

# 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*

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**Context:** Magnetic resonance imaging studies have identified hippocampal volume reductions in schizophrenia and amygdala volume enlargements in bipolar disorder, suggesting different medial temporal lobe abnormalities in these conditions. These studies have been limited by small samples and the absence of patients early in the course of illness.

**Objective:** To investigate hippocampal and amygdala volumes in a large sample of patients with chronic schizophrenia, patients with first-episode psychosis, and patients at ultra-high risk for psychosis compared with control subjects.

**Design:** Cross-sectional comparison between patient groups and controls.

**Setting:** Individuals with chronic schizophrenia were recruited from a mental health rehabilitation service, and individuals with first-episode psychosis and ultra-high risk were recruited from the ORYGEN Youth Health Service. Control subjects were recruited from the community.

**Participants:** The study population of 473 individuals included 89 with chronic schizophrenia, 162 with first-episode psychosis, 135 at ultra-high risk for psychosis (of whom 39 subsequently developed a psychotic illness), and 87 controls.

**Main Outcome Measures:** Hippocampal, amygdala, whole-brain, and intracranial volumes were estimated on high-resolution magnetic resonance images and compared across groups, including first-episode subgroups.

We used 1- and 2-way analysis of variance designs to compare hippocampal and amygdala volumes across groups, correcting for intracranial volume and covarying for age and sex. We investigated the effects of medication and illness duration on structural volumes.

**Results:** Patients with chronic schizophrenia displayed bilateral hippocampal volume reduction. Patients with first-episode schizophrenia but not schizophreniform psychosis displayed left hippocampal volume reduction. The remaining first-episode subgroups had normal hippocampal volumes compared with controls. Amygdala volume enlargement was identified only in first-episode patients with nonschizophrenic psychoses. Patients at ultra-high risk for psychosis had normal baseline hippocampal and amygdala volumes whether or not they subsequently developed a psychotic illness. Structural volumes did not differ between patients taking atypical vs typical antipsychotic medications, and they remained unchanged when patients treated with lithium were excluded from the analysis.

**Conclusions:** Medial temporal structural changes are not seen until after the onset of a psychotic illness, and the pattern of structural change differs according to the type of psychosis. These findings have important implications for future neurobiological studies of psychotic disorders and emphasize the importance of longitudinal studies examining patients before and after the onset of a psychotic illness.

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**A**TEMPTS TO FIND A BIOLOGICAL basis for the kraepelinian distinction between schizophrenia and affective psychoses have been largely unsuccessful,<sup>1,2</sup> although neuroimaging studies have identified more structural abnormalities in the former.<sup>1</sup> Although early neuropathologic and neuroimaging studies<sup>3,4</sup> comparing schizophrenic and affective psychoses did not identify structural brain differences, the re-

sults of recent magnetic resonance imaging (MRI) studies have raised the possibility that these 2 major psychiatric disorders may be characterized by differential structural changes involving hippocampal and amygdala volume reduction in schizophrenia<sup>5,6</sup> and amygdala enlargement in bipolar disorder.<sup>7-10</sup> This intuitively appealing distinction is not entirely supported by MRI studies, which have detected amygdala volume reduction in affective psychoses<sup>11</sup> and hippocampal volume reduction in bipolar

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disorder.<sup>12</sup> Methodological issues, including patient selection, study power, differing manual tracing methods, the effects of chronic psychiatric illness on the cortisol-hypothalamic-pituitary-adrenal axis, and the effects of medication, are possible explanations for the observed differences in findings.<sup>5,6,13,14</sup>

Results of our initial study<sup>15</sup> in first-episode patients suggested that hippocampal volume reduction was not specific to first-episode schizophrenia, although another similarly powered study<sup>16</sup> found evidence of specificity. Although a variety of studies<sup>17-20</sup> have subsequently investigated amygdala and hippocampal volumes in first-episode patients, there have been no further published comparisons of medial temporal volumes in patients with first-episode schizophrenia and affective psychosis.

Our recent research efforts have attempted to identify not only where in the medial temporal lobe structural changes are found but also when these changes are occurring. In addition to investigating first-episode and chronic disease groups, we identified people at ultra-high risk (UHR) for psychosis through a combination of trait and state risk factors. This approach yields a much higher rate of transition to psychosis than family history alone in a relatively short follow-up period (35% transition to psychosis within 12 months<sup>21</sup>). In a longitudinal MRI study,<sup>22</sup> we found that UHR individuals who develop a psychotic illness exhibit left medial temporal structural changes during the transition to psychosis. This is in accord with earlier studies that showed left hippocampal volume reduction in first-episode psychosis<sup>15</sup> but not in the baseline MRIs of UHR individuals who later developed first-episode psychosis.<sup>23</sup> One inference drawn from these studies is that left medial temporal structural change occurs during the transition to psychosis.

The present study sought to further address the specificity and timing of hippocampal and amygdala volume changes in patients with first-episode psychoses, patients with chronic schizophrenia, a UHR group, and control subjects. Based on our previous work and published reviews,<sup>5-16</sup> we predicted that (1) patients with chronic schizophrenia would exhibit bilaterally smaller hippocampal and amygdala volumes, (2) patients with all types of first-episode psychosis would exhibit smaller hippocampal volumes but those with affective first-episode psychoses would show increased amygdala volumes, and (3) UHR patients who later developed a psychotic illness would have normal baseline hippocampal and amygdala volumes.

## METHODS

### PARTICIPANTS

Patients with chronic schizophrenia, patients with first-episode psychoses, and control subjects underwent MRI between July 8, 1994, and November 20, 1999, and the UHR group was recruited between April 29, 1995, and May 4, 2001. Information on age, sex, and height was gathered from all the participants (**Table 1**). Inclusion criteria for patients with first-episode psychoses, patients with chronic schizophrenia, and control subjects have been previously described.<sup>15</sup> All the patients with first-episode psychoses were recruited from the Early Psychosis

Prevention and Intervention Centre, were aged 16 to 30 years, and were currently psychotic as reflected by the presence of at least 1 symptom (delusions, hallucinations, disorder of thinking or speech other than simple acceleration or retardation, or disorganized, bizarre, or markedly inappropriate behavior). Patients with chronic schizophrenia were recruited from the Adult Mental Health Rehabilitation services of the North Western Mental Health Program, and healthy volunteers were recruited from similar sociodemographic areas as the patients by approaching ancillary hospital staff and through advertisements. Patients with first-episode psychoses and chronic schizophrenia received *DSM-III-R* diagnoses<sup>24</sup> based on medical record review and either the Royal Park Multidiagnostic Instrument for Psychosis<sup>25</sup> or the Structured Clinical Interview for *DSM-III-R*.<sup>26</sup>

Based on these assessments, first-episode patients were further divided into 4 subgroups: (1) first-episode schizophrenia (because the diagnostic status of schizoaffective disorder remains under debate,<sup>27</sup> and given evidence that this disorder may be a variant of schizophrenia,<sup>28</sup> patients with first-episode schizoaffective disorder were included in this group), (2) first-episode schizophreniform psychosis (the *DSM-III-R*<sup>24</sup> and *DSM-IV*<sup>29</sup> distinguish schizophreniform psychosis from schizophrenia on the basis that the episode is of <6 months' duration, which provides an opportunity to investigate whether structural changes differ between patients with shorter and longer episodes of a first-episode schizophrenic illness), (3) affective psychosis (bipolar and major depressive psychoses), and (4) other psychoses (includes the remaining first-episode psychosis diagnostic categories, ie, delusional disorder, brief psychosis, substance-induced psychosis, and psychosis not otherwise specified).

The UHR group was recruited from the Personal Assessment and Crisis Evaluation (PACE) Clinic.<sup>30-32</sup> The UHR patients were aged 14 to 30 years and had not experienced a previous psychotic episode. The UHR identification criteria are outlined in **Table 2**, and the rationale for these criteria has been previously described.<sup>32</sup> Individuals were included in the study if they had been followed up for at least 12 months (mean, 13 months; maximum, 44 months) to determine whether they developed a psychotic illness. After baseline MRI, UHR patients were monitored regularly for the onset of psychotic symptoms and were then divided into subgroups based on operationalized criteria for the onset of psychosis<sup>21</sup> and Structured Clinical Interview for *DSM-IV*<sup>33</sup> diagnoses (Table 2). Thirty-nine UHR patients developed a psychotic illness (UHR-P) and 96 did not (UHR-NP) during follow-up. Seven UHR-NP patients did not receive a diagnostic interview at follow-up. Hippocampal volumes have been previously reported for 60 of the UHR patients.<sup>23</sup> After recruitment of these 60 patients, an intervention study commenced in the UHR cohort.<sup>34</sup> Sixty-eight patients in the UHR group who agreed to participate in the present study had been approached for the intervention study; 24 refused to participate in the intervention study but agreed to the MRI study, 21 received risperidone (mean dose, 1.3 mg/d) and cognitive behavior therapy (treatment group), and 23 received supportive therapy alone (control group). The MRI measures have not been previously reported in these 68 patients. Seven patients described herein were in neither of the 2 earlier studies.<sup>23,34</sup>

All the participants were screened for comorbid medical and psychiatric conditions by means of clinical, physical, and neurologic examinations. Exclusion criteria for all the participants were a history of substantial head injury, seizures, neurologic diseases, impaired thyroid function, corticosteroid use, or *DSM-III-R*<sup>24</sup> criteria of alcohol or substance abuse or dependence. Control subjects with a personal or family history of psychiatric illness were excluded. The study was approved by local research and ethics committees, and written informed consent was obtained from the participants or their parents/guardians where appropriate.

**Table 1. Demographic and Structural Data for the 473 Study Participants\***

	Patients, Total (M/F), No.	Age, y	Height, cm	SI†	Volume, mm <sup>3</sup>					
					Hippocampus		Amygdala		Intracranial	Whole Brain
					R	L	R	L		
Established schizophrenia	89 (76/13)	34.9 (9.6)	174 (7.8)	4674 (3613)	2915 (347)	2649 (367)	1525 (343)	1515 (326)	1 441 044 (130 443)	1 324 614 (119 145)
First-episode psychosis	162 (108/54)	21.5 (3.4)	173 (9.4)	54 (87)	3059 (437)	2741 (403)	1628 (316)	1610 (353)	1 422 159 (133 174)	1 304 667 (123 456)
Schizophrenia spectrum psychoses										
Schizophrenia	31 (23/8)	21.8 (3.9)	174 (9.8)	93 (150)	2997 (403)	2622 (385)	1526 (283)	1506 (354)	1 397 850 (136 896)	1 306 092 (125 094)
Schizophreniform	57 (42/15)	21.0 (3.0)	174 (8.2)	53 (67)	3156 (451)	2786 (399)	1573 (304)	1564 (297)	1 446 539 (117 682)	1 309 446 (118 259)
Schizoaffective	15 (11/4)	21.0 (2.9)	172 (8.9)	61 (105)	2868 (388)	2655 (269)	1588 (355)	1543 (305)	1 376 699 (131 375)	1 285 470 (116 971)
Subgroup	103 (76/27)	21.2 (3.3)	174 (8.8)	66 (104)	3066 (438)	2718 (384)	1561 (303)	1544 (314)	1 421 714 (127 671)	1 304 945 (119 273)
Affective psychoses										
Bipolar disorder	22 (11/11)	21.7 (2.4)	171 (10.0)	29 (19)	3039 (423)	2796 (387)	1685 (289)	1590 (276)	1 450 851 (166 977)	1 336 338 (154 282)
Major depression	12 (7/5)	22.6 (4.1)	167 (8.0)	39 (32)	3092 (383)	2849 (442)	1757 (227)	1751 (396)	1 401 520 (114 428)	1 270 088 (92 578)
Subgroup	34 (18/16)	22.0 (3.1)	170 (9.8)	32 (24)	3058 (404)	2815 (402)	1710 (268)	1647 (327)	1 433 440 (150 598)	1 312 955 (137 974)
Other psychoses										
Delusional disorder	3 (2/1)	26.4 (2.0)	173 (6.4)	14 (3)	3513 (709)	3200 (383)	1965 (209)	1818 (638)	1 477 184 (149 317)	1 348 178 (114 486)
Psychosis NOS	12 (6/6)	20.9 (3.5)	173 (8.6)	51 (79)	3023 (506)	2698 (527)	1761 (332)	1790 (385)	1 392 506 (149 967)	1 258 335 (131 038)
Brief psychosis	6 (2/4)	20.0 (4.6)	168 (15)	23 (23)	2768 (413)	2499 (413)	1770 (343)	1893 (324)	1 363 396 (131 250)	1 283 727 (133 980)
Substance induced	4 (4/0)	23.2 (4.6)	185 (5.5)	41 (40)	3072 (362)	2841 (362)	1802 (563)	1899 (744)	1 473 564 (60 597)	1 364 836 (79 223)
Subgroup	25 (14/11)	21.7 (4.2)	174 (9.8)	38 (42)	3028 (488)	2733 (484)	1794 (350)	1836 (442)	1 408 650 (134 705)	1 292 250 (123 891)
UHR	135 (78/57)	20.1 (3.6)	171 (9.0)	NA	3049 (401)	2763 (376)	1452 (293)	1432 (288)	1 428 460 (146 824)	1 318 333 (135 520)
UHR psychosis	39 (24/15)	19.0 (3.5)	172 (9.0)	NA	3075 (355)	2820 (361)	1483 (347)	1454 (316)	1 463 985 (143 285)	1 351 229 (130 132)
Schizophrenia spectrum Schizophrenia/form	19 (12/7)	18.6 (3.5)	173 (11.4)	NA	3078 (287)	2791 (289)	1480 (227)	1443 (223)	1 468 583 (108 155)	1 354 216 (106 130)
Schizoaffective	2 (2/0)	18.9 (1.6)	168 (0)	NA	2919 (138)	2701 (304)	1650 (536)	1551 (337)	1 422 963 (120 955)	1 336 743 (284)
Subtotal	21 (14/7)	18.7 (3.3)	172 (11.0)	NA	3063 (278)	2783 (284)	1496 (251)	1453 (227)	1 464 238 (106 993)	1 352 552 (100 821)
Other psychoses										
Bipolar disorder	6 (4/2)	19.8 (5.5)	173 (4.1)	NA	3090 (295)	2702 (277)	1398 (314)	1611 (427)	1 475 652 (171 405)	1 355 871 (161 344)
Depression	7 (3/4)	20.4 (2.5)	171 (7.6)	NA	3121 (512)	2915 (524)	1661 (512)	1525 (318)	1 462 756 (151 103)	1 348 694 (134 091)
Delusional disorder	1 (0/1)	17.2	173	NA	2457	2599	953	1038	1 726 721	1 593 447
Psychosis NOS	3 (3/0)	18.0 (3.5)	173 (9.7)	NA	3174 (620)	3034 (622)	1496 (469)	1311 (508)	1 443 529 (249 337)	1 320 533 (229 240)
Brief psychosis	1 (0/1)	16.6	162	NA	3241	3246	966	890	1 195 900	1 163 201
Subgroup	18 (10/8)	19.4 (3.8)	171 (6.6)	NA	3089 (436)	2865 (439)	1468 (442)	1456 (404)	1 463 690 (180 067)	1 349 685 (160 903)
UHR nonpsychosis	96 (54/42)‡	20.6 (3.6)	171 (9.0)	NA	3039 (420)	2740 (381)	1439 (269)	1422 (277)	1 414 029 (146 514)	1 304 969 (136 040)
Nonpsychotic psychiatric diagnosis§	36 (18/18)	21.0 (3.0)	170 (8.4)	NA	3078 (431)	2750 (358)	1451 (294)	1470 (295)	1 422 429 (173 344)	1 313 505 (143 716)
No psychiatric diagnosis	53 (29/24)	20.4 (3.8)	171 (9.8)	NA	3007 (424)	2707 (396)	1443 (244)	1383 (230)	1 402 017 (134 276)	1 302 212 (135 689)
Control	87 (55/32)	26.9 (10)	175 (9.7)	NA	3122 (388)	2870 (358)	1510 (230)	1500 (256)	1 449 789 (143 039)	1 360 533 (139 845)

Abbreviations: F, female; L, left; M, male; NA, not applicable; NOS, not otherwise specified; R, right; SI, scan interval; UHR, ultra-high risk.

\*Data are given as mean (SD) except where indicated otherwise.

†The SI is defined as the number of days between the first assessment and magnetic resonance imaging. Data on 4 participants (1 with chronic schizophrenia and 3 with first-episode psychosis) were not available.

‡Seven UHR patients did not receive a formal Structured Clinical Interview for DSM-III-R diagnosis at follow-up.

§Major depressive disorder (n = 7), generalized anxiety disorder (n = 2), panic disorder (n = 2), obsessive-compulsive disorder (n = 4), social phobia (n = 4), dysthymia (n = 8), adjustment disorder (n = 1), eating disorder (n = 4), substance-induced mood disorder (n = 2), and bipolar affective disorder without psychotic features (n = 2).

**Table 2. Ultra-High-Risk Intake and Exit Criteria**

<b>Intake Criteria</b>	
<b>Group 1: Attenuated psychotic symptoms</b>	
Presence of $\geq 1$ of the following symptoms: ideas of reference, magical thinking, perceptual disturbance, paranoid ideation, and odd thinking and speech (score of 2-3 on unusual thought content subscale, 1-2 on hallucinations subscale, 2-3 on suspiciousness subscale, or 1-3 on conceptual disorganization subscale of BPRS)	
Held with a reasonable degree of conviction, as defined by a score of 2 on the CASH rating scale for delusions	
Frequency of symptoms is several times per week	
Change in mental state present for $\geq 1$ wk and not longer than 5 y	
<b>Group 2: BLIPS</b>	
Transient psychotic symptoms: presence of $\geq 1$ of the following: ideas of reference, magical thinking, perceptual disturbance, paranoid ideation, and odd thinking and speech (score of $\geq 4$ on unusual thought content subscale, $\geq 3$ on hallucinations subscale, $\geq 4$ on suspiciousness subscale (or it is held with strong conviction, as defined by a score of $\geq 3$ on CASH rating subscale for delusions) or $\geq 4$ on conceptual disorganization subscale of BPRS)	
Duration of episode of $< 1$ wk	
Symptoms resolve spontaneously	
The BLIPS must have occurred within the past year	
<b>Group 3: Trait and state risk factors</b>	
First-degree relative with a psychotic disorder or schizotypal personality disorder or individual has schizotypal personality disorder	
Significant decrease in mental state or functioning maintained for $\geq 1$ mo (reduction in Global Assessment of Functioning scale score of 30 points from premorbid level)	
The decrease in functioning occurred within the past year	
<b>Exit Criteria: Acute Psychosis</b>	
Presence of $\geq 1$ of the following symptoms: hallucinations (defined by a score of $\geq 3$ on hallucinations subscale of BPRS), delusions (defined by a score of $\geq 4$ on unusual thought content subscale of BPRS or $\geq 4$ on suspiciousness subscale of BPRS), or it is held with strong conviction, as defined by a score of $\geq 3$ on CASH rating scale for delusions or formal thought disorder (defined by a score of $\geq 4$ on conceptual disorganization subscale of BPRS)	
Frequency of symptoms is at least several times a week to daily	
Duration of mental state change is $> 1$ wk	

Abbreviations: BLIPS, Brief Limited Intermittent Psychotic Symptoms; BPRS, Brief Psychiatric Rating Scale; CASH, Comprehensive Assessment of Symptoms and History.

A total of 510 individuals were initially included in the study, but 473 were included in the final analysis (Table 1). After MRI, 37 individuals were excluded owing to findings of an unsuspected brain lesion ( $n=12$ ), diagnosis revision ( $n=12$ ), or insufficient data ( $n=13$ ). The present study includes patients described in an earlier study<sup>15</sup> but excludes a subset of control subjects who underwent MRI at a second facility in the earlier study.

## MRI ACQUISITION AND PROCESSING

All chronic schizophrenia, first-episode patients, and controls underwent MRI using the same instrument (1.5T Signa; General Electric Medical Systems, Milwaukee, Wis) at the Royal Melbourne Hospital. The UHR patients underwent MRI at 2 separate locations (52 at Royal Melbourne Hospital and 83 at Royal Children's Hospital, Melbourne) using identical scanners (1.5T Signa) with identical sequences. A 3-dimensional volumetric spoiled-gradient recalled echo in the steady-state sequence generated 124 contiguous, 1.5-mm coronal sections. Imaging parameters were as follows: echo time, 3.3 milliseconds; repetition time, 14.3 mil-

liseconds; flip angle, 30°; matrix size, 256 × 256; field of view, 24 × 24-cm matrix; and voxel dimensions, 0.938 × 0.938 × 1.5 mm. Head movement was minimized by using foam padding and Velcro straps across the forehead and chin. Each scanner was calibrated fortnightly using the same proprietary phantom to ensure stability and accuracy of measurements. Direct comparison of the intracranial volumes (ICVs) of the UHR groups that underwent MRI at Royal Melbourne Hospital vs Royal Children's Hospital (covarying for sex) did not show a significant effect of MRI site ( $F_{1,134}=0.27$ ;  $P=.87$ ).

## Hippocampal Volumes

Hippocampal volumes were estimated using a manual tracing technique and defined anatomic criteria.<sup>35</sup> The hippocampal boundaries were as follows: posterior, the section with the greatest length of continuous fornix; medial, the open end of the hippocampal fissure posteriorly, the uncus fissure in the hippocampal body, and the medial aspect of the ambient gyrus anteriorly; lateral, the temporal horn of the lateral ventricle; inferior, the white matter inferior to the hippocampus; and superior, the superior border of the hippocampus. Anteriorly, the alveus was used to differentiate the hippocampal head from the amygdala. The anterior border was the most difficult to identify consistently and was aided by moving between sections before and after the index section. Interrater and intrarater reliabilities were assessed using intraclass correlation coefficients (ICCs). Interrater ICC reliabilities were 0.89 (right) and 0.77 (left). Intrarater ICC reliabilities were 0.94 (right) and 0.85 (left).

## Amygdala Volumes

The method used to estimate amygdala volumes was adapted from a previously described method.<sup>36</sup> The amygdala boundaries were as follows: posterior, appearance of amygdala gray matter above the temporal horn; superior-lateral, the thin strip of white matter that separates the amygdala from the claustrum and the tail of the caudate; medial, the angular bundle, which separates the amygdala from the entorhinal cortex; superior-medial, the semilunar gyrus; inferior, the hippocampus; inferior-lateral, the temporal lobe white matter and the extension of the temporal horn; and anterior, the section anterior to the appearance of the optic chiasm. Interrater ICC reliabilities were 0.70 (right) and 0.79 (left). Intrarater ICC reliabilities were 0.87 (right) and 0.88 (left).

## Whole-Brain Volumes

Whole-brain volumes were estimated using a 3-dimensional morphometric procedure that included the cerebellum, brainstem, and ventricles but not the cisterns or sulcal cerebrospinal fluid.<sup>15</sup> A thresholding technique maximally separated the brain and skull to produce minimum and maximum pixel values. These values were applied to all sections in a series of erosions and dilations. Interrater and intrarater ICC measurements were both 0.98 for 10 randomly selected volumes.

## Intracranial Volumes

The ICVs were estimated from a sagittal reformat of the original 3-dimensional data set.<sup>37</sup> The major anatomic boundary was the dura mater below the inner table, and it was generally visible as a white line. Where the dura mater was not visible, the cerebral contour was outlined. Other landmarks were the undersurfaces of the frontal lobe, the dorsum sellae, the clivus, and, at the craniovertebral junction, the attachment of the dura

to the anterior cutting across to the posterior arch of the C1 vertebra. Interrater and intrarater ICC measurements were both 0.99 for 10 randomly selected volumes.

## STATISTICAL ANALYSES

Four sets of analyses were performed to investigate our hypotheses: analysis 1, chronic schizophrenia/first-episode psychosis/UHR; analysis 2, first-episode subgroups (schizophrenia/schizophreniform/affective/other); analysis 3, first-episode (all)/UHR-P/UHR-NP; and analysis 4, UHR schizophrenia/UHR other psychoses. Within each analysis, patient groups were compared with the control group.

Demographic data were compared using  $\chi^2$  analyses for sex, independent-samples *t* tests for psychopathology scores, 1-way analyses of variance for age and premorbid IQ (using the Tukey test for post hoc comparisons), and univariate analysis of covariance, covarying for age and sex (using the Sidak test for post hoc comparisons).

The ICVs were compared between groups using a univariate analysis of variance, with height as a covariate. Hippocampal, amygdala, and whole-brain volumes were corrected for ICVs using a previously described formula<sup>38</sup>:  $CV = MV - gradient (M\ ICV - mean\ ICV)$ , where *CV* is corrected volume; *MV*, measured volume; *gradient*, gradient of the regression line between the volume of interest and ICV in control subjects; *MICV*, measured ICV; and *mean ICV*, mean ICV of the control group. The corrected volumes were compared among groups using a univariate analysis of variance, with sex and age as covariates.

All pairwise mean comparisons used post hoc contrasts to compare patient groups with control subjects, adjusting for covariates of relevance. To compare the magnitude of mean differences, and to distinguish substantive from statistically significant results, Cohen *d* standardized effect sizes (plus 95% confidence intervals) 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.

## RESULTS

### DEMOGRAPHIC VARIABLES

Comparison of the groups in analysis 1 revealed significant group differences in age ( $F_{3,469} = 109.6$ ;  $P < .001$ ; chronic schizophrenia > controls > first-episode = UHR), sex ( $\chi^2_3 = 19.4$ ;  $P < .001$ ; greater proportion of males in the chronic schizophrenia group compared with all other groups), and height ( $F_{3,461} = 4.22$ ;  $P = .006$ ; UHR patients shorter than control subjects) (Table 1).

### WHOLE-BRAIN AND INTRACRANIAL VOLUMES

There were no significant ICV differences among groups in any of the 4 analyses: analysis 1,  $F_{3,462} = 0.55$  ( $P = .65$ ); analysis 2,  $F_{4,248} = 2.14$  ( $P = .08$ ); analysis 3,  $F_{3,377} = 2.10$  ( $P = .10$ ); and analysis 4,  $F_{2,126} = 1.51$  ( $P = .22$ ). Whole-brain volumes differed in analysis 1 ( $F_{3,473} = 5.86$ ;  $P = .001$ ; chronic schizophrenia = controls > first-episode = UHR), analysis 2 ( $F_{4,249} = 6.54$ ;  $P < .001$ ; first-episode schizophreniform = first-episode affective < first-episode schizophrenia = first-episode other = controls), and analysis 3 ( $F_{3,384} = 4.81$ ;  $P = .003$ ; first-episode = UHR-NP < UHR-P = controls) but not in analysis 4 ( $F_{2,126} = 3.90$ ;  $P = .02$ ; UHR-NP = UHR-P = controls). See **Table 3** for percent-

age differences and effect sizes. In summary, compared with control subjects, ICVs were not different in any patient group. Whole-brain volumes were smaller in patients with first-episode schizophreniform disorder, patients with first-episode affective psychoses, and the UHR-NP group.

### HIPPOCAMPAL VOLUMES

Analysis 1 revealed a significant group effect for adjusted right ( $F_{3,473} = 7.4$ ) and left ( $F_{3,473} = 7.1$ ) hippocampal volumes ( $P < .001$  for both). Post hoc comparisons indicated that only the chronic schizophrenia group significantly differed from controls for right (7.7% smaller) and left (8.4% smaller) hippocampal volumes, with moderate effect sizes (Table 1 and **Table 4** and **Figure**). Analysis 2 revealed a significant group effect for left ( $F_{4,249} = 2.5$ ;  $P = .045$ ) but not right ( $F_{4,249} = 0.78$ ;  $P = .54$ ) hippocampal volumes. Left hippocampal volumes were significantly smaller than control subject volumes in patients with first-episode schizophrenia/schizoaffective disorder (6.3% smaller, moderate effect size). The first-episode schizophrenia subgroup left hippocampal volumes remained significantly smaller than those of control subjects after the exclusion of those patients with schizoaffective disorder ( $P = .04$ ). There was no significant effect of group for analysis 3 right ( $F_{3,384} = 0.11$ ;  $P = .95$ ) or left ( $F_{3,384} = 1.5$ ;  $P = .20$ ) hippocampal volumes. There was no significant effect of group for analysis 4 right ( $F_{2,126} = .26$ ;  $P = .77$ ) or left ( $F_{2,126} = 1.3$ ;  $P = .29$ ) hippocampal volumes. In summary, compared with control subjects, hippocampal volumes were reduced bilaterally in patients with chronic schizophrenia and on the left side in patients with first-episode schizophrenia but not first-episode schizophreniform disorder. Hippocampal volumes were not reduced in any other first-episode groups or the UHR-P and UHR-NP groups.

### AMYGDALA VOLUMES

Analysis 1 revealed significant group differences in right ( $F_{3,473} = 10.2$ ) and left ( $F_{3,473} = 10.6$ ) amygdala volumes ( $P < .001$  for both). Post hoc comparisons indicated that amygdala volumes of the first-episode psychosis group were significantly larger than those of controls on the right (8.3%, large effect size) and left (7.6%, large effect size) sides (Tables 1 and 4 and Figure 1). Analysis 2 of the first-episode subgroups revealed a significant group effect for right ( $F_{4,249} = 7.74$ ) and left ( $F_{4,249} = 8.33$ ) amygdala volumes ( $P < .001$  for both). Post hoc comparisons revealed that first-episode other psychoses patients had bilaterally larger volumes (right: 16.9%, large effect size; left: 20%, large effect size), whereas first-episode affective psychosis patients had larger right amygdala volumes (11%, moderate effect size). Analysis 3 revealed a significant effect of group for right ( $F_{3,384} = 11.5$ ) and left ( $F_{3,384} = 12.0$ ) amygdala volumes ( $P < .001$  for both). In this analysis, the first-episode group exhibited bilaterally larger amygdala volumes compared with both UHR groups, but no patient group was different from the control subjects. There was no significant effect of group in analysis 4 for right ( $F_{2,126} = 0.93$ ;  $P = .40$ ) or left ( $F_{2,126} = 2.8$ ;  $P = .07$ )

**Table 3. Intracranial and Whole-Brain Volumes of Patients and Control Subjects**

Group	Intracranial Volumes, mm <sup>3</sup>					Whole-Brain Volumes, mm <sup>3</sup>				
	Adjusted Volume, Controls (n = 87)/Patients*	% Diff†	P Value	95% CI‡	Effect Size	Adjusted Volume, Controls (n = 87)/Patients*	% Diff†	P Value	95% CI‡	Effect Size
<b>Analysis 1</b>										
Chronic Sz (n = 89)	1 434 871/1 436 508	0.1	>.99	-48 892 to 52 166	0.013	1 362 698/1 346 058	-1.2	.68	-44 446 to 11 166	-0.23
FE (n = 162)	1 434 871/1 425 172	-0.7	>.99	-53 964 to 34 565	-0.08	1 362 698/1 326 057	-2.7	<.001	-60 280 to -13 003	-0.55
UHR (n = 135)	1 434 871/1 443 981	0.6	>.99	-37 367 to 37 367	0.071	1 362 698/1 331 599	-2.3	.006	-55 981 to -62 17	-0.46
<b>Analysis 2</b>										
FE Sz (n = 46)	1 438 507/1 396 636	-2.9	.55	103 468 to 19 725	-0.35	1 364 590/1 351 337	-0.97	>.99	-48 127 to 21 621	-0.20
FE Sz/form (n = 57)	1 438 507/1 443 401	0.34	>.99	-52 514 to 62 302	0.041	1 364 590/1 310 464	-4.0	<.001	-87 210 to -21 042	-0.81
FE affective (n = 34)	1 438 507/1 466 320	1.9	>.99	-42 112 to 97 737	0.23	1 364 590/1 324 558	-2.9	.03	-78 186 to -1877	-0.60
FE other psychosis (n = 25)	1 438 507/1 408 722	-2.1	>.99	106 241 to 46 671	-0.25	1 364 590/1 326 266	-2.8	.11	-80 963 to 4317	-0.57
<b>Analysis 3</b>										
FE (all) (n = 162)	1 432 811/1 423 292	-0.66	>.99	-53 872 to 34 835	-0.08	1 364 590/1 329 410	-2.6	.001	-60 251 to -10 362	-0.52
UHR psychosis (n = 39)	1 432 811/1 480 421	3.3	.19	-18 388 to 113 609	0.37	1 364 717/1 335 420	-2.1	>.99	-65 458 to 6864	-0.42
UHR nonpsychosis (n = 96)	1 432 811/1 427 435	-0.38	>.99	-55 495 to 44 744	-0.04	1 364 717/1 335 110	-2.2	.03	-57 564 to -1649	-0.43
<b>Analysis 4</b>										
UHR Sz (n = 21)	1 443 751/1 496 914	3.7	.38	-30 389 to 136 715	0.40	1 363 870/1 331 493	-2.4	.08	-67 600 to 2846	-0.56
UHR other psychosis (n = 18)	1 443 751/1 480 767	2.6	.86	-46 844 to 120 874	0.28	1 363 870/1 330 322	-2.5	.09	-75 578 to 3482	-0.58

Abbreviations: CI confidence interval; Diff, difference; FE, first-episode; Sz, schizophrenia; Sz/form, schizophreniform; UHR, ultra-high risk.  
 \*Adjusted mean volumes (intracranial volume covaried for height and whole-brain volume corrected for intracranial volume and covaried for age and sex).  
 †Percentage difference compared with control subjects.  
 ‡Joint univariate 0.95 Bonferroni CIs for difference.

amygdala volumes. In summary, compared with control subjects, amygdala volumes were larger only in patients with first-episode nonschizophrenic psychoses. Amygdala volumes in patients with chronic schizophrenia, first-episode schizophrenia, first-episode schizophreniform disorder, UHR-P, and UHR-NP were not different than those in the control group.

**RELATIONSHIPS AMONG STRUCTURE, ILLNESS DURATION, AND MEDICATION VARIABLES**

Complete medication data were available for 69 of 89 patients with chronic schizophrenia and 157 of 162 first-episode patients. The percentages of patients taking typical antipsychotic agents, atypical antipsychotics, and no medications were 45%, 52%, and 3%, respectively, for patients with chronic schizophrenia and 26%, 69%, and 5%, respectively, for first-episode patients. Patients with chronic schizophrenia were divided according to whether they were taking typical (n=31) or atypical (n=36) antipsychotic drugs. There was no difference between the groups on any demographic (age and sex) or structural volume measures. First-episode patients with schizophrenia/schizoaffective disorder were the only first-episode sub-

group with sufficient numbers in each group to allow a similar analysis. Patients taking typical antipsychotic agents (n=22) and those taking atypical antipsychotics (n=20) were no different on any demographic or structural measures. Finally, excluding patients taking lithium from all analyses did not alter the findings.

Although none of the UHR patients were receiving psychotropic medications at the time of MRI, more than 50.4% entered an intervention study after MRI.<sup>34</sup> An analysis was undertaken to examine whether there were any demographic or structural differences among the 4 UHR groups: (1) patients not in the intervention study (n=67), (2) patients in the treatment group of the intervention study (n=21), (3) patients in the control group of the intervention study (n=23), and (4) patients who refused to enter the intervention study but agreed to the MRI study (n=24). Comparison of the 4 groups revealed no differences in age ( $F_{3,135}=1.4$ ;  $P=.25$ ), height ( $F_{3,129}=1.9$ ;  $P=.14$ ), or sex ( $\chi^2_3=3.4$ ;  $P=.33$ ). There were no differences in any structural measures among the 4 groups: right hippocampus,  $F_{5,135}=0.14$  ( $P=.94$ ); left hippocampus,  $F_{5,135}=1.5$  ( $P=.22$ ); right amygdala,  $F_{5,135}=1.8$  ( $P=.15$ ); left amygdala,  $F_{5,135}=0.06$  ( $P=.98$ ); whole-brain volume,

**Table 4. Hippocampal and Amygdala Volumes of Patients and Control Subjects**

Group	Side	Hippocampal Volumes, mm <sup>3</sup>					Amygdala Volumes, mm <sup>3</sup>				
		Adjusted Volume, Controls (n = 87)/ Patients*	% Diff†	P Value	95% CI‡	Effect Size, Controls	Adjusted Volume, Controls (n = 87)/ Patients*	% Diff†	P Value	95% CI‡	Effect Size
<b>Analysis 1</b>											
Chronic Sz (n = 89)	R	3118/2877	-7.7	<.001	-389 to -94	-0.63	1514/1521	0.5	>.99	-113 to 128	0.02
	L	2873/2632	-0.8	<.001	-380 to -101	-0.66	1509/1537	1.9	>.99	-92 to 148	0.08
FE (n = 162)	R	3118/3110	-0.03	>.99	-134 to 117	-0.02	1514/1640	8.3	.007	24 to 228	0.44
	L	2873/2778	-3.3	.21	-213 to 24	-0.29	1509/1623	7.6	.02	12 to 216	0.37
UHR (n = 135)	R	3118/3104	-0.4	>.99	-146 to 118	-0.04	1514/1466	-3.2	>.99	-156 to 60	-0.16
	L	2873/2804	-2.4	.87	-193 to 56	-0.20	1509/1443	-4.4	.61	-174 to 41	-0.21
<b>Analysis 2</b>											
FE Sz (n = 46)	R	3112/3039	-2.3	>.99	-262 to 114	-0.20	1544/1551	0.45	>.99	-128 to 143	0.03
	L	2875/2695	-6.3	.03	-353 to -9	-0.54	1546/1534	-0.8	>.99	-156 to 132	-0.04
FE Sz/form (n = 57)	R	3112/3160	1.5	>.99	-130 to 226	0.13	1544/1548	0.3	>.99	-125 to 133	0.02
	L	2875/2777	-3.4	.90	-262 to 65	-0.30	1546/1530	-1.0	>.99	-152 to 121	-0.06
FE affective (n = 34)	R	3112/3100	-0.4	>.99	-218 to 194	-0.03	1544/1714	11.0	.01	22 to 319	0.65
	L	2875/2853	-0.8	>.99	-211 to 166	-0.07	1546/1654	7.0	.52	-49 to 266	0.39
FE other psychosis (n = 25)	R	3112/3105	-0.2	>.99	-238 to 223	-0.02	1544/1805	16.9	<.001	95 to 427	1.0
	L	2875/2798	-2.7	>.99	-288 to 134	-0.23	1546/1856	20.0	<.001	134 to 486	1.1
<b>Analysis 3</b>											
FE (all) (n = 162)	R	3102/3098	-0.1	>.99	-135 to 126	-0.01	1541/1634	6.0	.24	-7 to 192	0.30
	L	2867/2771	-3.3	.20	-215 to 23	-0.29	1543/1622	5.1	.08	-22 to 180	0.28
UHR psychosis (n = 39)	R	3102/3068	-1.1	>.99	-223 to 155	-0.09	1541/1456	-5.5	.12	-229 to 60	-0.30
	L	2867/2805	-2.2	>.99	-235 to 111	-0.18	1543/1414	-8.4	.73	-276 to 18	-0.45
UHR nonpsychosis (n = 96)	R	3102/3106	0.1	>.99	-143 to 150	0.01	1541/1449	-6.0	.10	-229 to 60	-0.33
	L	2867/2795	-2.5	.93	-206 to 62	-0.22	1543/1440	-6.7	.18	-276 to 18	-0.37
<b>Analysis 4</b>											
UHR Sz (n = 21)	R	3115/3054	-2.0	>.99	-270 to 148	-0.18	1522/1457	-4.3	.97	-226 to 95	-0.25
	L	2875/2746	-4.5	.34	-328 to 68	-0.40	1518/1396	-8.0	.13	-268 to 23	-0.56
UHR other psychosis (n = 18)	R	3115/3088	-0.9	>.99	-247 to 192	-0.08	1522/1441	-5.3	.74	-250 to 88	-0.31
	L	2875/2841	-1.2	>.99	-242 to 174	-0.11	1518/14112	-7.0	.29	-259 to 47	-0.44

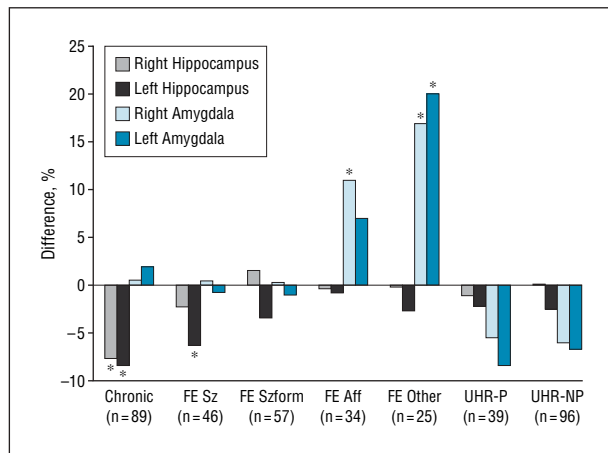
Abbreviations: CI, confidence interval; Diff, difference; FE, first-episode; L, left; R, right; Sz, schizophrenia; Sz/form, schizophreniform; UHR, ultra-high risk.  
 \*Adjusted mean volumes (see "Statistical Analyses" subsection of "Methods" section).  
 †Percentage difference compared with control subjects.  
 ‡Joint univariate 0.95 Bonferroni CIs for difference.

$F_{5,135}=0.39$  ( $P=.76$ ); or  $ICV, F_{4,129}=0.05$  ( $P=.98$ ). No correlation was observed between illness duration in the patient groups and any structural volume.

**COMMENT**

This study extends our previous works<sup>15,23</sup> through the inclusion of additional patients with chronic schizophrenia, patients with first-episode psychoses, and patients who are at UHR of psychosis and describes the largest published

study of hippocampal and amygdala volumetrics in these patient groups compared with control subjects. The study found that patients with chronic schizophrenia have bilaterally smaller hippocampi; that left-sided hippocampal volume reduction is seen in first-episode patients with schizophrenia but not in those with schizophreniform, affective psychosis, or other psychoses; and that bilateral amygdala enlargement was present only in first-episode nonschizophrenia patients. Neither the UHR-P group nor the UHR-NP group exhibited hippocampal or amygdala volume changes



**Figure.** Differences in adjusted hippocampal and amygdala volumes in the patient groups compared with control subjects. Chronic indicates chronic schizophrenia; FE Sz, first-episode schizophrenia spectrum; FE Szform, first-episode schizophreniform; FE Aff, first-episode affective psychoses; FE other, other first-episode psychoses; UHR-P, ultra-high risk patients who developed psychosis; UHR-NP, ultra-high risk patients who did not develop psychosis; and asterisk, statistically significant difference compared with the control group.

compared with control subjects. First-episode and UHR patients, but not those with chronic schizophrenia, had smaller whole-brain volumes compared with control subjects. There were no differences in ICVs between any patient group and control subjects. These results suggest that hippocampal and amygdala volumes are differentially affected depending on the type of psychosis and that such changes are not present in a UHR group before the onset of psychosis.

The finding that patients with chronic schizophrenia have bilaterally smaller hippocampal volumes is consistent with our previous study<sup>15</sup> and meta-analyses of MRI studies in schizophrenia.<sup>5</sup> The finding of left hippocampal volume reduction only in the first-episode schizophrenia group does not support our earlier study,<sup>15</sup> which identified a reduction in first-episode schizophrenia and affective psychosis groups, but is similar to the finding by Hirayasu et al<sup>16</sup> of left hippocampal volume reduction in first-episode patients with schizophrenia but not affective psychosis. A further new finding is that of normal hippocampal volumes in patients with first-episode schizophreniform psychosis. This is an important finding given that this group differed from patients with first-episode schizophrenia only in illness duration but not in age, sex, height, or time from presentation to MRI and is consistent with the finding of normal hippocampal volumes in patients with UHR-P schizophrenia.

Together with previous data<sup>15,39</sup> identifying that right hippocampal volume is associated with illness duration in patients with chronic schizophrenia, the current data are consistent with our previously stated hypothesis that left hippocampal volumes are altered during the early phases of schizophrenia and that reduction of right hippocampal volumes reflects illness duration.<sup>40</sup> This interpretation is also consistent with recent longitudinal MRI UHR data that show progressive left medial temporal volume reduction during the transition from the UHR phase to first-episode psychosis in a group of patients, half of whom received a diagnosis of schizophrenia.<sup>22</sup>

The findings of greater amygdala volumes in first-episode patients with affective and other psychoses but not in schizophrenia are consistent with other studies in patients with bipolar disorder.<sup>7,9</sup> The present study suggests that these findings are also evident in patients with psychotic depression and nonschizophrenic psychoses. Studies of patients with psychoses of epilepsy, which have prominent affective features, have reported a similar degree of amygdala enlargement<sup>41</sup> or a larger anterior aspect of the amygdala-hippocampal complex,<sup>42</sup> raising the possibility that increased amygdala volume is a nonspecific marker for the presence of a major affective syndrome. The association of affective symptoms with amygdala abnormality is consistent with the known role of the amygdala in affect regulation.<sup>43,44</sup>

In contrast to our original hypothesis, we did not demonstrate amygdala volume reductions in patients with chronic schizophrenia or first-episode schizophrenia. This finding may be attributable to methodological differences in amygdala estimation between studies. Studies that, like the present study, used a method that defines the amygdalae and hippocampi separately have not identified amygdala volume reduction in schizophrenia.<sup>8</sup> Early positive studies may have been limited through the use of only 1 or 2 amygdala sections or by reporting a combined amygdala-hippocampal complex, which relies on external landmarks to divide the amygdala and hippocampus.<sup>45</sup> The method used in this study<sup>36</sup> for measuring amygdala rated well (a quality score of 14 of 19) among other methods in terms of validity and reliability.<sup>46</sup>

This study is unique in that we studied intracranial, whole-brain, hippocampal, and amygdala volumes in a large sample of people at UHR for psychosis. In contrast to our previous study in a smaller group,<sup>23</sup> hippocampal volume is not reduced, although the largest effect sizes were seen in those who later developed schizophrenia or schizoaffective disorder. There are 2 possible explanations for the difference between the 2 studies. First, the sample size in the present study is more than double that of our previous study, providing a better estimate of the true population mean. Second, our previous analyses did not incorporate ICV as a covariate and adjusted only for whole-brain volume. Reanalysis of the current data using whole-brain volume only as a covariate did not alter the findings. Amygdala volumes did not differ from those of the control group for any of the UHR groups, although the largest effect sizes were seen for left amygdala reduction across the UHR groups compared with control subjects. Smaller total brain volumes were characteristic of the at-risk mental state and were not in themselves predictive of later development of psychotic illness.

These data strongly suggest that altered hippocampal or amygdala volumes are not a premorbid marker of vulnerability for psychosis. This is in agreement with recent findings of normal medial temporal biochemical findings on magnetic resonance spectroscopy<sup>47</sup> and normal neuropsychologic function<sup>48</sup> in an overlapping group of patients and also with our longitudinal UHR study<sup>22</sup> showing a reduction in left medial temporal volume during the transition to psychosis. In addition, our findings support studies that suggest that hippocampal volume reduction is a marker of illness rather than a marker of risk.<sup>49,50</sup> The normal amygdala volumes in the UHR group



are of further interest given our findings in first-episode psychosis and chronic schizophrenia and suggest that there may be active enlargement of the amygdala during the transition to psychosis that occurs only in nonschizophrenic psychoses.

The differences between the current findings and other previously published high-risk research,<sup>51</sup> which found reduced medial temporal lobe volumes in a group genetically at risk for schizophrenia, are likely to stem from differences in our selection criteria. First, we examined a group at risk for psychosis rather than a group at risk for schizophrenia, although most of the UHR-P group received a diagnosis of schizophrenia or schizoaffective disorder. This would be an important consideration if there were real biological differences between the schizophrenia spectrum and affective psychoses. Our combining of the 2 groups might have concealed these differences. Second, a genetic vulnerability for schizophrenia was neither a necessary nor a sufficient reason for entry into the Personal Assessment and Crisis Evaluation Clinic, meaning that comparison with studies of at-risk individuals identified solely on family history grounds is inappropriate.

The mechanisms that lead to medial temporal volume changes remain unclear but could be mediated through medication use, substance use, or genetic, environmental, and developmental factors. Two recent studies<sup>52,53</sup> have suggested that morphologic brain changes may differ between patients treated with atypical vs typical antipsychotic agents. Most patients with chronic schizophrenia and first-episode psychosis in this study were medicated, but there was no difference in medial temporal volumes between patients with chronic or first-episode schizophrenia taking typical vs atypical antipsychotic drugs. In addition, the finding that different subgroups of the first-episode population displayed volume changes (hippocampal or amygdala) despite most first-episode patients undergoing antipsychotic drug treatment for brief periods and at low doses makes it unlikely that medication type can be invoked as a factor in the differential structural changes across diagnostic groups. The present study did not quantify substance use and cannot address the effect of substances on structural volumes. Although some studies have suggested that patients with a family history of psychosis are more likely to have reduced hippocampal volumes,<sup>54</sup> other studies do not support this finding.<sup>55</sup> The medial temporal lobe is highly sensitive to environmental insults, such as hypoxia,<sup>56</sup> hypoglycemia,<sup>57</sup> and undernutrition.<sup>58</sup> Patients with schizophrenia have an increased prevalence of antenatal and perinatal complications<sup>59</sup> but do not display the same degree of hippocampal volume reduction described in patients with prematurity<sup>60</sup> or in animal models of intrauterine hypoxia.<sup>61</sup>

The effects of stress, cortisol, and the hypothalamic-pituitary-adrenal axis may provide a possible explanation for the observed structural changes. Hippocampal atrophy has been known to be associated with the effects of stress and cortisol,<sup>62,63</sup> although it is difficult to account for unilateral hippocampal volume reduction and the absence of hippocampal volume reduction in the nonschizophrenic first-episode group if stress was to entirely explain hippocampal volume change. The role of

stress hormones in amygdala volume enlargement is more difficult to identify, although a recent study<sup>64</sup> has associated chronic stress in rats with atrophy of hippocampal neurons and hypertrophy of amygdala neurons. Allowing for the question of whether such effects lead to volume change, this finding would still not explain the observed dissociation of medial temporal changes. The present study did not quantify subjective stress levels, and neither did it examine stress hormone levels, which may have allowed further exploration of this issue. Such a study is currently in progress.

The neurobiologic process of amygdala enlargement is difficult to explain, but posited mechanisms include response to medication or chronic stress, increased vascular perfusion and metabolism, increased size or numbers of neurons and glia, increased connective tissue, increased intercellular fluid, and increased dopaminergic neurotransmission.<sup>8,64,65</sup> The normal amygdala volumes in patients with chronic schizophrenia argue against the finding being related to an effect of antipsychotic medication, and a neurotrophic effect of lithium is unlikely given that amygdala volumes were enlarged in patients not receiving lithium at the time of MRI.

In addition to the limitations outlined herein, this study is limited by factors related to the diagnostic classification of first-episode patients and the comparability of the patient groups, especially the UHR group. The inclusion of patients with first-episode schizoaffective disorder in the first-episode schizophrenia group is open to debate, although exclusion of this group from the analyses did not alter the results. The first-episode other psychosis group similarly includes small numbers of patients with different diagnoses, and analyses of each diagnostic group were not undertaken. Further studies including more patients with these less common diagnoses would shed further light on their pattern of medial temporal structural changes. The UHR patients who developed a first-episode psychosis were predominantly diagnosed as having schizophrenia and likely represent a subset of all first-episode patients given the recruitment criteria for UHR patients. This may limit any conclusions regarding the comparability of the UHR-P and first-episode psychosis patients. Finally, the inference that changes across the different stages of psychosis represent longitudinal structural changes needs to be confirmed in further longitudinal studies of the UHR and first-episode groups.<sup>22,66</sup>

The pattern of hippocampal and amygdala volume changes in the first-episode group and the absence of hippocampal and amygdala volume changes in the UHR-P group are not consistent with a neurodevelopmental model, which would predict that brain changes are present before the onset of illness. It remains a possibility, however, that early insults may lead to subtle hippocampal or amygdala effects, without associated volume change, which render these structures vulnerable to later insults or to abnormal development during critical phases of development.<sup>67</sup> The identified dissociation of medial temporal volume changes is displayed in the Figure and provides structural neurobiologic support for psychotic illness as a spectrum of disorders with schizophrenia at one end and nonschizophrenic psychoses at the other end.<sup>3</sup> To-

gether with the finding that hippocampal and amygdala volumes are normal in UHR patients, our data provide further evidence that structural medial temporal changes occur during and immediately after the transition to first-episode psychosis and provide an impetus for further studies in the neurobiologic process of early psychosis, particularly nonschizophrenic psychoses, such as bipolar disorder.

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