .617
Cerebellum								
T1—baseline	153.46 (14.67)	153.56 (13.25)	P = .913	152.74 (12.71)	157.11 (15.83)	P = .851	P = .423	P = .638
T2—follow-up	151.61 (14.41)	152.84 (13.58)		152.50 (12.89)	154.34 (17.22)			
% Change/y	−0.57 (1.04)	−0.25 (1.07)	P = .397	−0.10 (1.06)	−0.91 (1.02)	P = .315	P = .819	P = .108
Lateral ventricles								
T1—baseline	11.22 (11.38)	12.73 (7.07)	P = .624	12.45 (7.56)	13.99 (4.50)	P = .558	P = .831	P = .604
T2—follow-up	11.58 (11.09)	13.63 (7.76)		13.15 (8.30)	15.78 (4.46)			
% Change/y	1.66 (5.03)	3.53 (6.36)	P = .112	2.60 (4.32)	7.26 (9.14)	P = .206	**P = .003**	P = .053

Note: Significant group differences are highlighted in bold letter type.
[a]Data not available for 2 control subjects. Abbreviations are explained in the first footnote to table 1.

that these changes occur even in young adolescent individuals. Although we cannot completely rule out a possible influence of antipsychotic medication on our outcome measures, the UHR-P group was not receiving any antipsychotic medication at T1 and only 2 of the 8 UHR-P individuals received (a very low dose of atypical) antipsychotic medication at T2. Thus, it is highly unlikely that the brain changes in the individuals who developed psychosis can be attributed to the effects of antipsychotic medication.

Two longitudinal studies examining regional volumes included a sample of typically developing controls.[34,35]
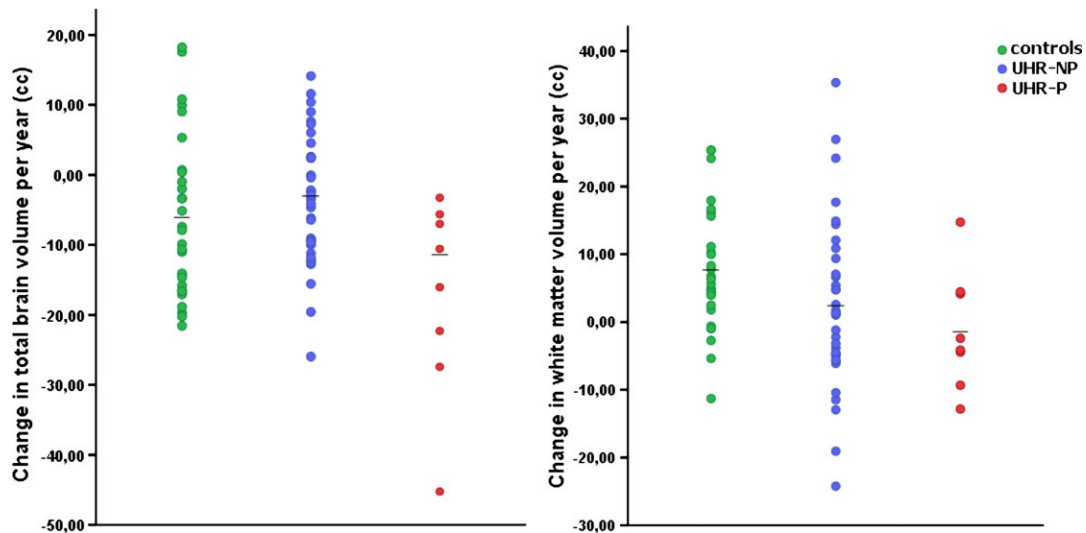
Fig. 1. Change in total brain (left panel) and white matter (right panel) volume per year for controls, ultra–high risk individuals without psychosis (UHR-NP) and with psychosis (UHR-P). Individual data and group means are shown.
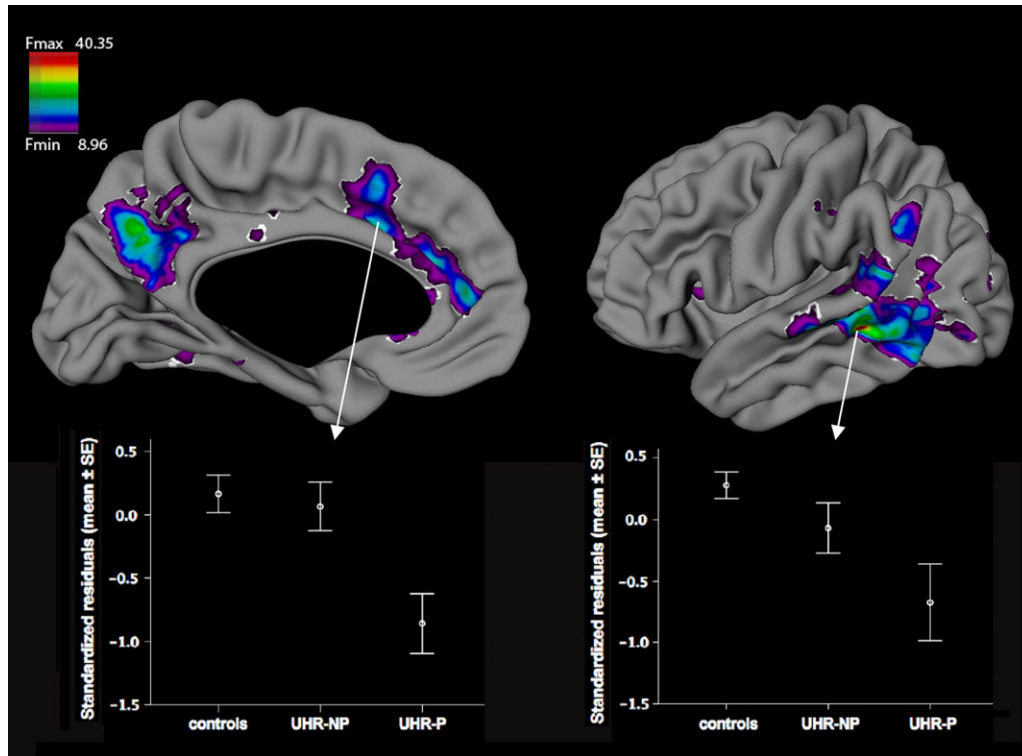
Fig. 2. Cortical thinning in the left hemisphere for ultra–high risk individuals with psychosis (UHR-P) compared with controls, controlled for age, sex, handedness and total IQ. The critical F value was 8.96. Boxes illustrate mean standardized residuals for all groups ± standard errors for peak vertices in anterior cingulate cortex (left) and middle temporal gyrus (right).

They found that UHR-P individuals displayed progressive loss of volume in the insular cortex[34] and STG[35] compared with controls. Although we did not measure regional volumes, our cortical thickness results confirm changes in these brain areas around the onset of psychosis, as shown by an increased thinning in the left (caudal) STG and the left insular region in our study. Our findings add to these results by suggesting that the cortical changes in these areas associated with the onset of psychosis cannot be attributed to the use of antipsychotic medication.

Our results are also in general agreement with studies using automated whole-brain approaches reporting that individuals who become psychotic show progressive GM and WM changes over time in particular in (pre-)frontal, temporal, and parietal cortices.[31–33,36] However, the interpretation of these studies was hampered by the fact that they failed to include typically developing control subjects. Our results therefore suggest that the previously reported changes in GM and WM around the time of onset of psychosis are indeed different from those seen during normal development and may therefore be attributed to the development of psychosis.

The presence of structural brain changes associated with the onset of psychosis supports the notion that brain changes take place at an early stage of the disorder and that these changes may be progressive.[1,61] In our study, regional changes were most pronounced in cortical GM areas that have previously been associated with clinical risk for psychosis and disease onset.[7,9,11,15,23,25,31,32,35] Anterior cingulate and temporal gyri in the speech area are also often associated with changes in the later stages of schizophrenia spectrum disorders.[62] Interestingly, the cortical changes in this study were only present in the left hemisphere, indicating a more lateralized disease effect, which has often been suggested as a key feature of abnormal brain development in schizophrenia.[63,64] However, numerous studies have not found support for this, and a recent longitudinal MRI study in individuals with childhood-onset schizophrenia failed to find abnormalities in cortical asymmetry.[65]

Several factors affect the interpretation of the outcome of this study. First, while our UHR inclusion criteria were identical to those used in the European Prediction of Psychosis Study[66] and closely resemble criteria used in Melbourne[5], North America,[67] and other sites, we cannot rule out that our cohort may have included a different type of high-risk subject than those in other studies. Most of the adolescents in our study had already sought help at an early age,[68] while at other UHR sites individuals usually do not have a history of contact with mental health services. Accordingly, a relatively high percentage (49%) of our subjects was already using some form of psychotropic medication at T1, although interestingly most of the subjects who subsequently developed psychosis did not. Arguably, (antipsychotic) medication was prescribed

for individuals who were more severely affected clinically, which may have helped prevent the onset of psychosis. Additionally, lack of medication use may (partially) explain why psychosis could occur in UHR-P individuals. Either way, this does not dismiss the interpretation that observed brain changes in this study were related to the development of psychosis. Second, the transition rate in this study was relatively low compared with other sites, although a much larger clinical cohort study recently reported a declining transition rate of 16% (from initial transition rates over 40%) after a follow-up of 2 years.[69] The low transition rate may be due to potential preventative treatment effects, a high number of "false positives," or the fact that our participants were relatively young and recruited within a narrow age range at baseline (12 y, 0 mo to 18 y, 11 mo). This view is supported by the fact that the UHR-P group was on average 1.5 years older than the UHR-NP group, even though this difference was not statistically significant. Future follow-up studies will have to address whether the transition rate in this cohort increases as it moves into adulthood. Third, due to the small number of individuals in our UHR-P group, some brain changes associated with the onset of psychosis may have remained obscure. Although some of the well-established brain changes associated with schizophrenia were already present, other commonly reported changes such as enlarged ventricles and reduced prefrontal GM were not. Interestingly, a recent longitudinal study of individuals with adolescent-onset psychosis showed that progressive changes in these markers differentiated between patients and healthy control individuals.[70] Additional diagnosis-specific analyses for our UHR-P subgroup were not performed because of the number of diverse diagnoses (6) in this small group. However, it ought to be emphasized that while small sample size greatly impacts cross sectional MRI designs, the statistical power to detect subtle, disease-related brain changes in small groups is much greater in longitudinal designs.[71]

A final limitation concerns the statistical corrections for multiple comparisons. As we expected that any group differences in brain structure would be subtle, these corrections were not overly conservative: For the VBM and cortical thickness analyses, we applied a correction using FDR, but for the volumetric analyses, no formal correction was applied. This is not unusual in the literature because the volume of various GM and WM compartments are dependent on one another and it is therefore not obvious how to control for multiple comparisons in this instance. As a consequence, it is possible that the differences, in particular in brain volumes, represent false positive findings. As such, these results require further replication. The lack of significant findings in our VBM analysis supports the idea that between-group differences were subtle because they could not be detected at the voxel level and required concatenated data over larger areas/volumes. Eyeballing the VBM analysis at a more lenient statistical threshold indicated that subthreshold differences were present in similar areas as for the cortical thickness findings. However, this should clearly be viewed with caution because these findings did not reach statistical significance.

In summary, we report structural brain changes in total brain volume, WM volume, and cortical thickness at the time of onset of psychosis in adolescence. Importantly, these effects could not be attributed to use of antipsychotic medication. Our findings suggest that progressive brain changes are present at the time of, and related to, the development of psychosis. Future longitudinal studies are needed to compare the efficacy of early intervention strategies and address how these can prevent psychosis and associated brain changes from occurring.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org/.

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